Subject: Statistical Review of K161201 ClearRead CT Insight Lung CAD by Riverain Technologies.

Date: June 8, 2016

From: Mathematical Statistician (Qin Li, PhD)
      CDRH/OSB/DBS/DX

To: Yanna Kang
    CDRH/OIR/DRH/MUIS

1. Background and introduction

This pre-submission is related to 510k K152418, for which the ClearRead CT lung CAD device was issued a decision of Not Substantially Equivalent by FDA on Dec 7, 2015. Sponsor responded to the deficiencies cited in the NSE letter in subsequent pre-submission.
2. Indication for use

ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

The device content is intended to be read concurrently, that is the radiologist will have access to the vessel suppressed series with CADe marks superimposed while viewing the original CT series. These marks fall into the following four categories: a true positive, a true negative, a false positive, or a false negative.

ClearRead CT is intended for use by trained medical professionals only. The device is not supplied sterile or intended to be sterilized by the operator, and is not intended for single use. The operation of the device is controlled by the CT software program, ClearRead Connect.

3. Brief device description

ClearRead CT is a dedicated post-processing application that generates a secondary vessel suppressed Lung CT series with CADe marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

The original Lung CT series is sent to the ClearRead CT application from the acquisition device or the PACS. ClearRead CT generates a vessel suppressed series with regions of interest (ROIs), CAD markers, and characterizations. The application sends the resulting information through the same DICOM network connection to the PACS.

This system is illustrated in Figure 8.1.
Figure 8.1: ClearRead CT Work Flow

Internal Scoring methodology

(b) (4)
Study cases

(b) (4)
Determination of Truth

(b) (4)
Reading session design

(b) (4)
Statistical model and analyses
Table E.1 Radiologist reading assignments in third reading session

<table>
<thead>
<tr>
<th>(b) (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
(b) (4)
6. Potential deficiencies meant to the sponsor

(b) (4)
MEMORANDUM

Date: May 26, 2016
From: Marios A Gavrielides, Ph.D.
Device: ClearRead CT™
Sponsor: Riverain Technologies, LLC.
Product Code: OEB/LLZ

Note: (b) (4)

Overview: ClearRead CT is a dedicated post-processing application that generates a secondary vessel suppressed Lung CT series with CADe marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest. The ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Revised Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Testing Summary:

(b) (4)
## Premarket Notification 510(k) Review

**Date:** June 17, 2016  
**Reviewer:** Yanna Kang  
**Subject:** Traditional 510(k)# K161201

<table>
<thead>
<tr>
<th>Applicant</th>
<th>Riverain Technologies, LLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Name</td>
<td>Jennifer Butsch</td>
</tr>
<tr>
<td>Correspondent Firm</td>
<td>Riverain Technologies, LLC</td>
</tr>
<tr>
<td>Received Date</td>
<td>April 28, 2016</td>
</tr>
<tr>
<td>Pro Code(s)</td>
<td>OEB Class: II Reg #: 892.2050</td>
</tr>
<tr>
<td>Pro Code(s)</td>
<td>LLZ Class: II Reg #: 892.2050</td>
</tr>
</tbody>
</table>

### Predicate Devices:

<table>
<thead>
<tr>
<th>Submission #</th>
<th>Pro Code</th>
<th>Device Trade Name</th>
<th>Owner</th>
</tr>
</thead>
<tbody>
<tr>
<td>K143196</td>
<td>OEB</td>
<td>Syngo.ct Lung Cad</td>
<td>Siemens Ag Medical Solutions</td>
</tr>
<tr>
<td>K093621</td>
<td>LLZ</td>
<td>Syngo.pet&amp;ct Oncology</td>
<td>Siemens Medical Solutions Usa, Inc.</td>
</tr>
<tr>
<td>K092363</td>
<td>LLZ</td>
<td>Softview, Model 2.01</td>
<td>Riverain Medical Group</td>
</tr>
</tbody>
</table>

### Review Summary

(b)(4)

### Review Team

- **Lead Reviewer:** Yanna Kang (CDRH/OIR/DRH/MUIS)  
- **Consult Reviewer (Statistics):** Qin Li (CDRH/OSB/DBS/DSBI)  
- **Consult Reviewer (Medical Imaging):** Marios Gavrielides (CDRH/OSEL/DIDSR)
I. **Purpose and History**

The 510(k) holder would like to introduce ClearRead CT into interstate commerce. ClearRead CT is a new CADe device intended to assist radiologists in the detection of nodules in chest CT series. There is a prior submission of this device (K152418) which was determined to be Not Substantially Equivalent due to lack of performance data and no response. Following the NSE decision, Riverain submitted a pre-submission package (Q152108) to seek our feedback on their proposed responses to the NSE deficiencies. Most of the proposed responses included in Q152108 appear to be adequate. For the following deficiencies, the sponsor agreed to provide additional data to meet our requirements (Some of the questions have not been addressed in the current submission):

(b) (4)
### Reviewer Recommendation

The 510(k) Summary/Statement is [not] acceptable.

### III. Device/System Description

<table>
<thead>
<tr>
<th>Device Characteristics</th>
<th>Inadequate</th>
<th>Or Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the intended use or fundamental technology new?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Is the device life-supporting or life sustaining?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Are there any direct or indirect patient contacting components?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Does the device use software/firmware?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>• Is the device, or does it contain, a Mobile Medical App?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Does the device or a component need sterilization (by manufacturer or user)?</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>The device/system uses or is...</td>
<td>a reusable multi-patient use device(s)</td>
<td></td>
</tr>
<tr>
<td>The environment for use of the device/system includes...</td>
<td>Hospital</td>
<td></td>
</tr>
<tr>
<td>Is the device a combination product?</td>
<td>N - Not a Part 3 Combination Product</td>
<td></td>
</tr>
<tr>
<td>Is the device/system electrical (battery or wall powered)?</td>
<td>No, the device is not electrical</td>
<td></td>
</tr>
</tbody>
</table>

Check the attributes that are applicable to this submission.

<table>
<thead>
<tr>
<th>Nanotechnology</th>
<th>Reprocessed SUD</th>
<th>Companion Diagnostic</th>
<th>Medical Counter Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Device Description Table: Summary of important device characteristics
V. Comparison of Technology to Predicate Devices

<table>
<thead>
<tr>
<th>Device &amp; Predicate Device(s):</th>
<th>K161201</th>
<th>K143196</th>
<th>K093621</th>
<th>K092363</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject device:</td>
<td>ClearRead CT, Riverain</td>
<td>Predicate: Syngo CT Lung CAD, Siemens</td>
<td>Reference:</td>
<td>Reference:</td>
</tr>
<tr>
<td>General Device Characteristics</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
</tr>
<tr>
<td>Intended use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure, Regulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Image Source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of nodules</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Automatic Segmentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Machine learning techniques</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodule detection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodule measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary image display</td>
<td>Vessel suppressed image</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Reviewer Recommendation
The Comparison of the Technology to Predicate Devices is acceptable.

#### VI. Labeling

<table>
<thead>
<tr>
<th>Labeling Review Needed?</th>
<th>Yes</th>
<th>Undo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usability Consult Needed?</td>
<td>Undo</td>
<td>No</td>
</tr>
</tbody>
</table>

### A General Labeling Requirements

<table>
<thead>
<tr>
<th>General Labeling Requirements</th>
<th>Inadequate or Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the prescription statement (or &quot;Rx only&quot;) included?</td>
<td>Yes</td>
</tr>
<tr>
<td>The indications for use are consistent with the IFU page?</td>
<td>Yes</td>
</tr>
<tr>
<td>Appropriate contraindications, warnings, precautions and adverse events provided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Instructions are in accordance with the guidance (if applicable)?</td>
<td>Yes</td>
</tr>
<tr>
<td>Appropriate labeling inside device?</td>
<td>Yes</td>
</tr>
<tr>
<td>Appropriate label/indicator outside device?</td>
<td>Inapplicable</td>
</tr>
<tr>
<td>Appropriate Manual labeling?</td>
<td>No</td>
</tr>
<tr>
<td>What MRI safety information does the labeling contain?</td>
<td>Not Evaluated and Not Needed</td>
</tr>
</tbody>
</table>

Labeling Table: A summary of the adequacy of several labeling requirements.

(b)(4)
VII. Reprocessing, Sterilization, and Shelf-Life

Reviewers of this record recommended that reprocessing, sterilization, and shelf-life requirements be updated to reflect the current process. The updated requirements will be included in the next revision of the manual.

VIII. Biocompatibility

Reviewers of this record recommended that biocompatibility testing be performed on the device to ensure that it is safe for use in humans. The testing will be completed within the next three months.

IX. Software/Firmware

<table>
<thead>
<tr>
<th>Software/Firmware Version</th>
<th>Present</th>
<th>Absent</th>
<th>Inadequate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClearRead CT 1.1 - ClearRead CT Common Platform 2.0</td>
<td>☑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Level of Concern (LOC):** Identified as Moderate
- **Software/Firmware Description:**
  - Adequacy Comments: Acceptable. Section 13.2 of the submission.
  - Device Hazard Analysis: Acceptable. Section 3 of Appendix B.
  - Software Requirements Specifications:
    - Adequacy Comments: Acceptable. Section 6 and 7 of Appendix B.
  - Architecture Design Chart: N/A if Minor LOC
    - Adequacy Comments: Acceptable. Section 5 of Appendix B.
  - Software Design Specifications: N/A if Minor LOC
    - Adequacy Comments: Acceptable. Section 8 of Appendix B.

K161201 Lead Memo Riverain Technology... Clearread Ct

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOIA STATUS@fda.hhs.gov or 301-796-8118
X. EMC & Electrical, Mechanical and Thermal Safety & Risk Analysis

XI. Performance Testing

Study Cases
A Bench Testing

(b)(4)
Secondary Analyses

(b) (4)
XII. **Kit Certification**
Not applicable.

XIII. **Manufacturing Information**
Not applicable.

XIV. **References**

**Standards**
- IEC 62304: 2006 Medical Device Software – Software Life cycle Processes

**Guidance**
XV. **SE Flowchart Questions**

(b) (4)

XVI. **Original Deficiencies**

(b) (4)
Software

(b) (4)

Performance Testing

(b) (4)
XVII.

<table>
<thead>
<tr>
<th>Digital Signature Concurrence Table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer Sign-Off</td>
</tr>
<tr>
<td>Yanna S. Kang -S</td>
</tr>
<tr>
<td>2016.06.17 10:38:48 -04'00'</td>
</tr>
</tbody>
</table>
Premarket Notification 510(k) Review

Date: June 28, 2016
Reviewer: Yanna Kang
Subject: Traditional 510(k)# K161201/S001

Applicant: Riverain Technologies, LLC
Contact Name: Jennifer Butsch
Correspondent Firm: Riverain Technologies, LLC
Received Date: July 1, 2016
Pro Code(s): OEB Class: II Reg #: 892.2050
Pro Code(s): LLZ Class: II Reg #: 892.2050

Device Trade Name: Clearead Ct
Contact Title: Director Of Regulatory Affairs & Quality Assurance
Phone: (937) 425-6811 Email: jbutsch@riveraintech.com
Due Date: August 10, 2016
Reg Name: Picture Archiving And Communications System
Reg Name: Picture archiving and communications system

Predicate Devices:
Submission # Pro Code Device Trade Name Reg Name Owner
K143196 OEB Syngo.ct Lung Cad Siemens Ag Medical Solutions
K093621 LLZ Syngo.pet&ct Oncology Siemens Medical Solutions Usa, Inc.
K092363 LLZ Softview, Model 2.01 Riverain Medical Group

Review Summary

Review Team:
Lead Reviewer: Yanna Kang (CDRH/OIR/DRH/MUIS)
Consult Reviewer (Statistics): Qin Li (CDRH/OSB/DBS/DSSBI)
Consult Reviewer (Medical Imaging): Marios Gavrielides (CDRH/OSEL/DIDSR)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118.
I. **Purpose and History**

   (b) (4)

II. **510(k) Summary/Statement**
### III. Device/System Description

#### Device Characteristics

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Inapplicable Or Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the intended use or fundamental technology new?</td>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the device life-supporting or life sustaining?</td>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are there any direct or indirect patient contacting components?</td>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the device use software/firmware?</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Is the device, or does it contain, a Mobile Medical App?</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the device or a component need sterilization (by manufacturer or user)?</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The device/system uses or is...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The environment for use of the device/system includes...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the device a combination product?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the device/system electrical (battery or wall powered)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Check the attributes that are applicable to this submission.**

<table>
<thead>
<tr>
<th>ATTRIBUTE</th>
<th>Nanotechnology</th>
<th>Reprocessed SUD</th>
<th>Companion Diagnostic</th>
<th>Medical Counter Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>No</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Unknown</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

**Device Description Table: Summary of important device characteristics**

(b) (4)
Third-party Components and Accessories:
Not applicable.

IV. **Comparison of Indications for Use to Predicate Devices**

<table>
<thead>
<tr>
<th>Subject</th>
<th>510(k) #: K161201</th>
<th>Rx/OTC: Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intended Population</td>
<td>Adults Only</td>
<td>Adults and Pediatrics</td>
</tr>
<tr>
<td>Yes</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Comparison of Indications for Use

(b) (4)

### Reviewer Recommendation

(b) (4)

### V. Comparison of Technology to Predicate Devices

<table>
<thead>
<tr>
<th>Device &amp; Predicate Device(s):</th>
<th>K161201</th>
<th>K143196</th>
<th>K093621</th>
<th>K092363</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject device:</td>
<td>ClearRead CT, Riverain</td>
<td>Syngo CT Lung CAD, Siemens</td>
<td>Reference:</td>
<td>Reference:</td>
</tr>
<tr>
<td>Predicate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) (4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

K161201/S001 Lead Memo  Riverain Technology...  Clearread Ct
VI. **Labeling**

<table>
<thead>
<tr>
<th>Device &amp; Predicate</th>
<th>K161201</th>
<th>K143196</th>
<th>K093621</th>
<th>K092363</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device(s):</td>
<td>Subject device: ClearRead CT, Riverain</td>
<td>Predicate: Syngo CT Lung CAD, Siemens</td>
<td>Reference:</td>
<td>Reference:</td>
</tr>
</tbody>
</table>

(b) (4)

<table>
<thead>
<tr>
<th>Labeling Review Needed?</th>
<th>Yes</th>
<th>Undo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usability Consult Needed?</td>
<td>Undo</td>
<td>No</td>
</tr>
</tbody>
</table>

A **General Labeling Requirements**

<table>
<thead>
<tr>
<th>General Labeling Requirements</th>
<th>K161201/S001 Lead Memo</th>
<th>Riverain Technology...</th>
<th>Clearread Ct</th>
<th>K093621</th>
<th>K092363</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the <em>prescription statement</em> (or &quot;Rx only&quot;) included?</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The indications for use are consistent with the IFU page?</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate contraindications, warnings, precautions and adverse events provided?</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instructions are in accordance with the guidance (if applicable)?</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate labeling <em>inside device</em>?</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate label/indicator <em>outside device</em>?</td>
<td>Inapplicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate <em>Manual labeling</em>?</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
IX. Software/Firmware

<table>
<thead>
<tr>
<th>Software/Firmware Version: ClearRead CT 1.1 - ClearRead CT Common Platform 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Concern (LOC): Identified as Moderate</td>
</tr>
<tr>
<td>Software/Firmware Description: Adequacy Comments: Acceptable. Section 13.2 of the submission.</td>
</tr>
<tr>
<td>Device Hazard Analysis: Adequacy Comments: Acceptable. Section 3 of Appendix B.</td>
</tr>
<tr>
<td>Software Requirements Specifications: Adequacy Comments: Acceptable. Section 6 and 7 of Appendix B.</td>
</tr>
<tr>
<td>Architecture Design Chart: N/A if Minor LOC Adequacy Comments: Acceptable. Section 5 of Appendix B.</td>
</tr>
<tr>
<td>Software Design Specifications: N/A if Minor LOC Adequacy Comments: Acceptable. Section 8 of Appendix B.</td>
</tr>
<tr>
<td>Traceability Analysis/Matrix: Adequacy Comments: Acceptable. Section 9.2 of Appendix B.</td>
</tr>
<tr>
<td>SW Development Environment Descrip. : N/A if Minor LOC Adequacy Comments: Acceptable. Section 2 of Appendix B.</td>
</tr>
<tr>
<td>Verification &amp; Validation Testing: Adequacy Comments: Acceptable. Section 9 of Appendix B.</td>
</tr>
<tr>
<td>Revision level history: Adequacy Comments: Acceptable. Section 10 of Appendix B.</td>
</tr>
<tr>
<td>Unresolved anomalies: N/A if Minor LOC Adequacy Comments: Acceptable. Section 11 of Appendix B.</td>
</tr>
</tbody>
</table>

Software Table: Demonstrates the adequacy of the software documentation according to the Guidance Document.

X. EMC & Electrical, Mechanical and Thermal Safety & Risk Analysis

Reviewer Recommendation

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
XI. Performance Testing

Study Cases

(b) (4)
B Animal Testing
Not applicable.

C Clinical Testing

(b) (4)
XII. **Kit Certification**
Not applicable.

XIII. **Manufacturing Information**
Not applicable.

XIV. **References**

**Standards**
- IEC 62304: 2006 Medical Device Software – Software Lifecycle Processes

**Guidance**

XV. **SE Flowchart Questions**

(b) (4)
XVI. **Original Deficiencies**

**Administrative Information**

(b) (4)

**Device Description**

(b) (4)

**Labeling**

(b) (4)
XVII. Supplement Deficiencies

Labeling

(b) (4)

Performance Testing

(b) (4)
### Digital Signature Concurrence Table

| Reviewer Sign-Off | Yanna S. Kang-S  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2016.07.28 08:57:29 -04'00'</td>
</tr>
</tbody>
</table>
Date: July 7, 2016  
From: Marios A Gavrielides, Ph.D.  
Device: ClearRead CT™  
Sponsor: Riverain Technologies, LLC.  
Product Code: OEB/LLZ  
Note: (b)(4)

Overview: ClearRead CT is a dedicated post-processing application that generates a secondary vessel suppressed Lung CT series with CADe marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest. The ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Revised Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

(b)(4)
Subject: Statistical Review of K161201S001 ClearRead CT Insight Lung CAD by Riverain Technologies.

Date: July 26, 2016

From: Mathematical Statistician (Qin Li, PhD)
CDRH/OSB/DBS/DX

To: Yanna Kang
CDRH/OIR/DRH/MUIS

In this supplement K161201S001, the sponsor provided responses to FDA deficiencies to the original K161201. My comments to responses 3 and 5-10 are provided below.
Premarket Notification 510(k) Review

Date: September 9, 2016
Reviewer: Yanna Kang
Subject: Traditional 510(k)# K161201/S002

Applicant: Riverain Technologies, LLC
Contact Name: Jennifer Butsch

Correspondent Firm: Riverain Technologies, LLC
Received Date: September 7, 2016

Pro Code(s): OEB Class: II Reg #: 892.2050
Pro Code(s): LLZ Class: II Reg #: 892.2050

Predicate Devices:
Submission # Pro Code Device Trade Name Owner
K143196 OEB Syngo.ct Lung Cad Siemens Ag Medical Solutions
K093621 LLZ Syngo.pet&ct Oncology Siemens Medical Solutions Usa, Inc.
K092363 LLZ Softview, Model 2.01 Riverain Medical Group

Review Summary

Review Team
Lead Reviewer Yanna Kang (CDRH/OIR/DRH/MUIS)
Consult Reviewer (Statistics) Qin Li (CDRH/OSB/DBS/DSBII)
Consult Reviewer (Medical Imaging) Marios Gavrielides (CDRH/OSEL/DIDSR)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
I. Purpose and History

(b) (4)

II. 510(k) Summary/Statement

<table>
<thead>
<tr>
<th>510(k) Summary/Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a 510(k) Summary or Statement provided?</td>
</tr>
</tbody>
</table>
**Reviewer Recommendation**  
The 510(k) Summary/Statement is acceptable.

### III. Device/System Description

#### Device Characteristics

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the intended use or fundamental technology new?</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Is the device life-supporting or life sustaining?</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Are there any direct or indirect patient contacting components?</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Does the device use software/firmware?</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>- Is the device, or does it contain, a Mobile Medical App?</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Does the device or a component need sterilization (by manufacturer or user)?</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The device/system uses or is...</td>
<td></td>
<td>a reusable multi-patient use device(s)</td>
<td></td>
</tr>
<tr>
<td>The environment for use of the device/system includes...</td>
<td></td>
<td>Hospital</td>
<td></td>
</tr>
<tr>
<td>Is the device a combination product?</td>
<td></td>
<td>N - Not a Part 3 Combination Product</td>
<td></td>
</tr>
<tr>
<td>Is the device/system electrical (battery or wall powered)?</td>
<td></td>
<td>No, the device is not electrical</td>
<td></td>
</tr>
</tbody>
</table>

#### Check the attributes that are applicable to this submission.

<table>
<thead>
<tr>
<th></th>
<th>Nanotechnology</th>
<th>Reprocessed SUD</th>
<th>Companion Diagnostic</th>
<th>Medical Counter Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>No</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>Unknown</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
</tbody>
</table>

**Device Description Table:** Summary of important device characteristics
**Third-party Components and Accessories:**
Not applicable.

**Reviewer Recommendation**
(b) (4)

**IV. Comparison of Indications for Use to Predicate Devices**

<table>
<thead>
<tr>
<th>Intended Population</th>
<th>Adults Only</th>
<th>Adults and Pediatrics</th>
<th>Transitional Adolescent A</th>
<th>Transitional Adolescent B</th>
<th>Adolescent</th>
<th>Infant</th>
<th>Neonate/Newborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(b) (4)
V. Comparison of Technology to Predicate Devices

(b) (4)
### VI. Labeling

<table>
<thead>
<tr>
<th>Labeling Review Needed?</th>
<th>Yes</th>
<th>Undo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usability Consult Needed?</td>
<td>Undo</td>
<td>No</td>
</tr>
</tbody>
</table>

#### A General Labeling Requirements

<table>
<thead>
<tr>
<th>General Labeling Requirements</th>
<th>Inadequate or Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the prescription statement (or &quot;Rx only&quot;) included?</td>
<td>Yes</td>
</tr>
<tr>
<td>The indications for use are consistent with the IFU page?</td>
<td>Yes</td>
</tr>
<tr>
<td>Appropriate contraindications, warnings, precautions and adverse events provided?</td>
<td>Yes</td>
</tr>
<tr>
<td>Instructions are in accordance with the guidance (if applicable)?</td>
<td>Yes</td>
</tr>
<tr>
<td>Appropriate labeling inside device?</td>
<td>Yes</td>
</tr>
<tr>
<td>Appropriate label/indicator outside device?</td>
<td>Inapplicable</td>
</tr>
<tr>
<td>Appropriate Manual labeling?</td>
<td>Yes</td>
</tr>
<tr>
<td>What MRI safety information does the labeling contain?</td>
<td>Not Evaluated and Not Needed</td>
</tr>
</tbody>
</table>

Labeling Table: A summary of the adequacy of several labeling requirements.
(b) (4)

VII. Reprocessing, Sterilization, and Shelf-Life

<table>
<thead>
<tr>
<th>Reviewer Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b) (4)</td>
</tr>
</tbody>
</table>

VIII. Biocompatibility

<table>
<thead>
<tr>
<th>Reviewer Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b) (4)</td>
</tr>
</tbody>
</table>
### IX. Software/Firmware

<table>
<thead>
<tr>
<th>Software Review Needed?</th>
<th>Yes</th>
<th>Not Applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Software Consult Needed?</td>
<td>Not Applicable</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Software Documentation</th>
<th>Present</th>
<th>Absent</th>
<th>Inadequate</th>
</tr>
</thead>
</table>
| Software/Firmware Version: ClearRead CT 1.1 - ClearRead CT  
Common Platform 2.0 | | | |
| Level of Concern (LOC): Identified as Moderate | ○ | ○ | ○ |

**Software/Firmware Description:**  
**Adequacy Comments:** Acceptable. Section 13.2 of the submission.  
**Device Hazard Analysis:** Acceptable. Section 3 of Appendix B.  
**Software Requirements Specifications:** Acceptable. Section 6 and 7 of Appendix B.  
**Architecture Design Chart:** N/A if Minor LOC  
**Adequacy Comments:** Acceptable. Section 5 of Appendix B.  
**Software Design Specifications:** N/A if Minor LOC  
**Adequacy Comments:** Acceptable. Section 8 of Appendix B.  
**Traceability Analysis/Matrix:** Acceptable. Section 9.2 of Appendix B.  
**SW Development Environment Description:** N/A if Minor LOC  
**Adequacy Comments:** Acceptable. Section 2 of Appendix B.  
**Verification & Validation Testing:**  
**Adequacy Comments:** Acceptable. Section 9 of Appendix B.  
**Revision History:** Acceptable. Section 10 of Appendix B.  
**Unresolved Anomalies:** N/A if Minor LOC  
**Adequacy Comments:** Acceptable. Section 11 of Appendix B.  

**Software Table:** Demonstrates the adequacy of the software documentation according to the Guidance Document.

### X. EMC & Electrical, Mechanical and Thermal Safety & Risk Analysis

**Reviewer Recommendation**  
(b) (4)

---

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
XI. Performance Testing

Study Cases

(b)(4)
B Animal Testing
   Not applicable.

C Clinical Testing

(b) (4)
XII. Kit Certification
Not applicable.

XIII. Manufacturing Information
Not applicable.

XIV. References

Standards
- IEC 62304: 2006 Medical Device Software – Software Lifecycle Processes

Guidance
XV. **SE Flowchart Questions**

(b) (4)


**Device Description**
<table>
<thead>
<tr>
<th>Group of</th>
<th>Reading session</th>
</tr>
</thead>
</table>

**Performance Testing**

(b) (4)
XVII. **Supplement Deficiencies**

**Labeling**

(b) (4)
XVIII. Contact History

<table>
<thead>
<tr>
<th>Reviewer Sign-Off</th>
<th>Yanna S. Kang-S</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2016.09.09 11:33:54 -04'00'</td>
</tr>
</tbody>
</table>
SAVE REQUEST

USER: (Latroy.Tinch@fda.hhs.gov)
FOLDER: K161201 - 1361 pages
COMPANY: ()
PRODUCT: LUNG COMPUTED TOMOGRAPHY SYSTEM, COMPUTER-AIDED DETECTION (OEB)
SUMMARY: Product: CLEARREAD CT

DATE REQUESTED: Oct 20, 2017
DATE PRINTED: Oct 20, 2017

Note: Printed
April 25, 2016

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Premarket Notification (510(k)) Submission
ClearRead CT™
Riverain Technologies, LLC

Dear Sir or Madam:

In accordance with the provisions of Section 510(k) of the Federal Food, Drug and Cosmetic Act (the Act), notification is hereby made of Riverain Technologies, LLC’s (“Riverain Technologies,” or “the Submitter”)’s intent to manufacture and distribute ClearRead CT.

A prior submission, K152418, was determined to be not substantially equivalent (NSE) on December 7, 2015. Subsequent to that communication, Riverain requested a Presubmission meeting, (b)(4), with the Agency to review the issues identified in the NSE letter. Riverain has addressed the identified issues and is resubmitting a 510(k) for the ClearRead CT device. Traceability of previous FDA communications and resulting actions is included in Appendix G for convenience.

The ClearRead CT described in this 510(k) is intended to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on asymptomatic populations. The ClearRead CT series provides adjunctive information and is not a substitute for the original CT series.

The cited predicate devices, syngo.CT Lung CAD (K143196), syngo.PET&CT Oncology (K093621), and ClearRead Bone Suppression (K092363) are also intended for the identification of pulmonary nodules that may have been overlooked or interpreted incorrectly.

The Submitter believes that ClearRead CT is substantially equivalent to the cited predicate devices. Differences in the design and performance from the cited predicate devices do not affect either the safety or effectiveness of ClearRead CT for its intended use. The information presented in this 510(k) supports these conclusions.

ClearRead CT is intended for use by trained medical professionals only and is therefore subject to 21 CFR §801, Subpart D. The device is not supplied sterile or intended to be sterilized by the operator, and is not intended for single use. The operation of the device is controlled by the CT software program, ClearRead Connect.
In preparing this 510(k) submission, the Submitter has carefully considered the relevant statutory and regulatory requirements, and believes that the information contained within satisfies the requirements for demonstrating substantial equivalence. Furthermore, the Submitter considers the regulatory approach outlined in this 510(k) to be in accord with the least burdensome provisions of the Food and Drug Administration (FDA) Modernization Act of 1997. This 510(k) has been prepared to meet the requirements outlined in 21 CFR §807, Subpart E – “Premarket Notification Procedures.” One (1) printed version of this 510(k) premarket notification is hereby enclosed. We are also enclosing an electronic version on a CD-ROM, which is an exact duplicate of the printed version.

The CD-ROM also includes data files in SAS Codes and Raw Data for ClearRead CT.zip and an example simulated nodules in DICOM format. This data is not included in printed form.

Confidentiality
We request that this 510(k), including commercial information and Riverain Technologies' intent to market the device described in this notification, be maintained by FDA in confidence pursuant to 21 CFR §807.95 for the maximum period allowed by 21 CFR §807.95(b) and (c), and including the maximum post-determination period specified in 21 CFR §807.95(e).

Please notify me directly of any request for release of information pertaining to this 510(k) prior to public disclosure of such information.

Respectfully Submitted,

Riverain Technologies
By: Jennifer Butsch
Director of Regulatory Affairs and Quality Assurance
April 25, 2016

U.S. Food and Drug Administration
Center for Devices and Radiological Heath
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD  20993-0002

Re: Premarket Notification (510(k)) Submission
ClearRead CT™
Riverain Technologies, LLC

Dear Sir or Madam:

In accordance with the provisions of Section 510(k) of the Federal Food, Drug and Cosmetic Act (the Act), notification is hereby made of Riverain Technologies, LLC’s (“Riverain Technologies,” or “the Submitter”)’s intent to manufacture and distribute ClearRead CT.

A prior submission, K152418, was determined to be not substantially equivalent (NSE) on December 7, 2015. Subsequent to that communication, Riverain requested a Pre-submission meeting, [b](4), with the Agency to review the issues identified in the NSE letter. Riverain has addressed the identified issues and is resubmitting a 510(k) for the ClearRead CT device. Traceability of previous FDA communications and resulting actions is included in Appendix G for convenience.

The ClearRead CT described in this 510(k) is intended to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on asymptomatic populations. The ClearRead CT series provides adjunctive information and is not a substitute for the original CT series.

The cited predicate devices, syngo.CT Lung CAD (K143196), syngo.PET&CT Oncology (K093621), and ClearRead Bone Suppression (K092363) are also intended for the identification of pulmonary nodules that may have been overlooked or interpreted incorrectly.

The Submitter believes that ClearRead CT is substantially equivalent to the cited predicate devices. Differences in the design and performance from the cited predicate devices do not affect either the safety or effectiveness of ClearRead CT for its intended use. The information presented in this 510(k) supports these conclusions.

ClearRead CT is intended for use by trained medical professionals only and is therefore subject to 21 CFR §801, Subpart D. The device is not supplied sterile or intended to be sterilized by the operator, and is not intended for single use. The operation of the device is controlled by the CT software program, ClearRead Connect.
In preparing this 510(k) submission, the Submitter has carefully considered the relevant statutory and regulatory requirements, and believes that the information contained within satisfies the requirements for demonstrating substantial equivalence. Furthermore, the Submitter considers the regulatory approach outlined in this 510(k) to be in accord with the least burdensome provisions of the Food and Drug Administration (FDA) Modernization Act of 1997. This 510(k) has been prepared to meet the requirements outlined in 21 CFR §807, Subpart E – “Premarket Notification Procedures.” One (1) printed version of this 510(k) premarket notification is hereby enclosed. We are also enclosing an electronic version on a CD-ROM, which is an exact duplicate of the printed version.

The CD-ROM also includes data files in SAS Codes and Raw Data for ClearRead CT.zip and an example simulated nodules in DICOM format. This data is not included in printed form.

Confidentiality
We request that this 510(k), including commercial information and Riverain Technologies’ intent to market the device described in this notification, be maintained by FDA in confidence pursuant to 21 CFR §807.95 for the maximum period allowed by 21 CFR §807.95(b) and (c), and including the maximum post-determination period specified in 21 CFR §807.95(e).

Please notify me directly of any request for release of information pertaining to this 510(k) prior to public disclosure of such information.

Respectfully Submitted,

Riverain Technologies
By: Jennifer Butsch
Director of Regulatory Affairs and Quality Assurance
TRADITIONAL [510(K)] PREMARKET NOTIFICATION

CLEARREAD CT™

Submitter:

Jennifer Butsch
Riverain Technologies, LLC.
3020 South Tech Blvd.
Miamisburg, OH 45342-4860
800.990.3387
937.425.6811
jbutsch@riveraintech.com
## CDRH PREMARKET REVIEW SUBMISSION COVER SHEET

### Date of Submission

<table>
<thead>
<tr>
<th>User Fee Payment ID Number</th>
<th>FDA Submission Document Number (if known)</th>
</tr>
</thead>
</table>

### SECTION A

<table>
<thead>
<tr>
<th>TYPE OF SUBMISSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMA</td>
</tr>
<tr>
<td>- Original Submission</td>
</tr>
<tr>
<td>- Premarket Report</td>
</tr>
<tr>
<td>- Modular Submission</td>
</tr>
<tr>
<td>- Amendment</td>
</tr>
<tr>
<td>- Report</td>
</tr>
<tr>
<td>- Report Amendment</td>
</tr>
<tr>
<td>- Licensing Agreement</td>
</tr>
<tr>
<td>PMA &amp; HDE Supplement</td>
</tr>
<tr>
<td>- Regular (180 day)</td>
</tr>
<tr>
<td>- Special</td>
</tr>
<tr>
<td>- Panel Track (PMA Only)</td>
</tr>
<tr>
<td>- 30-day Supplement</td>
</tr>
<tr>
<td>- 30-day Notice</td>
</tr>
<tr>
<td>- 135-day Supplement</td>
</tr>
<tr>
<td>- Real-time Review</td>
</tr>
<tr>
<td>- Amendment to PMA &amp; HDE Supplement</td>
</tr>
<tr>
<td>- Other</td>
</tr>
<tr>
<td>PDP</td>
</tr>
<tr>
<td>- Original PDP</td>
</tr>
<tr>
<td>- Notice of Completion</td>
</tr>
<tr>
<td>- Amendment to PDP</td>
</tr>
<tr>
<td>510(k)</td>
</tr>
<tr>
<td>- Original Submission:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

### TYPE OF SUBMISSION

<table>
<thead>
<tr>
<th>IDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Original Submission</td>
</tr>
<tr>
<td>- Amendment</td>
</tr>
<tr>
<td>- Supplement</td>
</tr>
<tr>
<td>Humanitarian Device Exemption (HDE)</td>
</tr>
<tr>
<td>- Original Submission</td>
</tr>
<tr>
<td>- Amendment</td>
</tr>
<tr>
<td>- Supplement</td>
</tr>
<tr>
<td>- Report</td>
</tr>
<tr>
<td>- Report Amendment</td>
</tr>
</tbody>
</table>

### Class II Exemption Petition

<table>
<thead>
<tr>
<th>Evaluation of Automatic Class III Designation (De Novo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Original Submission</td>
</tr>
<tr>
<td>- Additional Information</td>
</tr>
</tbody>
</table>

### Evaluation of Automatic Class III Designation (De Novo)

### Other Submission

<table>
<thead>
<tr>
<th>Other Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Original Submission</td>
</tr>
<tr>
<td>- Additional Information</td>
</tr>
</tbody>
</table>

### Request for Feedback

<table>
<thead>
<tr>
<th>Request for Feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pre-Submission</td>
</tr>
<tr>
<td>- Informational Meeting</td>
</tr>
<tr>
<td>- Submission Issue Meeting</td>
</tr>
<tr>
<td>- Day 100 Meeting</td>
</tr>
<tr>
<td>- Agreement Meeting</td>
</tr>
<tr>
<td>- Determination Meeting</td>
</tr>
<tr>
<td>- Study Risk Determination</td>
</tr>
<tr>
<td>- Other (specify):</td>
</tr>
</tbody>
</table>

### Have you used or cited Standards in your submission?  
- Yes  
- No  

### SECTION B

<table>
<thead>
<tr>
<th>SUBMITTER, APPLICANT OR SPONSOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company / Institution Name</td>
</tr>
<tr>
<td>Riverain Technologies, LLC</td>
</tr>
<tr>
<td>Division Name (if applicable)</td>
</tr>
<tr>
<td>Establishment Registration Number (if known)</td>
</tr>
<tr>
<td>Phone Number (including area code)</td>
</tr>
<tr>
<td>937-425-6811</td>
</tr>
<tr>
<td>Street Address</td>
</tr>
<tr>
<td>3020 South Tech Blvd.</td>
</tr>
<tr>
<td>FAX Number (including area code)</td>
</tr>
<tr>
<td>937-425-6493</td>
</tr>
<tr>
<td>City</td>
</tr>
<tr>
<td>Miamisburg</td>
</tr>
<tr>
<td>State / Province</td>
</tr>
<tr>
<td>OH</td>
</tr>
<tr>
<td>ZIP/Postal Code</td>
</tr>
<tr>
<td>45324</td>
</tr>
<tr>
<td>Country</td>
</tr>
<tr>
<td>US</td>
</tr>
<tr>
<td>Contact Name</td>
</tr>
<tr>
<td>Jennifer Butsch</td>
</tr>
<tr>
<td>Contact Title</td>
</tr>
<tr>
<td>Director of Regulatory Affairs &amp; Quality Assurance</td>
</tr>
<tr>
<td>Contact E-mail Address</td>
</tr>
<tr>
<td><a href="mailto:jbutsch@riveraintech.com">jbutsch@riveraintech.com</a></td>
</tr>
</tbody>
</table>

### SECTION C

<table>
<thead>
<tr>
<th>APPLICATION CORRESPONDENT (e.g., consultant, if different from above)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company / Institution Name</td>
</tr>
<tr>
<td>Division Name (if applicable)</td>
</tr>
<tr>
<td>Phone Number (including area code)</td>
</tr>
<tr>
<td>Street Address</td>
</tr>
<tr>
<td>FAX Number (including area code)</td>
</tr>
<tr>
<td>City</td>
</tr>
<tr>
<td>State / Province</td>
</tr>
<tr>
<td>ZIP Code</td>
</tr>
<tr>
<td>Country</td>
</tr>
<tr>
<td>Contact Name</td>
</tr>
<tr>
<td>Contact Title</td>
</tr>
<tr>
<td>Contact E-mail Address</td>
</tr>
</tbody>
</table>

### FORM FDA 3514 (1/13)

**Questions?** Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### SECTION D1
**REASON FOR APPLICATION - PMA, PDP, OR HDE**

- **New Device**
- **Withdrawal**
- **Additional or Expanded Indications**
- **Request for Extension**
- **Post-approval Study Protocol**
- **Request for Applicant Hold**
- **Request for Removal of Applicant Hold**
- **Request to Remove or Add Manufacturing Site**

- **Process change:**
  - Manufacturing
  - Packaging
  - Sterilization
  - Other (specify below)

- **Response to FDA correspondence:**

- **Other Reason (specify):**

### SECTION D2
**REASON FOR APPLICATION - IDE**

- **New Device**
- **New Indication**
- **Addition of Institution**
- **Expansion / Extension of Study**
- **IRB Certification**
- **Termination of Study**
- **Withdrawal of Application**
- **Unanticipated Adverse Effect**
- **Notification of Emergency Use**
- **Compassionate Use Request**
- **Treatment IDE**
- **Continued Access**

- **Change in:**
  - Correspondent / Applicant
  - Design / Device
  - Informed Consent
  - Manufacturer
  - Manufacturing Process
  - Protocol - Feasibility
  - Protocol - Other
  - Sponsor

- **Report submission:**
  - Current Investigator
  - Annual Progress Report
  - Site Waiver Report
  - Final

- **Other Reason (specify):**

### SECTION D3
**REASON FOR SUBMISSION - 510(k)**

- **New Device**
- **Additional or Expanded Indications**
- **Change in Technology**

- **Other Reason (specify):**

---

**Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### SECTION E  ADDITIONAL INFORMATION ON 510(K) SUBMISSIONS

<table>
<thead>
<tr>
<th>Device Code</th>
<th>Trade or Proprietary or Model Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>K143196</td>
<td>syngo.CT Lung CAD</td>
<td>Siemens AG Medical Solutions</td>
</tr>
<tr>
<td>K093621</td>
<td>syngo.PET&amp;CT Oncology</td>
<td>Siemens AG Medical Solutions</td>
</tr>
<tr>
<td>K092363</td>
<td>SoftView (now trade named ClearRead Bone Suppression)</td>
<td>Riverain Technologies, LLC.</td>
</tr>
</tbody>
</table>

### SECTION F  PRODUCT INFORMATION - APPLICATION TO ALL APPLICATIONS

- **Common or usual name or classification name**: Lung computed tomography system, computer-aided detection

<table>
<thead>
<tr>
<th>Trade or Proprietary or Model Name for This Device</th>
<th>Model Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClearRead CT</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

### SECTION G  PRODUCT CLASSIFICATION - APPLICATION TO ALL APPLICATIONS

- **Product Code**: OEB/LLZ
- **C.F.R. Section (if applicable)**: 892.2050

**Classification Panel**
- **Radiology**

**Indications (from labeling)**

ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.
**SECTION H**

**MANUFACTURING / PACKAGING / STERILIZATION SITES RELATING TO A SUBMISSION**

<table>
<thead>
<tr>
<th>Original</th>
<th>Add</th>
<th>Delete</th>
</tr>
</thead>
</table>

**Facility Establishment Identifier (FEI) Number**

41-2141323

**Company / Institution Name**

Riversain Technologies, LLC.

**Establishment Registration Number**

(b)(4)

**Division Name (if applicable)**

**Phone Number (including area code)**

937-425-6811

**Street Address**

3020 South Tech Blvd

**FAX Number (including area code)**

937-425-6493

**City**

Miamisburg

**State / Province**

OH

**ZIP Code**

45342

**Country**

US

**Contact Name**

Takasi Sibuya

**Contact Title**

Director of Manufacturing

**Contact E-mail Address**

tsibuya@riversaintech.com

**Facility Establishment Identifier (FEI) Number**

**Company / Institution Name**

**Establishment Registration Number**

**Division Name (if applicable)**

**Phone Number (including area code)**

**Street Address**

**FAX Number (including area code)**

**City**

**State / Province**

**ZIP Code**

**Country**

**Contact Name**

**Contact Title**

**Contact E-mail Address**

---

**Questions?** Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

---

**FORM FDA 3514 (1/13)**

---

Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018
### UTILIZATION OF STANDARDS

**Note:** Complete this section if your application or submission cites standards or includes a *Declaration of Conformity to a Recognized Standard* statement.

<table>
<thead>
<tr>
<th>Standards No.</th>
<th>Standards Organization</th>
<th>Standards Title</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.1-3.20</td>
<td>NEMA</td>
<td>Digital Imaging and Communications in Medicine (DICOM) Set</td>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>14971</td>
<td>ISO</td>
<td>Medical Devices – Application of Risk Assessment to Medical Devices</td>
<td>2007</td>
<td>01-Mar-2007</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Please include any additional standards to be cited on a separate page.**

This section applies only to requirements of the Paperwork Reduction Act of 1995.

*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF ADDRESS BELOW.*

The burden time for this collection of information is estimated to average 0.5 hour per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

- Department of Health and Human Services
- Food and Drug Administration
- Office of Chief Information Officer
- Paperwork Reduction Act (PRA) Staff
- 1350 Piccard Drive, Room 400
- Rockville, MD 20850

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

<table>
<thead>
<tr>
<th>SPONSOR / APPLICANT / SUBMITTER INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Name of Sponsor/Applicant/Submitter</td>
</tr>
<tr>
<td>Riverain Technologies LLC</td>
</tr>
<tr>
<td>2. Date of the Application/Submission Which This Certification Accompanies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address 1 (Street address, P.O. box, company name c/o)</td>
</tr>
<tr>
<td>3020 South Tech Blvd.</td>
</tr>
<tr>
<td>Address 2 (Apartment, suite, unit, building, floor, etc.)</td>
</tr>
<tr>
<td>City</td>
</tr>
<tr>
<td>Miamisburg</td>
</tr>
<tr>
<td>State/Province/Region</td>
</tr>
<tr>
<td>OH</td>
</tr>
<tr>
<td>Country</td>
</tr>
<tr>
<td>US</td>
</tr>
<tr>
<td>ZIP or Postal Code</td>
</tr>
<tr>
<td>45342</td>
</tr>
</tbody>
</table>

| Telephone and Fax Numbers (Include country code if applicable and area code) |
| (Tel): 937-425-6811 |
| (Fax): 937-425-6493 |

PRODUCT INFORMATION

5. For Drugs/Biologics: Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s).
   For Devices: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)

   Lung computed tomography system, computer-aided detection, Class II, ClearRead CT 1.1

APPLICATION / SUBMISSION INFORMATION

6. Type of Application/Submission Which This Certification Accompanies

   - [ ] IND  - [ ] NDA  - [ ] ANDA  - [ ] BLA  - [ ] PMA  - [ ] HDE  - [X] 510(k)  - [ ] PDP  - [ ] Other

7. Include IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/ Other Number (If number previously assigned)
   If BLA was selected in item 6, provide Supplement Number

8. Serial Number Assigned to Application/Submission Which This Certification Accompanies

CERTIFICATION STATEMENT / INFORMATION

9. Check only one of the following boxes (See instructions for additional information and explanation)
   - [ ] A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply because the application/submission which this certification accompanies does not reference any clinical trial.
   - [ ] B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act do not apply to any clinical trial referenced in the application/submission which this certification accompanies.
   - [X] C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.

Certification Statement / Information section continued on page 2

FORM FDA 3674 (2/15)
### CERTIFICATION STATEMENT / INFORMATION (Continued)

10. If you checked box C, in number 9, provide the National Clinical Trial (NCT) Number(s) for any "applicable clinical trial(s)," under 42 U.S.C. § 282(j)(1)(a)(i), section 402(j)(1)(a)(i) of the Public Health Service Act, referenced in the application/submission which this Certification accompanies. (Add continuation page as necessary.)

NCT Number(s): NCT02440139

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.

**Warning:** A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. Name and Title of the Person who Signs Number 15

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennifer Butsch</td>
<td>Director, Regulatory Affairs and Quality Assurance</td>
</tr>
</tbody>
</table>

12. Address

<table>
<thead>
<tr>
<th>Address 1 (Street address, P.O. box, company name c/o)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3630 South Tech Blvd.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Address 2 (Apartment, suite, unit, building, floor, etc.)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>City</th>
<th>State/Province/Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miamisburg</td>
<td>OH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>ZIP or Postal Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>45342</td>
</tr>
</tbody>
</table>

13. Telephone and Fax Numbers

(Include country code if applicable and area code)

<table>
<thead>
<tr>
<th>(Tel):</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Fax):</td>
</tr>
</tbody>
</table>

14. Date of Certification

15. Signature of Sponsor/Applicant/Submitter or an Authorized Representative (Sign)

---

This section applies only to requirements of the Paperwork Reduction Act of 1995.

***DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.***

The burden time for this collection of information is estimated to average 15 minutes and 45 minutes (depending on the type of application/submission) per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to:

- Department of Health and Human Services
- Food and Drug Administration
- Office of Chief Information Officer
- Paperwork Reduction Act (PRA) Staff
- PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

---

FORM FDA 3674 (2/15)

Page 2 of 2

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
# TABLE OF CONTENTS

1.0 TRADITIONAL 510(K) ACCEPTANCE CHECKLIST .............................................. 3  
2.0 INDICATIONS FOR USE STATEMENT (FORM 3881) ..................................... 4  
3.0 510(K) SUMMARY ............................................................................................ 5  
4.0 TRUTHFUL AND ACCURATE STATEMENT ................................................... 8  
5.0 CLASS III SUMMARY AND CERTIFICATION .............................................. 8  
6.0 FINANCIAL CERTIFICATION OR DISCLOSURE STATEMENT (3454 OR 3455) ................................................................................................................ 9  
7.0 DECLARATION OF CONFORMITY AND SUMMARY REPORTS ............. 10  
7.1 FDA Recognized Consensus Standards ........................................................ 10  
8.0 DEVICE DESCRIPTION .................................................................................. 11  
8.1 Device Name ............................................................................................... 11  
8.2 Device Classification .................................................................................. 11  
8.3 Establishment Registration: ...................................................................... 11  
8.4 Performance Standards ............................................................................. 11  
8.5 Predicate Devices ...................................................................................... 12  
8.6 Description of Device .............................................................................. 12  
9.0 SUBSTANTIAL EQUIVALENCE .................................................................. 14  
9.1 Predicate Device Description ................................................................... 14  
9.2 Device Comparison ................................................................................... 14  
10.0 PROPOSED LABELING .............................................................................. 17  
11.0 STERILIZATION INFORMATION AND SHELF LIFE ............................... 17  
12.0 BIOCOMPATIBILITY .................................................................................. 17  
13.0 SOFTWARE ................................................................................................... 18  
13.1 Level of Concern ..................................................................................... 18  
13.2 Software Description .............................................................................. 19

CONFIDENTIAL
13.3 ClearRead Image Processing Engine Design ........................................ 20
13.4 Device Hazard Analysis ........................................................................ 53
13.5 Software Requirements Specification ................................................... 53
13.6 Architecture Design Chart ................................................................. 53
13.7 Software Design Specification (SDS) ................................................... 54
13.8 Traceability Analysis ............................................................................ 54
13.9 Software Development Environment Description ............................... 54
13.10 Verification and Validation Documentation ........................................ 54
13.11 Revision History ................................................................................ 54
13.12 Unresolved Anomalies (Bugs or Defects) .......................................... 54

14.0 ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY
............................................................................................................................... 55

15.0 PERFORMANCE TESTING – ANIMAL .................................................... 55

16.0 PERFORMANCE TESTING – CLINICAL .............................................. 55

16.1 Summary of Studies ............................................................................ 55
16.2 Study Design ....................................................................................... 57
16.3 Data Characteristics ............................................................................ 58
16.4 Data Analysis and Result .................................................................... 60
16.5 Conclusions Drawn from the Reader Study ........................................ 71

APPENDICES
APPENDIX A PROPOSED DRAFT LABELING
APPENDIX B DESIGN CONTROL DOCUMENTS
APPENDIX C CLEARREAD CT ROI FEATURE LIST
APPENDIX D CLEARREAD CT READER STUDY PROTOCOL
AND REPORT
APPENDIX E PREDICATE DEVICE LABELING
APPENDIX F REFERENCES
APPENDIX G TRACEABILITY OF PREVIOUS FDA
COMMUNICATIONS

CONFIDENTIAL
1.0 TRADITIONAL 510(K) ACCEPTANCE CHECKLIST
Acceptance Checklist
for Traditional 510(k)s

(should be completed within 15 days of DCC receipt)

The following information is not intended to serve as a comprehensive review.

510(k) Number: ____________ Date Received by DCC: ________

Lead Reviewer Name: ______________ Branch: ______ Division: _____ Office: _______

Note: If an element is left blank on the checklist, it does not mean the checklist is incomplete; it means the reviewer did not assess the element during RTA and that element will be assessed during substantive review.

<table>
<thead>
<tr>
<th>Preliminary Questions</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the product a device (per section 201(h) of the FD&amp;C Act) or a combination product (per 21 CFR 3.2(e)) with a device constituent part subject to review in a 510(k)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If it appears not to be a device (per section 201(h) of the FD&amp;C Act) or such a combination product, or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Office Jurisdiction Liaison to determine the appropriate action, and inform division management. Provide a summary of the Jurisdictional Officer's/Liaison's determination. If the product does not appear to be a device or such a combination product, mark “No.”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:

2. Is the application with the appropriate Center?

If the product is a device or a combination product with a device constituent part, is it subject to review by the Center in which the submission was received? If you believe the application is not with the appropriate Center or you are unsure, consult with the CDRH Jurisdictional Officer or CBER Office Jurisdiction Liaison to determine the appropriate action and inform your division management. Provide a summary of the Jurisdictional Officer’s/Liaison’s determination. If application should not be reviewed by your Center mark “No.”

Comments:

3. If a Request for Designation (RFD) was submitted for the device or combination product with a device constituent part and assigned to your center, identify the RFD # and confirm the following:

Acceptance Checklist for Traditional 510(k)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Contains Nonbinding Recommendations

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Is the device or combination product the same (e.g., design, formulation) as that presented in the RFD submission?</td>
<td></td>
</tr>
<tr>
<td>b) Are the indications for use for the device or combination product identified in the 510(k) the same as those identified in the RFD submission?</td>
<td></td>
</tr>
</tbody>
</table>

If you believe the product or the indications presented in the 510(k) have changed from the RFD, or you are unsure, consult with the CDRH Jurisdictional Officer or appropriate CBER Jurisdiction Liaison to determine the appropriate action and inform your division management. *Provide summary of Jurisdictional Officer’s/Liaison’s determination.*

If the answer to either question above is no, mark “No.” If there was no RFD, skip this question.

**Comments:**

4. Is this device type eligible for a 510(k) submission?

If a 510(k) does not appear to be appropriate (e.g., Class III type and PMA required, or Class I or II type and 510(k)-exempt), you should consult with the CDRH 510(k) Program Director or appropriate CBER staff during the acceptance review. If 510(k) is not the appropriate regulatory submission, mark “No.”

**Comments:**

5. Is there a pending PMA for the same device with the same indications for use?

If yes, consult division management and the CDRH 510(k) Program Director or appropriate CBER staff to determine the appropriate action.

**Comments:**

6. If clinical studies have been submitted, is the submitter the subject of an Application Integrity Policy (AIP)?

If yes, consult with the CDRH Office of Compliance/Division of Bioresearch Monitoring (OC/DBM - BIMO) or CBER Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Bioresearch Monitoring Branch (OCBQ/DIS/BMB) to determine the appropriate action. Check on web at [http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm).  

If the answer to 1 or 2 appears to be “No,” then stop review of the 510(k) and issue the “Original Jurisdictional Product” letter. If the answer to 3a or 3b appears to be “No,” then stop the review and contact the CDRH Jurisdictional Officer or CBER Office of Jurisdiction Liaison. If the answer to 4 is “No”, the lead reviewer should consult division management and other Center resources to determine the appropriate action. If the answer to 5 is “Yes,” then stop review of the 510(k), contact the CDRH 510(k) Staff and PMA Staff, or appropriate CBER staff.

Acceptance Checklist for Traditional 510(k)
**Contains Nonbinding Recommendations**

If the answer to 6 is “Yes,” then contact CDRH/OC/DBM – BIMO or CBER/OCBQ/DIS/BMB, provide a summary of the discussion with the BIMO Staff, and indicate BIMO’s recommendation/action.

### Organizational Elements

*Failure to include these items alone generally should not result in an RTA designation*

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Submission contains Table of Contents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Each section is labeled (e.g., headings or tabs designating Device Description section, Labeling section, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. All pages of the submission are numbered</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
  *All pages should be numbered in such a manner that information can be referenced by page number. This may be done either by consecutively numbering the entire submission, or numbering the pages within a section (e.g., 12-1, 12-2...).* | | |
| d. Type of 510(k) is identified – traditional, abbreviated, or special  
  *If type of 510(k) is not designated, review as a traditional* | | |

**Comments:**

### Elements of a Complete Submission (RTA Items)  
**21 CFR 807.87 unless otherwise indicated**

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

- Any “No” answer will result in a “Refuse to Accept” decision.  
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Administrative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. All content used to support the submission is written in English (including translations of test reports, literature articles, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comments:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Submission identifies the following (such as in CDRH Premarket Review Submission Cover Sheet [Form 3514] or 510(k) cover letter):</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
  a. Device trade name or proprietary name | | | |
  b. Device common name | | | |

Acceptance Checklist for Traditional 510(k)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Elements of a Complete Submission (RTA Items)
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed.

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

<table>
<thead>
<tr>
<th>c. Device class and panel or Classification regulation or Statement that device has not been classified with rationale for that conclusion</th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

**Comments:**

3. Submission contains Indications for Use Statement with Rx and/or OTC designated (see also 21 CFR 801.109)

*Submitter should use format appropriate for the reviewing Center/Office (CDRH/ODE, CDRH/OIVD, CBER/OBRR, CBER/OCTGT). If not provided in correct format, request the correct format during substantive review.*

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

**Comments:**

4. Submission contains 510(k) Summary or 510(k) Statement

*Either a) or b) must be answered “Yes” to be considered complete. Identify any missing element(s) in Comments.*

- a. Summary contains all elements per 21 CFR 807.92
  *See also 510(k) Summary Checklist*

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

- b. Statement contains all elements per 21 CFR 807.93

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

**Comments:**

5. Submission contains Truthful and Accuracy Statement per 21 CFR 807.87(k)

*See recommended format. Select “Yes” if statement is present and includes the text in the recommended format, and is signed by a responsible person of the firm (not consultant).*

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

**Comments:**

Acceptance Checklist for Traditional 510(k)
### Elements of a Complete Submission (RTA Items)

(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Submission contains Class III Summary and Certification</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

*See recommended content. Form should be signed by a responsible person of the firm, not a consultant. Select “N/A” only if submission is not a Class III 510(k).*

Comments:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Submission contains clinical data</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Select “N/A” if the submission does not contain clinical data. If “N/A” is selected, parts a and b below are omitted from the checklist.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Submission includes completed Financial Certification (FDA Form 3454) or Disclosure (FDA Form 3455) information for each covered clinical study included in the submission. Select “N/A” if the submitted clinical data is not a “covered clinical study” as defined in the Guidance for Industry-Financial Disclosures by Clinical Investigators</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Submission includes completed Certification of Compliance with requirements of ClinicalTrials.gov Data Bank (FDA Form 3674) (42 U.S.C. 282(j)(5)(B)) for each applicable device clinical trial included in the submission. Select “N/A” if the submitted clinical data is not an “applicable device clinical trial” as defined in Title VIII of FDAAA, Sec. 801(i)</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Comments:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>8. If submission references use of a national or international standard as part of demonstration of substantial equivalence, submission contains complete Standards Data Report for 510(k)s (FDA Form 3654) There should be a completed form for each referenced national or international standard. Select “N/A” only if submission does not reference any standards.</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Acceptance Checklist for Traditional 510(k)
**Elements of a Complete Submission (RTA Items)**

(21 CFR 807.87 unless otherwise indicated)

Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

Comments:

9. The submission identifies prior submissions for the same device for which FDA provided feedback related to the data or information needed to support substantial equivalence (e.g., submission numbers for Pre-Submission, IDE, prior not substantially equivalent (NSE) determination, prior 510(k) that was deleted or withdrawn) or states that there were no prior submissions for the subject device.

   *This information may be included in the Cover Letter (i.e., as a statement that there were no prior submissions for the device or a listing of the number(s) of the prior submissions). Alternatively, a list of submission numbers may be found in Section F (prior related submissions section) of the CDRH Cover Sheet (Form 3514) to address this criterion. Please be advised that if this section of the form is left blank, it should not be considered a statement that there were no prior submissions.*

   □ □

a. If there were prior submissions, the submitter has identified where in the current submission any issues related to a determination of substantial equivalence outlined in prior communications are addressed.

   *To address this criterion, the submission may include a separate section with the prior submission number(s), a copy of the FDA feedback (e.g., letter, meeting minutes), and a statement of how or where in the submission this prior feedback was addressed. Note that the adequacy of how the feedback was addressed should be assessed during the substantive review. For additional information regarding the Pre-Submission process, please refer to the Draft Guidance “Medical Devices: The Pre-Submission Program and Meetings with FDA Staff.” [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm310375.htm). Once finalized, this guidance will represent the*

Acceptance Checklist for Traditional 510(k)
Contains Nonbinding Recommendations

Elements of a Complete Submission (RTA Items)
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

Agency’s current thinking on this topic.
Select “N/A” if the submitter states there were no prior submissions in criterion above.

Comments:

B. Device Description

10. a. If there are requirements regarding the device description, such as special controls, in a device-specific regulation that are applicable to the device, the submission includes device description information to establish that the submitter has followed the device-specific requirement.
Select “N/A” if there are no applicable requirements in a device-specific regulation. Select “No” if the submission does not include a rationale for any omitted information. Note that the adequacy of how such requirements have been addressed should be assessed during the substantive review.

Comments:

Acceptance Checklist for Traditional 510(k)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Elements of a Complete Submission (RTA Items)
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>Any “No” answer will result in a “Refuse to Accept” decision. Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td>A description of the principle of operation and mechanism of action for achieving the intended effect.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td>A description of proposed conditions of use, such as surgical technique for implants; anatomical location of use; user interface; how the device interacts with other devices; and/or how the device interacts with the patient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.</td>
<td>A list and description of each device for which clearance is requested. Select “N/A” if there is only one device or model. “Device” may refer to models, part numbers, or various sizes, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Submission contains representative engineering drawing(s), schematics, illustrations and/or figures of the device that are clear, legible, labeled, and include dimensions.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In lieu of drawings, schematics, etc. of each device to be marketed, “representative” drawings, etc. may be provided, where “representative” is intended to mean that the drawings, etc. provided capture the differences in design, size, and other important characteristics of the various models, sizes, or versions of the device(s) to be marketed.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Select “N/A” if the submitter provided a rationale for why the submission does not contain engineering drawings, schematics, etc. (e.g., device is a reagent and figures are not pertinent to describe the device).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Acceptance Checklist for Traditional 510(k)
**Elements of a Complete Submission (RTA Items)**
*(21 CFR 807.87 unless otherwise indicated)*

Submission should be designated RTA if not addressed

<table>
<thead>
<tr>
<th>Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.</th>
</tr>
</thead>
</table>
| • Any “No” answer will result in a “Refuse to Accept” decision.  
  • Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission. |

<table>
<thead>
<tr>
<th>13. If device is intended to be marketed with multiple components, accessories, and/or as part of a system, Select “N/A” if the device is not intended to be marketed with multiple components, accessories, and/or as part of a system.</th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Submission includes a list of all components and accessories to be marketed with the subject device.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| b. Submission includes a description (as detailed in item 11.a. and b. and 12 above) of each component or accessory.  
  *Select “N/A” if the component(s)/accessory(ies) has been previously cleared, or is exempt, and the proposed indications for use are consistent with the cleared indications.* | | | |
| c. A 510(k) number is provided for each component or accessory that received a prior 510(k) clearance.  
  *Select “N/A” if the submission states that the component(s)/accessory(ies) does not have a prior 510(k) clearance or the component(s)/accessory(ies) is 510(k) exempt.* | | | |

Comments:

**C. Substantial Equivalence Discussion**

<table>
<thead>
<tr>
<th>14. Submitter has identified a predicate(s) device</th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>
| a. Predicate’s 510(k) number, trade name, and model number (if applicable) provided.  
  For predicates that are preamendments devices, information is provided to document preamendments status.  
  *Information regarding documenting preamendment status is available online ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance))* | | | |

Acceptance Checklist for Traditional 510(k)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Elements of a Complete Submission (RTA Items)

**Contains Nonbinding Recommendations**

**21 CFR 807.87 unless otherwise indicated**

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**

15. Submission includes a comparison of the following for the predicate(s) and subject device

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**

16. Submission includes an analysis of why any differences between the subject device and predicate(s) do not render the device NSE (e.g., does not constitute a new intended use; and any differences in technological characteristics are accompanied by information that demonstrates the device is as safe and effective as the predicate and do not raise different questions of safety and effectiveness than the predicate), affect safety or effectiveness, or raise different questions of safety and effectiveness (see section 513(i)(1)(A) of the FD&C Act and 21 CFR 807.87(f)

**If there is no difference between the subject and predicate(s) with respect to indications for use or technology, this should be explicitly stated, in which case “N/A” should be selected. Select “No” only if the submission does not include an analysis of differences as described above or a statement that there are no differences. Note that the adequacy of the analysis should be assessed during the substantive review; only the presence of such an analysis is required for acceptance. In addition, note that due to potential differences in**

### Acceptance Checklist for Traditional 510(k)

---

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Elements of a Complete Submission (RTA Items)

(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

<table>
<thead>
<tr>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

*manufacturing that may not be known to the submitter, the fact that no differences are identified does not necessarily mean that no performance testing is needed.*

#### Comments:

### D. Proposed Labeling (see also 21 CFR part 801)

*If in vitro diagnostic (IVD) device, criteria 17, 18, and 19 may be omitted. These criteria will be omitted from the checklist if “N/A” is selected. IVD labeling is addressed in section 21 below.*

17. Submission includes proposed package labels and labeling (e.g., instructions for use, package insert, operator’s manual) that include a description of the device, its intended use, and the directions for use.

| □ | □ | □ |

a. Indications for use are stated in labeling and are identical to Indications for Use form and 510(k) Summary (if 510(k) Summary provided).

| □ | □ | □ |

b. Submission includes directions for use that
   - include statements of all conditions, purposes or uses for which the device is intended (e.g., hazards, warnings, precautions, contraindications) (21 CFR 801.5) AND
   - Includes directions for layperson (see 21 CFR 801.5) OR submission states that device qualifies for exemption per 21 CFR 801 Subpart D

| □ | □ | □ |

Comments:

### 18. If indicated for prescription use, labeling includes the prescription use statement (see 21 CFR 801.109(b)(1)) or “Rx only” symbol [See also Alternative to Certain Prescription Device Labeling Requirements]

Select “N/A” if not indicated for prescription use.

| □ | □ | □ |
# Elements of a Complete Submission (RTA Items)

(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

### Comments:

#### 19. General labeling provisions

- **a.** Labeling includes name and place of business of the manufacturer, packer, or distributor (21 CFR 801.1)
  - [ ] Yes
  - [ ] N/A
  - [ ] No

- **b.** Labeling includes device common or usual name (21 CFR 801.61)
  - Select “N/A” if device is for prescription use only.
  - [ ] Yes
  - [ ] N/A
  - [ ] No

### Comments:

#### 20. If there are requirements regarding labeling, such as special controls, in a device-specific regulation that are applicable to the device, the submission includes labeling to establish that the submitter has followed the device-specific requirement.

- **a.** Select “N/A” if there are no applicable requirements in a device-specific regulation. Select “No” if the submission does not include a rationale for any omitted information. Note that the adequacy of how such requirements have been addressed should be assessed during the substantive review.
  - [ ] Yes
  - [ ] N/A
  - [ ] No

- **b.** If there is a device-specific guidance, other than a special controls guidance document, applicable to the device, the submission includes labeling to establish that the submitter has addressed the recommendations or otherwise has met the applicable statutory or regulatory criteria through an alternative approach.
  - Select “N/A” if there is no applicable device-specific guidance.
  - Select “No” if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how recommendations in a device-specific guidance have been addressed should be assessed during the substantive review.
  - [ ] Yes
  - [ ] N/A
  - [ ] No

**Acceptance Checklist for Traditional 510(k)**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Elements of a Complete Submission (RTA Items)

**21 CFR 807.87 unless otherwise indicated**

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If there is a special controls document applicable to the device, the submission includes labeling to establish that the submitter has complied with the particular mitigation measures set forth in the special controls document or uses alternative mitigation measures but provides a rationale to demonstrate that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness. Select “N/A” if there is no applicable special controls document. Select “No” if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how mitigation measures in a special controls document have been addressed should be assessed during the substantive review.</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

### Comments:

21. If the device is an in vitro diagnostic device, provided labeling includes all applicable information required per 21 CFR 809.10. Select “N/A” if not an in vitro diagnostic device. | ☐ | ☐ | ☐ |

#### E. Sterilization

*If in vitro diagnostic (IVD) device and sterilization is not applicable, select “N/A.” The criteria in this section will be omitted from the checklist if “N/A” is selected.*

<table>
<thead>
<tr>
<th></th>
<th>☐</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission states that the device and/or accessories are: (one of the below must be checked)</td>
<td>☐</td>
</tr>
<tr>
<td>☐ provided sterile</td>
<td>☐ provided non-sterile but sterilized by the end user</td>
</tr>
</tbody>
</table>

This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination. *If “non-sterile when used” is selected, the sterility-related criteria below are omitted from*

---

**Acceptance Checklist for Traditional 510(k)**
**Elements of a Complete Submission (RTA Items)**

*(21 CFR 807.87 unless otherwise indicated)*

Submission should be designated RTA if not addressed

<table>
<thead>
<tr>
<th>Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any “No” answer will result in a “Refuse to Accept” decision.</td>
</tr>
<tr>
<td>Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.</td>
</tr>
</tbody>
</table>

*the checklist.*

If information regarding the sterility status of the device is not provided, select “No.”

**Comments:**

- **22. Assessment of the need for sterilization information**
  - a. Identification of device, and/or accessories, and/or components that are provided sterile.
  - b. Identification of device, and/or accessories, and/or components that are end user sterilized.
  - c. Identification of device, and/or accessories, and/or components that are reusable and cleaning/disinfection instructions are provided.

**Comments:**

- **23. If the device, and/or accessory, and/or a component is provided sterile:**
  Select “N/A” if no part of the device, accessories, or components is provided sterile, otherwise complete a-e below.
  - a. Sterilization method is stated for each component (including parameters such as dry time for steam sterilization, radiation dose, etc.)
  - b. A description of method to validate the sterilization parameters (e.g., half-cycle method and full citation of FDA-recognized standard, including date) is provided for each proposed sterilization method. *Note, the sterilization validation report is not required.*
  - c. For devices sterilized using chemical sterilants such as ethylene oxide (EO) and hydrogen peroxide, submission states maximum

**Acceptance Checklist for Traditional 510(k)**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
## Elements of a Complete Submission (RTA Items)
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Any sterilant residual concentration exceeding the sterilant residual limit. Select “N/A” if not sterilized using chemical sterilants.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Submission includes description of packaging and packaging contents (e.g., if multiple devices are included within the same package, Tyvek packaging, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Sterility Assurance Level (SAL) stated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:

24. If the device, and/or accessory, and/or a component is end user sterilized:
* Select “N/A” if no part of the device, accessories, or components are end user sterilized, otherwise complete a-d below.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Sterilization method is stated for each component (including parameters such as dry time for steam sterilization, radiation dose, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. A description of method to validate the sterilization parameters (e.g., half-cycle method and full citation of FDA-recognized standard, including date) is provided for each proposed sterilization method. <em>Note, the sterilization validation is not required.</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Submission includes description of packaging and packaging contents (e.g., if multiple devices are included within the same package, Tyvek packaging, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Submission includes sterilization instructions for end user</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:

25. a. If there are requirements regarding sterility, such as special |     |     |    |

Acceptance Checklist for Traditional 510(k)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
**Elements of a Complete Submission (RTA Items)**

*21 CFR 807.87 unless otherwise indicated*

Submission should be designated RTA if not addressed

| Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed. |
|---|---|---|
| **-** Any “No” answer will result in a “Refuse to Accept” decision.  
  Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission. | Yes | N/A | No |
| controls, in a device-specific regulation that are applicable to the device, the submission includes sterility information to establish that the submitter has followed the device-specific requirement.  
*Select “N/A” if there are no applicable requirements in a device-specific regulation. Select “No” if the submission does not include a rationale for any omitted information.*  
*Note that the adequacy of how such requirements have been addressed should be assessed during the substantive review.* |  |  |  |
| b. If there is a device-specific guidance, other than a special controls guidance document, applicable to the device, the submission includes sterility information to establish that the submitter has addressed the recommendations or otherwise has met the applicable statutory or regulatory criteria through an alternative approach.  
*Select “N/A” if there is no applicable device-specific guidance. Select “No” if the submission does not include a rationale for any omitted information or any alternative approach as outlined above.*  
*Note that the adequacy of how recommendations in a device-specific guidance have been addressed should be assessed during the substantive review.* |  |  |  |
| c. If there is a special controls document applicable to the device, the submission includes sterility information to establish that the submitter has complied with the particular mitigation measures set forth in the special controls document or uses alternative mitigation measures but provides a rationale to demonstrate that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness.  
*Select “N/A” if there is no applicable special controls document. Select “No” if the submission does not include a rationale for any omitted information or any alternative approach as outlined above.*  
*Note that the adequacy of how mitigation measures in a* |  |  |  |

Acceptance Checklist for Traditional 510(k)

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Elements of a Complete Submission (RTA Items)
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

<table>
<thead>
<tr>
<th>Special controls document have been addressed should be assessed during the substantive review.</th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### F. Shelf Life

- **Proposed shelf life/expiration date stated**
  - Select “N/A” if the device is not provided sterile and the submitter states that storage conditions could not affect device safety or effectiveness.

  | Comments: | | | |
  | | | |

- **For sterile device, submission includes summary of methods used to establish that device sterility will remain substantially equivalent to that of the predicate through the proposed shelf life, or a rationale for why testing to establish shelf life is not applicable.**
  - Select “N/A” if the device is not provided sterile.

  | Comments: | | | |
  | | | |

- **Submission includes summary of methods used to establish that device performance is not adversely affected by aging and therefore device performance will remain substantially equivalent to that of the predicate, or includes a rationale for why the storage conditions are not expected to affect device safety or effectiveness.**

  | Comments: | | |
  | | | |

### G. Biocompatibility

*If in vitro diagnostic (IVD) device, select “N/A.” The criteria in this section will be omitted from the checklist if “N/A” is selected.*

- Submission states that there: *(one of the below must be checked)*
  - are

  | Comments: | |
  | | | |

Acceptance Checklist for Traditional 510(k)
**Elements of a Complete Submission (RTA Items)**
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

<table>
<thead>
<tr>
<th>Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td><strong>29.</strong> Submission includes list of patient-contacting device components and associated materials of construction, including identification of color additives, if present</td>
</tr>
<tr>
<td>Comments:</td>
</tr>
<tr>
<td><strong>30.</strong> Submission identifies contact classification (e.g., surface-contacting, less than 24 hour duration)</td>
</tr>
<tr>
<td>Comments:</td>
</tr>
<tr>
<td><strong>31.</strong> Biocompatibility assessment of patient-contacting components</td>
</tr>
<tr>
<td>Submission includes: Test protocol (including identification and description of test article), methods, pass/fail criteria, and results provided for each completed test, OR a statement that biocompatibility testing is not needed with a rationale (e.g., materials and manufacturing/processing are identical to the predicate).</td>
</tr>
<tr>
<td>Comments:</td>
</tr>
</tbody>
</table>

**H. Software**

Acceptance Checklist for Traditional 510(k)
### Elements of a Complete Submission (RTA Items)  
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

<table>
<thead>
<tr>
<th>Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any “No” answer will result in a “Refuse to Accept” decision. Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

Submission states that the device: *(one of the below must be checked)*

- [ ] does
- [ ] does not contain software/firmware.

This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.  
*If “does not” is selected, the software-related criterion is omitted from the checklist. If information regarding whether the device contains software is not provided, select “No.”*

Comments:

32. Submission includes a statement of software level of concern and rationale for the software level of concern

   Comments:

33. All applicable software documentation provided based on level of concern identified by the submitter, as described in [Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices](https://www.fda.gov), or the submission includes information to establish that the submitter has otherwise met the applicable statutory or regulatory criteria through an alternative approach (i.e., the submitter has identified an alternate approach with a rationale).

   Comments:

---

### I. EMC and Electrical Safety

Submission states that the device: *(one of the below must be checked)*

- [ ] does
- [ ] does not require EMC and Electrical Safety evaluation.

---

**Acceptance Checklist for Traditional 510(k)**
## Elements of a Complete Submission (RTA Items)

**21 CFR 807.87 unless otherwise indicated**

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any “No” answer will result in a “Refuse to Accept” decision.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.

*If “does not” is selected, the EMC-related and Electrical Safety-related criteria below are omitted from the checklist. If information regarding whether the device requires EMC and Electrical Safety evaluation is not provided, select “No.”*

**Comments:**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>34.</td>
<td>Submission includes evaluation of electrical safety (e.g., per IEC 60601-1, or equivalent FDA-recognized standard, and if applicable, the device-specific standard), OR submission includes electrical safety evaluation using methods or standards that are not FDA-recognized and submission includes information to establish that the submitter has otherwise met the applicable statutory or regulatory criteria through this alternative approach (i.e., the submitter has identified alternate methods or standards with a rationale).</td>
<td>□</td>
</tr>
</tbody>
</table>

**Comments:**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>35.</td>
<td>Submission includes evaluation of electromagnetic compatibility (e.g., per IEC 60601-1-2 or equivalent FDA-recognized standard and if applicable, the device-specific standard) OR submission includes electromagnetic compatibility evaluation using methods or standards that are not FDA-recognized and submission includes information to establish that the submitter has otherwise met the applicable statutory or regulatory criteria through this alternative approach (i.e., the submitter has identified alternate methods or standards with a rationale).</td>
<td>□</td>
</tr>
</tbody>
</table>

**Comments:**

**Acceptance Checklist for Traditional 510(k)**

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Elements of a Complete Submission (RTA Items)

*(21 CFR 807.87 unless otherwise indicated)*

Submission should be designated RTA if not addressed

<table>
<thead>
<tr>
<th>Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any “No” answer will result in a “Refuse to Accept” decision.</td>
</tr>
<tr>
<td>Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

### J. Performance Data – General

*If in vitro diagnostic (IVD) device, select “N/A.” The criteria in this section will be omitted from the checklist if “N/A” is selected. Performance data criteria relating to IVD devices will be addressed in Section K.*

#### Comments:

<table>
<thead>
<tr>
<th>36. Full test report is provided for each completed test. A full test report includes: objective of the test, description of the test methods and procedures, study endpoint(s), pre-defined pass/fail criteria, results summary, conclusions, and an explanation of how the data generated from the test supports a finding of substantial equivalence. Full test reports provided for all completed tests/evaluations (e.g., bench evaluations, comparative performance tests, etc.). Select “N/A” if the submission does not include performance data.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

#### Comments:

<table>
<thead>
<tr>
<th>37. a. If there are requirements regarding performance data, such as special controls, in a device-specific regulation that are applicable to the device, the submission includes performance data to establish that the submitter has followed the device-specific requirement. Select “N/A” if there are no applicable requirements in a device-specific regulation. Select “No” if the submission does not include a rationale for any omitted information. Note that the adequacy of how such requirements have been addressed should be assessed during the substantive review.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b. If there is a device-specific guidance, other than a special controls guidance document, applicable to the device, the submission includes performance data to establish that the submitter has addressed the recommendations or otherwise has met the applicable statutory or regulatory criteria through an alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

---

Acceptance Checklist for Traditional 510(k)
## Elements of a Complete Submission (RTA Items)
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

- Any “No” answer will result in a “Refuse to Accept” decision.
- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.

Select “N/A” if there is no applicable device-specific guidance. Select “No” if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how recommendations in a device-specific guidance have been addressed should be assessed during the substantive review.

c. If there is a special controls document applicable to the device, the submission includes performance data to establish that the submitter has complied with the particular mitigation measures set forth in the special controls document or uses alternative mitigation measures but provides a rationale to demonstrate that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness. Select “N/A” if there is no applicable special controls document. Select “No” if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how mitigation measures in a special controls document have been addressed should be assessed during the substantive review.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

Comments:

38. If literature is referenced in the submission, submission includes:
Select “N/A” if the submission does not reference literature. Note that the applicability of the referenced article to support a substantial equivalence finding should be assessed during the substantive review; only the presence of a discussion is required to support acceptance.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
</table>

a. Legible reprints or a summary of each article

b. Discussion of how each article is applicable to support the

Acceptance Checklist for Traditional 510(k)
### Elements of a Complete Submission (RTA Items)

*(21 CFR 807.87 unless otherwise indicated)*

Submission should be designated RTA if not addressed

<table>
<thead>
<tr>
<th>Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.</th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any “No” answer will result in a “Refuse to Accept” decision. Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>substantial equivalence of the subject device to the predicate.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**

39. For each completed nonclinical (i.e., animal) study conducted, *Select “N/A” if no animal study was conducted. Note that this section does not address biocompatibility evaluations, which are assessed in Section G of the checklist,*

<table>
<thead>
<tr>
<th>a. Submission includes a study protocol which includes all elements as outlined in 21 CFR 58.120</th>
<th>□</th>
<th>□</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. Submission includes final study report which includes all elements outlined in 21 CFR 58.185</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c. Submission contains a statement that the study was conducted in compliance with applicable requirements in the GLP regulation (21 CFR Part 58), or, if the study was not conducted in compliance with the GLP regulation, the submission explains why the noncompliance would not impact the validity of the study data provided to support a substantial equivalence determination.</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

**Comments:**

**K. Performance Characteristics – In Vitro Diagnostic Devices Only (see also 21 CFR 809.10(b)(12))**

Submission indicates that device: *(one of the below must be checked)*

- [ ] is
- [ ] is not an in vitro diagnostic device (IVD).

*If “is not” is selected, the performance data-related criteria below are omitted from the checklist.*

**Comments:**

Acceptance Checklist for Traditional 510(k)
**Elements of a Complete Submission (RTA Items)**  
*(21 CFR 807.87 unless otherwise indicated)*

Submission should be designated RTA if not addressed

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.</td>
<td>Submission includes the following studies, as appropriate for the device type, including associated protocol descriptions, study results and line data:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a.</td>
<td>Precision/reproducibility</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>b.</td>
<td>Accuracy (includes as appropriate linearity; calibrator or assay traceability; calibrator and/or assay stability protocol and acceptance criteria; assay cut-off; method comparison or comparison to clinical outcome; matrix comparison; and clinical reference range or cutoff.)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>c.</td>
<td>Sensitivity (detection limits, LoB, LoD, LoQ where relevant for the device type).</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>d.</td>
<td>Analytical specificity</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Comments:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

41. | If there are requirements regarding performance data, such as special controls, in a device-specific regulation that are applicable to the device, the submission includes performance data to establish that the submitter has followed the device-specific requirement. Select “N/A” if there are no applicable requirements in a device-specific regulation. Select “No” if the submission does not include a rationale for any omitted information. Note that the adequacy of how such requirements have been addressed should be assessed during the substantive review. | ☐ | ☐ | ☐ |
| b. | If there is a device-specific guidance, other than a special controls guidance document, applicable to the device, the submission includes performance data to establish that the submitter has addressed the recommendations or otherwise has met the | ☐ | ☐ | ☐ |

Acceptance Checklist for Traditional 510(k)
Contains Nonbinding Recommendations

Elements of a Complete Submission (RTA Items)
(21 CFR 807.87 unless otherwise indicated)

Submission should be designated RTA if not addressed.

Check “Yes” if item is present, “N/A” if it is not needed and “No” if it is not included but needed.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>N/A</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Any “No” answer will result in a “Refuse to Accept” decision. Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission. applicable statutory or regulatory criteria through an alternative approach. Select “N/A” if there is no applicable device-specific guidance. Select “No” if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how recommendations in a device-specific guidance have been addressed should be assessed during the substantive review.</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>c. If there is a special controls document applicable to the device, the submission includes performance data to establish that the submitter has complied with the particular mitigation measures set forth in the special controls document or uses alternative mitigation measures but provides a rationale to demonstrate that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness. Select “N/A” if there is no applicable special controls document. Select “No” if the submission does not include a rationale for any omitted information or any alternative approach as outlined above. Note that the adequacy of how mitigation measures in a special controls document have been addressed should be assessed during the substantive review.</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Comments:

Acceptance Checklist for Traditional 510(k)
Contains Nonbinding Recommendations

Decision: Accept ___  Refuse to Accept ___

If Accept, notify applicant; if Refuse to Accept, notify applicant in writing and include a copy of this checklist.

Reviewer Signature: ________________________________  Date: __________

Supervisory Signature: _________________________________  Date: __________
2.0 INDICATIONS FOR USE STATEMENT (FORM 3881)
Indications for Use

ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Type of Use (Select one or both, as applicable)

- Prescription Use (Part 21 CFR 801 Subpart D)
- Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."
3.0 510(K) SUMMARY

Submission Date: April 25, 2016

Submitter Information:

Company Name: Riverain Technologies, LLC.
Company Address: 3020 South Tech Blvd., Miamisburg, OH 45342-4860
Contact Person: Jennifer Butsch
Director, Regulatory Affairs and Quality Assurance
Riverain Technologies
800.990.3387
937.425.6493
jbutsch@riveraintech.com

Device Information:

Trade Name: ClearRead CT™
Regulation Number: 21 CFR §892.2050
Regulation Name: Picture archiving and communications system
Regulatory Class: Class II
Product Code: OEB/LLZ

Device Description: ClearRead CT is a dedicated post-processing application that generates a secondary vessel suppressed Lung CT series with CADe marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Predicate Devices:
syngo.CT Lung CAD
(K143196)
Siemens AG Medical Solutions
Class II

syngo.PET&CT Oncology

CONFIDENTIAL
Traditional 510(k) Premarket Notification
Riverain Technologies
ClearRead CT™

(K093621)
Siemens AG Medical Solutions
Class II

ClearRead Bone Suppression (SoftView)
(K092363)
Riverain Technologies, LLC
Class II

Comparison to Predicate Device Technical Characteristics:
Riverain is of the opinion that the ClearRead CT is substantially equivalent, both in intended use and technical characteristics to the listed predicate devices. Differences in the design and performance from the cited predicate devices do not affect either the safety or the effectiveness of ClearRead CT for its intended use.

<table>
<thead>
<tr>
<th>Predicate: syngo.CT Lung CAD (Siemens AG Medical Solutions) K143196</th>
<th>Predicate: syngo.PET &amp; CT Oncology (Siemens AG Medical Solutions) K093621</th>
<th>Predicate: ClearRead Bone Suppression (Riverain Technologies) K092363</th>
<th>Subject Device: ClearRead CT (Riverain Technologies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Code</td>
<td>OEB</td>
<td>LLZ</td>
<td>LLZ</td>
</tr>
<tr>
<td>Intended Use</td>
<td>Computer-aided detection tool designed to assist radiologists in the detection of solid pulmonary nodules during review of MDCT examinations of the chest</td>
<td>Viewing, manipulation, 3D-Visualization, and comparison of medical images from multiple imaging modalities.</td>
<td>Generating bone suppressed image from an original PA/AP chest radiograph</td>
</tr>
</tbody>
</table>

Testing Summary:
Clinical validation was conducted in a multi-reader multi-case (MRMC) study to validate that the device conformed to the defined user needs and intended uses. The reader study measured the area under the curve (AUC) of the localization receiver operating characteristic (LROCC) response when using ClearRead CT relative to the unaided read. The study also measured the radiologists’ interpretation time when using ClearRead CT relative to unaided interpretations. ClearRead CT was found to significantly increase the AUC, indicating use of the device is superior to the unaided
read for detecting nodules. ClearRead CT was found to significantly decrease read times with and without outliers.

Developmental testing was conducted to verify requirements according to the ClearRead CT device specifications. The Risk Analysis was completed and risk control measures implemented to mitigate hazards. Documentation required for software with a Moderate Level of Concern is included as part of the submission. Device labeling together with results from verification & validation testing demonstrate the device is safe and effective.

Conclusion:

In preparing this 510(k) submission, Riverain has carefully considered the relevant statutory and regulatory requirements, and believes that the information contained within satisfies the requirements for demonstrating substantial equivalence.
4.0 TRUTHFUL AND ACCURATE STATEMENT

As Required per 21 CFR §807.87(k)

I certify that, in my capacity as Director, Regulatory Affairs and Quality Assurance at Riverain Technologies, I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

______________________________
Jennifer Butsch
Riverain Technologies
Director of Regulatory Affairs and Quality Assurance

K

510(k) Number

5.0 CLASS III SUMMARY AND CERTIFICATION

As Required per 21 CFR §807.87(j) and 807.94

This section is not applicable to the current 510(k).
6.0 FINANCIAL CERTIFICATION OR DISCLOSURE STATEMENT (3454 OR 3455)
Insert Financial Certification Form
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME
Steve Worrell

TITLE
CEO

FIRM/ORGANIZATION
Riverain Technologies

SIGNATURE

DATE (mm/dd/yyyy)

This section applies only to the requirements of the Paperwork Reduction Act of 1995.
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.
Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."
### 7.0 DECLARATION OF CONFORMITY AND SUMMARY REPORTS

#### 7.1 FDA Recognized Consensus Standards

<table>
<thead>
<tr>
<th>Standard</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEMA PS 3.1-3.20</td>
<td>Digital Imaging and Communications in Medicine (DICOM) Set 2011</td>
</tr>
<tr>
<td>ISO 14971:2007</td>
<td>Medical Devices – Application of Risk Assessment to Medical Devices</td>
</tr>
<tr>
<td>IEC 62304:2006</td>
<td>Medical Device Software Life Cycle Processes</td>
</tr>
</tbody>
</table>
Department of Health and Human Services  
Food and Drug Administration  

STANDARDS DATA REPORT FOR 510(k)s  
(To be filled in by applicant)

This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

<table>
<thead>
<tr>
<th>TYPE OF 510(K) SUBMISSION</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>Special</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

STANDARD TITLE ¹
NEMA PS 3.1-3.20 Digital Imaging and Communications in Medicine (DICOM) Set 2015

Please answer the following questions

Is this standard recognized by FDA ² ? ................................................................. ☒ ❌

FDA Recognition number ³ ................................................................. #12-238

Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)? ................................................................. ❌ ☒

Is a summary report ⁴ describing the extent of conformance of the standard used included in the 510(k)? ................................................................. ☒ ❌

If no, complete a summary report table.

Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device? ................................................................. ☒ ❌

Does this standard include acceptance criteria? ................................................................. ☒ ❌

If no, include the results of testing in the 510(k).

Does this standard include more than one option or selection of tests? ................................................................. ☒ ❌

If yes, report options selected in the summary report table.

Were there any deviations or adaptations made in the use of the standard? ................................................................. ❌ ☒

If yes, were deviations in accordance with the FDA supplemental information sheet (SIS) ⁵ ? ................................................................. ❌ ☒

Were deviations or adaptations made beyond what is specified in the FDA SIS? ................................................................. ❌ ☒

If yes, report these deviations or adaptations in the summary report table.

Were there any exclusions from the standard? ................................................................. ❌ ☒

If yes, report these exclusions in the summary report table.

Is there an FDA guidance ⁶ that is associated with this standard? ................................................................. ☒ ❌

If yes, was the guidance document followed in preparation of this 510(k)? ................................................................. ☒ ❌

Title of guidance: Guidance for the Submission of Premarket Notifications for Medical Image Management Devices

---

¹ The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]
³ http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/cfStandards/search.cfm
⁴ The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.
⁵ The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm
⁶ The online search for CDRH Guidance Documents can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm
### EXTENT OF STANDARD CONFORMANCE
#### SUMMARY REPORT TABLE

**STANDARD TITLE**
NEMA PS 3.1-3.20 Digital Imaging and Communications in Medicine (DICOM) Set 2015

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.1</td>
<td>Introduction and Overview</td>
<td>☑ Yes</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED**

**DESCRIPTION**

**JUSTIFICATION**

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.2</td>
<td>Conformance</td>
<td>☑ Yes</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED**

**DESCRIPTION**
DICOM Conformance Statement provided with submission.

**JUSTIFICATION**

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.3</td>
<td>Information Object Definitions</td>
<td>☑ Yes</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED**
Only CT and GSPS

**DESCRIPTION**
A CT series is the input and the output is a derived CT series and/or a GSPS object. Populated tags are described in the DICOM Conformance Statement.

**JUSTIFICATION**
CT and GSPS DICOM objects are the only relevant information objects to the device.

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

* Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

---

This section applies only to requirements of the Paperwork Reduction Act of 1995.

**DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.**

The burden time for this collection of information is estimated to average 1 hour per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

- Department of Health and Human Services
- Food and Drug Administration
- Office of Chief Information Officer
- Paperwork Reduction Act (PRA) Staff
- PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."
## EXTENT OF STANDARD CONFORMANCE SUMMARY REPORT TABLE

**STANDARD TITLE**
NEMA PS 3.1-3.20 Digital Imaging and Communications in Medicine (DICOM) Set 2015

### CONFORMANCE WITH STANDARD SECTIONS*

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.4</td>
<td>Service Class Specification</td>
<td>☑ Yes</td>
</tr>
</tbody>
</table>

* **TYPE OF DEVIATION OR OPTION SELECTED** *
  Only Computed Tomography Image Storage, Grayscale Softcopy Presentation State, Storage Commitment Push Model and Verification

* **DESCRIPTION**
  All input and output for the device is via DICOM Image Storage.

* **JUSTIFICATION**
  Only Network Storage and Verification (as both SCU and SCP) are relevant to the device.

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.5</td>
<td>Data Structures and Encoding</td>
<td>☑ Yes</td>
</tr>
</tbody>
</table>

* **TYPE OF DEVIATION OR OPTION SELECTED** *
  Only uncompressed, JPEG Lossless and JPEG2K Lossless formats are supported

* **DESCRIPTION**
  All input and output of the device is via DICOM Network Message Exchange

* **JUSTIFICATION**
  All DICOM compliant devices must support uncompressed format. Only compression formats which are lossless are deemed acceptable.

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.6</td>
<td>Data Dictionary</td>
<td>☑ Yes</td>
</tr>
</tbody>
</table>

* **DESCRIPTION**
  Use tags defined by data dictionary described in the conformance statement

* **JUSTIFICATION**

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.7</td>
<td>Message Exchange</td>
<td>☑ Yes</td>
</tr>
</tbody>
</table>

* **TYPE OF DEVIATION OR OPTION SELECTED** *
  C-ECHO and C-STORE supported

* **DESCRIPTION**
  All input and output of the device is via DICOM Network Message Exchange

* **JUSTIFICATION**
  Network Storage is relevant to the device. C-ECHO used only to verify end-to-end communication testing

---

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under “justification.” Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under “type of deviation or option selected,” “description” and “justification” on the report. More than one page may be necessary.

* Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.
## Extent of Standard Conformance Summary Report Table

**Standard Title**
NEMA PS 3.1-3.20 Digital Imaging and Communications in Medicine (DICOM) Set 2015

### Conformance with Standard Sections*

<table>
<thead>
<tr>
<th>Section Number</th>
<th>Section Title</th>
<th>Conformance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.8</td>
<td>Network Communication Support for Message Exchange</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### Description
All input and output of the device is via DICOM Network Message Exchange

#### Justification
Standard TCP/IP stack provided by Windows based operating system

<table>
<thead>
<tr>
<th>Section Number</th>
<th>Section Title</th>
<th>Conformance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.9</td>
<td>Retired</td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### Description

#### Justification

<table>
<thead>
<tr>
<th>Section Number</th>
<th>Section Title</th>
<th>Conformance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.10, 3.11, 3.12</td>
<td>Media Storage (3 sections covered)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### Description

#### Justification
File Media Storage interchange is not relevant to the device

<table>
<thead>
<tr>
<th>Section Number</th>
<th>Section Title</th>
<th>Conformance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.13</td>
<td>Retired</td>
<td>N/A</td>
</tr>
</tbody>
</table>

#### Description

#### Justification

---

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

* Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

---

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### Extent of Standard Conformance Summary Report Table

**Standard Title**
NEMA PS 3.1-3.20 Digital Imaging and Communications in Medicine (DICOM) Set 2015

<table>
<thead>
<tr>
<th>Section Number</th>
<th>Section Title</th>
<th>Conformance?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.14</td>
<td>Grayscale Standard Display Function</td>
<td>N/A</td>
</tr>
<tr>
<td>PS 3.15</td>
<td>Security and System Management Profiles</td>
<td>N/A</td>
</tr>
<tr>
<td>PS 3.16</td>
<td>Content Mapping Resource</td>
<td>N/A</td>
</tr>
<tr>
<td>PS 3.17</td>
<td>Explanatory Information</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under “justification.” Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under “type of deviation or option selected,” “description” and “justification” on the report. More than one page may be necessary.

*Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.
### EXTENT OF STANDARD CONFORMANCE
SUMMARY REPORT TABLE

**STANDARD TITLE**
NEMA PS 3.1-3.20 Digital Imaging and Communications in Medicine (DICOM) Set 2015

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.18</td>
<td>Web Services</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED** *

**DESCRIPTION**

**JUSTIFICATION**
Not supported by the device

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.19</td>
<td>Application Hosting</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED** *

**DESCRIPTION**

**JUSTIFICATION**
Not supported by the device

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 3.20</td>
<td>Imaging Reports using HL7 Clinical Document Architecture</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED** *

**DESCRIPTION**

**JUSTIFICATION**
Not supported by the device

---

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under “justification.” Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under “type of deviation or option selected,” “description” and “justification” on the report. More than one page may be necessary.

* Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

---

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

**FORM FDA 3654 (4/14)**
Page 5 of 5
This report and the Summary Report Table are to be completed by the applicant when submitting a 510(k) that references a national or international standard. A separate report is required for each standard referenced in the 510(k).

### TYPE OF 510(K) SUBMISSION
- [x] Traditional
- [ ] Special
- [ ] Abbreviated

### STANDARD TITLE
ISO 14971:2007 Medical Devices – Application of Risk Assessment to Medical Devices

Please answer the following questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this standard recognized by FDA?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDA Recognition number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is a summary report describing the extent of conformance of the standard used included in the 510(k)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, complete a summary report table.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does this standard include acceptance criteria?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, include the results of testing in the 510(k).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does this standard include more than one option or selection of tests?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, report options selected in the summary report table.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were there any deviations or adaptations made in the use of the standard?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, were deviations in accordance with the FDA supplemental information sheet (SIS)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were deviations or adaptations made beyond what is specified in the FDA SIS?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, report these deviations or adaptations in the summary report table.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were there any exclusions from the standard?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, report these exclusions in the summary report table.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there an FDA guidance that is associated with this standard?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, was the guidance document followed in preparation of this 510k?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Title of guidance: __________________________________________________________

---

1. The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]
4. The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.
5. The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfsStandards/search.cfm
6. The online search for CDRH Guidance Documents can be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm
## EXTENT OF STANDARD CONFORMANCE
### SUMMARY REPORT TABLE

**STANDARD TITLE**
ISO 14971:2007 Medical Devices – Application of Risk Assessment to Medical Devices

**CONFORMANCE WITH STANDARD SECTIONS**

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes No N/A</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED**

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUSTIFICATION</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes No N/A</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED**

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUSTIFICATION</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes No N/A</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED**

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>JUSTIFICATION</td>
</tr>
</tbody>
</table>

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

* Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

---

**DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.**

The burden time for this collection of information is estimated to average 1 hour per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."
### Please answer the following questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this standard recognized by FDA?</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>FDA Recognition number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#13-32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was a third party laboratory responsible for testing conformity of the device to this standard identified in the 510(k)?</td>
<td></td>
<td>☒</td>
</tr>
<tr>
<td>Is a summary report describing the extent of conformance of the standard used included in the 510(k)?</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>If no, complete a summary report table.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the test data for this device demonstrate conformity to the requirements of this standard as it pertains to this device?</td>
<td>☒</td>
<td></td>
</tr>
<tr>
<td>Does this standard include acceptance criteria?</td>
<td></td>
<td>☒</td>
</tr>
<tr>
<td>If no, include the results of testing in the 510(k).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does this standard include more than one option or selection of tests?</td>
<td></td>
<td>☒</td>
</tr>
<tr>
<td>If yes, report options selected in the summary report table.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were there any deviations or adaptations made in the use of the standard?</td>
<td></td>
<td>☒</td>
</tr>
<tr>
<td>If yes, were deviations in accordance with the FDA supplemental information sheet (SIS)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were deviations or adaptations made beyond what is specified in the FDA SIS?</td>
<td></td>
<td>☒</td>
</tr>
<tr>
<td>If yes, report these deviations or adaptations in the summary report table.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Were there any exclusions from the standard?</td>
<td></td>
<td>☒</td>
</tr>
<tr>
<td>If yes, report these exclusions in the summary report table.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there an FDA guidance that is associated with this standard?</td>
<td></td>
<td>☒</td>
</tr>
<tr>
<td>If yes, was the guidance document followed in preparation of this 510k?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Title of guidance:** [Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 2005](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)

---

1. The formatting convention for the title is: [SDO] [numeric identifier] [title of standard] [date of publication]
4. The summary report should include: any adaptations used to adapt to the device under review (for example, alternative test methods); choices made when options or a selection of methods are described; deviations from the standard; requirements not applicable to the device; and the name and address of the test laboratory or certification body involved in conformance assessment to this standard. The summary report includes information on all standards utilized during the development of the device.
5. The supplemental information sheet (SIS) is additional information which is necessary before FDA recognizes the standard. Found at [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm)
6. The online search for CDRH Guidance Documents can be found at [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)
## EXTENT OF STANDARD CONFORMANCE
### SUMMARY REPORT TABLE

### STANDARD TITLE
IEC 62304:2006 Medical Device Software Life Cycle Processes

### CONFORMANCE WITH STANDARD SECTIONS*

<table>
<thead>
<tr>
<th>SECTION NUMBER</th>
<th>SECTION TITLE</th>
<th>CONFORMANCE?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes No N/A</td>
</tr>
</tbody>
</table>

**TYPE OF DEVIATION OR OPTION SELECTED**

**DESCRIPTION**

**JUSTIFICATION**

---

* For completeness list all sections of the standard and indicate whether conformance is met. If a section is not applicable (N/A) an explanation is needed under "justification." Some standards include options, so similar to deviations, the option chosen needs to be described and adequately justified as appropriate for the subject device. Explanation of all deviations or description of options selected when following a standard is required under "type of deviation or option selected," "description" and "justification" on the report. More than one page may be necessary.

* Types of deviations can include an exclusion of a section in the standard, a deviation brought out by the FDA supplemental information sheet (SIS), a deviation to adapt the standard to the device, or any adaptation of a section.

---

*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*

The burden time for this collection of information is estimated to average 1 hour per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

- Department of Health and Human Services
- Food and Drug Administration
- Office of Chief Information Officer
- Paperwork Reduction Act (PRA) Staff

PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."
8.0 DEVICE DESCRIPTION

8.1 Device Name

Trade/Proprietary Name: ClearRead CT™

Common/Usual Name: Lung computed tomography system, computer-aided detection

Regulation Name: Picture archiving and communications system

8.2 Device Classification

Regulatory Class: II

Product Code: OEB/LLZ

Reviewing Panel: Radiology

8.3 Establishment Registration:

Manufacturer: Riverain Technologies, LLC
3020 South Tech Blvd.
Miamisburg, OH 45342-4860

Registration Number: (b) (4)

8.4 Performance Standards

Performance Standards: There are no additional standards for this device.

Special Controls: There are no additional special controls for this device.

FDA Recognized Standards: NEMA PS 3.1-3.20 2011 Digital Imaging and Communications in Medicine (DICOM) Set
ISO 14971:2007 Medical Devices – Application of Risk Assessment to Medical Devices
IEC 62304:2006 Medical Device Software Life Cycle Processes

CONFIDENTIAL
8.5 Predicate Devices

The predicate devices for ClearRead CT are listed below.

Predicate Device: syngo.CT Lung CAD  
510(k) Number: K143196  
Manufactured by: Siemens AG Medical Solutions

Predicate Device: syngo.PET&CT Oncology  
510(k) Number: K093621  
Manufactured by: Siemens AG Medical Solutions

Predicate Device: ClearRead Bone Suppression  
510(k) Number: K092363  
Manufactured by: Riverain Technologies, LLC

8.6 Description of Device

ClearRead CT™ is a dedicated post-processing application which generates a secondary, vessel suppressed, lung CT series with CADe marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

The original Lung CT series is sent to the ClearRead CT application from the acquisition device or the PACS. ClearRead CT generates a vessel suppressed series with regions of interest (ROIs), CAD markers, and characterizations, resulting in a secondary series that improves the detectability of pulmonary nodules. The application sends the resulting information through the same DICOM network connection to the PACS.

ClearRead CT receives series according to DICOM® protocol, processes the Lung CT series, and outputs the resulting information through the same DICOM network connection. Series inputs can be limited to Computed Tomography (CT). The ClearRead CT Processor processes each series received and generates a secondary vessel suppressed series with CADe. The ClearRead CT output is sent to a destination device that conforms to the ClearRead CT DICOM Conformance Statement, such as a storage archive.

This system is illustrated in Figure 8.1.
Figure 8.1: ClearRead CT Work Flow

ClearRead CT processing is described in greater detail in Section 13.2 Software Description.
9.0 SUBSTANTIAL EQUIVALENCE

9.1 Predicate Device Description

The predicate devices for ClearRead CT are described below.

Predicate Device: syngo.CT Lung CAD
Trade Name: syngo.CT Lung CAD
Classification Name: Picture archiving and communications system
Product Code: OEB
510(k) Number: K143196
Manufactured by: Siemens AG Medical Solutions
510(k) Submitter: Siemens AG Medical Solutions

Predicate Device: syngo.PET&CT Oncology
Trade Name: syngo. PET&CT Oncology
Classification Name: Picture archiving and communications system
Product Code: LLZ
510(k) Number: K093621
Manufactured by: Siemens AG Medical Solutions
510(k) Submitter: Siemens AG Medical Solutions

Predicate Device: ClearRead Bone Suppression
Trade Name: ClearRead Bone Suppression
Classification Name: Picture archiving and communications system
Product Code: LLZ
510(k) Number: K092363
Manufactured by: Riverain Technologies, LLC
510(k) Submitter: Riverain Technologies, LLC

9.2 Device Comparison

(b) (4)
<table>
<thead>
<tr>
<th>Predicate: syngo.CT Lung CAD (Siemens AG Medical Solutions) K143196</th>
<th>Predicate: syngo.PET &amp; CT Oncology (Siemens AG Medical Solutions) K093621</th>
<th>Predicate: ClearRead Bone Suppression (Riverain Technologies) K092363</th>
<th>Subject Device: ClearRead CT (Riverain Technologies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Code</td>
<td>OEB</td>
<td>LLZ</td>
<td>LLZ</td>
</tr>
<tr>
<td>Intended Use</td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Intended Use:**
- Interfaces with Class II Devices
- Image Source:
  - Adjunctive Content
- Original Image Altered
- Automatic Segmentation
- Nodule Detection
- Characterization
<table>
<thead>
<tr>
<th>Predicate: syngo.CT Lung CAD (Siemens AG Medical Solutions) K143196</th>
<th>Predicate: syngo.PET &amp; CT Oncology (Siemens AG Medical Solutions) K093621</th>
<th>Predicate: ClearRead Bone Suppression (Riverain Technologies) K092363</th>
<th>Subject Device: ClearRead CT (Riverain Technologies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurements</td>
<td>(b) (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>View Station Post Processing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient exposed to Increased Radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DICOM Communication</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 9.1: Substantial Equivalence Comparison

CONFIDENTIAL
10.0 PROPOSED LABELING

Labeling for ClearRead CT is provided in draft form (Appendix A) to satisfy the 510(k) requirements of 21 CFR §807.87(e). Final device labeling will meet the requirements of 21 CFR §801 – Labeling before the Device is shipped in Interstate Commerce.

11.0 STERILIZATION INFORMATION AND SHELF LIFE

(b) (4)

12.0 BIOCOMPATIBILITY

This section is not applicable to the current 510(k).
13.0 SOFTWARE

13.1 Level of Concern

The modules are illustrated in Figure 13.2.

Figure 13.2: ClearRead CT Modules
13.3 ClearRead Image Processing Engine Design

(b) (4)
Figure 13.3: System Diagram for ClearRead CT
13.3.3.2 Volume Normalization

(b) (4)
Figure 13.4: CT Volume Normalization Process
CONFIDENTIAL
CONFIDENTIAL

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
13.3.6 Internal Databases

CONFIDENTIAL

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Table 13.27: Manufacturer and scanner model distribution

(b) (4)
13.3.7 Internal Reference standard

(b) (4)
Figure 13.32 shows the ClearRead CT architecture design.

(b)(4)

Figure 13.32: ClearRead CT Architecture Design

DICOM is the registered trademark of the National Electrical Manufacturers Association for its standards publications relating to digital communications of medical information.

CONFIDENTIAL

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
13.7  Software Design Specification (SDS)

(b) (4)
14.0 ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

(b) (4)
16.2 Study Design

(b) (4)
16.3 Data Characteristics

(b) (4)
(b) (4)
(b) (4)
Machine Test Analysis

(b) (4)

(b) (4)
Proposed Labeling

1: LB-1074-14 ClearRead CT Physician's Training Manual 2
2: LB-1175-15 ClearRead CT Installation and Service Manual 32
3: LB-1176-05 ClearRead CT DICOM Conformance Statement 94
4: Marketing Brochures 116
ClearRead CT Suite

Physician’s Training Manual

The Best Practice Requires the Best Tools™
Safe Operation Precautions

**GENERAL USE WARNINGS**

**WARNING:** Use of the device on any image projection other than the axial CT chest views is not supported.

**WARNING:** Only the original chest CT series is to be used for diagnostic interpretation by physicians. ClearRead CT output is designed only as an aid to the interpretation process.

**WARNING:** For continued safe use of this equipment, follow the instructions contained in this Physician's Training Manual. Read this guide carefully before using the equipment, and refer to it as necessary.

**WARNING:** Federal law restricts this device to sale by or on the order of a physician.

**WARNING:** Conditions of image quality that diminish chest radiographic sensitivity, such as under- or over-exposure or artifacts, may also diminish the effectiveness of the device.

**WARNING:** Incorrect DICOM headers or other factors can cause ClearRead CT to reject an input CT series for processing, in which case no result will be returned for viewing. Do not delay your reading of the primary image in order to view the ClearRead CT output.

**WARNING:** ClearRead CT relies on Patient Position and Patient Orientation information from the DICOM header. If the header is incorrect, the system might fail to process the series.

**WARNING:** Users should never be dissuaded from working up an earlier finding even if it is not seen on the ClearRead CT output image. The device will not identify all areas that represent nodules.

**WARNING:** ClearRead CT has an option to send CAD results with an overlay. If your site uses a PACS that can receive and display overlays, and your ClearRead CT has been configured to send overlays, you must establish controls to prevent or record user editing of the CAD results.

**WARNING:** ClearRead CT is a medical device. It should be used only as described in the accompanying Riverain manuals. Other activities (such as web browsing, email, or installation of third-party software without specific authorization from Riverain) are prohibited. Software authorized by Riverain Technologies should be scanned with anti-virus software before use.

**NOTE:** A standard CT series is expected to contain both lungs. Images not containing both lungs might fail to be processed.
REGULATORY REQUIREMENTS

This product complies with the following regulatory requirements:

- FCC (class A)
- UL or CSA
- CE 0413
# Table of Contents

1 : Introduction ............................................................................. 6  
2 : Definitions ............................................................................... 6  
3 : Indications for Use ..................................................................... 6  
4 : Motivation for Creating ClearRead CT .............................................. 7  
5 : Summary of ClearRead CT ............................................................ 7  
6 : How ClearRead CT Works ............................................................. 7  
7 : Performance Expectations ........................................................... 10  
  7.1 : General Performance Characteristics ........................................ 10  
  7.2 : ROI Markers ....................................................................... 10  
  7.3 : ROI Characteristics .............................................................. 11  
  7.4 : True Positive And False Positive Marker Types...................... 11  
8 : Using ClearRead CT ................................................................... 12  
  8.1 : Interpreting A Case .............................................................. 12  
  8.2 : Detection Errors vs. Interpretation Errors .......................... 12  
  8.3 : How to Respond to ClearRead CT Markers ......................... 12  
  8.4 : Potential Effects of ClearRead CT False Negatives .............. 12  
9 : Configurability: Selective Processing .............................................. 13  
10 : Contraindications .................................................................... 13  
11 : Adverse Effects ...................................................................... 13  
12 : Conformance to Standards ......................................................... 13  
13 : Connectivity .......................................................................... 13  
14 : Examples of ClearRead CT Detection ............................................ 14  
  Example 1: True Positive Detection ................................................. 15  
  Example 2: True Positive Detection ............................................... 16  
  Example 3: True Positive Detection ............................................... 17  
  Example 4: True Positive Detection ............................................... 17  
  Example 5: True Positive Detection ............................................... 18  
  Example 6: True Positive Detection ............................................... 18  
  Example 7: True Positive & False Positives .................................... 19  
  Example 8: False Positives ............................................................ 19  
  Example 9: False Negative ............................................................ 20  
  Example 10: False Negative .......................................................... 21  
  Example 11: Nodule Under Segmented .......................................... 21  
  Example 12: Nodule Under Segmented .......................................... 22
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 : Possible Error Messages</td>
<td>22</td>
</tr>
<tr>
<td>16 : ClearRead CT Clinical Study</td>
<td>24</td>
</tr>
<tr>
<td>Introduction</td>
<td>24</td>
</tr>
<tr>
<td>Study Summary</td>
<td>24</td>
</tr>
<tr>
<td>Study Data Description</td>
<td>24</td>
</tr>
<tr>
<td>Reader Study</td>
<td>25</td>
</tr>
<tr>
<td>Machine Test</td>
<td>29</td>
</tr>
</tbody>
</table>
1: Introduction

Your institution has installed the Riverain ClearRead CT system for chest computed tomography volumes. ClearRead CT consists of Computer-Aided Detection (CAD) markers on a vessel suppressed volume. The CAD component identifies regions of interest associated with solid, sub-solid, and/or ground glass nodules. This manual provides physicians who use the ClearRead CT system with an understanding of how the system works, what to expect when using ClearRead CT, and most importantly, the indications for use.

For any questions or concerns not addressed in this manual, go to:
http://www.riveraintech.com

Or contact Riverain Technologies directly at the address below:

Riverain Technologies
3020 S. Tech Blvd
Miamisburg, Ohio 45342
+1-800-990-3387
info@riveraintech.com

2: Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>Computer-Aided Detection</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
</tr>
<tr>
<td>802.3</td>
<td>IEEE Standard for Wired Ethernet</td>
</tr>
</tbody>
</table>

3: Indications for Use

ClearRead CT is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.
4: Motivation for Creating ClearRead CT

Low dose CT is the preferred method for annual lung cancer screening for at risk patients. However, interpreting a chest CT is a challenging task, owing to the large number of images commonly present in a chest CT series and number of interfering structures that compete with the detection of lung nodules. Given the clinical importance of detection of lung cancer using CT, it is clear that a technology that aids in the detection of nodules would be useful to medical professionals and patients alike.

The American Cancer Society statistics show that if lung cancer is found early enough, the 5-year survival rates more than triples. A proactive approach to early lung cancer detection is essential to turning the tide in the fight against this devastating disease. ClearRead CT is designed to provide assistance in the detection of nodules which may represent cancer.

5: Summary of ClearRead CT

ClearRead CT is a computer-aided detection (CAD) system intended to identify and mark regions of interest (ROIs). The ClearRead CT system operates on a chest CT exam. It identifies nodules, optimized for those between 5mm and 30mm in size. The system is limited to marking 5 ROIs per CT series deemed to be worthy of review. The use of ClearRead CT leads to a reduction in oversight errors.

6: How ClearRead CT Works

ClearRead CT is a software solution for automated detection of solid, sub-solid, and/or ground glass nodules designed to operate on chest CT exams. ClearRead CT relies on advanced algorithms from the engineering disciplines of image analysis and machine learning. The algorithms compute measurements to analyze the tissue in the CT series.

The software performs a series of steps to detect regions of interest containing features associated with nodules. Figure 1 is a block diagram illustrating the ClearRead CT nodule detection process.
The system receives, as input, a thoracic CT scan along with its associated acquisition parameters (pixel spacing, slice spacing, and slice thickness) via the DICOM header. The first step, *volume preparation*, segments the reconstruction circle so that the content outside this region can be excluded from further consideration. The next step is *body segmentation*. *Body segmentation* uses a combination of thresholding and morphological post-processing to separate patient tissue from the surrounding air and table content. After body segmentation, *air segmentation* is performed. Air segmentation detects air regions within the patient’s body using a combination of thresholding and morphological post-processing. After the body and air components have been segmented, *volume normalization* is performed. In volume normalization we standardize the appearance of CT scans so that they have similar noise, contrast, and voxel dimensions.

Once the CT scan has been normalized, it is passed to *airway segmentation*. This routine begins by finding the trachea to separate the left and right lungs. Once the airways have been segmented the next step is *lung segmentation*. The segmentation of the lungs is done using a series of thresholding, airway suppression, and morphological post-processing. As part of lung segmentation
Routine, the left and right lungs are defined separately as merging can happen if care is not taken. ClearRead CT is designed to detect nodules only within the lung-field region. Regions outside the lungs are not considered for nodule detection.

Having normalized the CT volume for acquisition effects, and having segmented the lung field from the rest of the body, ClearRead CT then begins the vessel suppression process.

The vessel suppression module takes the normalized CT scan and associated lung segmentation as inputs. As an output, it generates a version of the normalized CT scan where vascular structure is suppressed (it also removes structures such as bronchial walls and fissure lines). It does not, however, remove nodular structures. This includes nodules that may be attached to vascular structure. The normalized image and vessel suppressed volume are fed to the nodule detection process.

Figure 2 provides a high-level diagram of the CAD solution for ClearRead CT. The ROI generation process uses a combination of thresholding and morphological post-processing on the lung regions within the vessel suppressed volume. Post detection, the candidate ROIs are sent to the ROI feature extraction step. The feature extraction module computes a collection of measurements meant to separate true nodules from non-nodules. Example of non-nodules includes residual vessel, bronchial structures, protrusions on the pleural surface that are not nodules, or lung tissue in the ground glass range. Once features have been computed for each ROI, the ROI classification is invoked.

The ROI classification step labels each ROI as nodule or non-nodule. The ROI classification step removes suspected calcified nodules by rejecting ROIs whose average density exceeds 200HU, or 250HU in the case of contrast scans. The ROI classification module limits the number of ROIs to at most five, where the ROIs with the highest classifier scores are selected. Lastly, the CAD engine returns four measurements extracted for the purpose of characterizing an ROI. Each of the four measurements has clinical significance that could aid a clinician in their decision task and although simple for a CAD to measure, are
burdensome for the radiologist at best or in some cases not possible (e.g., volume). The four measurements returned are as follows:

- **Volume**
  - The estimated volume in the segmented region in mm$^3$ units.

- **Maximum Diameter**
  - The largest diameter of the segmented region along the axial direction, in mm units.

- **Minimum Diameter**
  - The length of the diameter perpendicular to the one yielding the maximum, in mm units.

- **Average Density**
  - The median Hounsfield value within the entire segmented region, as measured from the original CT volume.

### 7: Performance Expectations

#### 7.1: General Performance Characteristics

ClearRead CT has been designed to detect nodules greater than or equal to 5mm in size. However, ClearRead CT may detect some nodules smaller than 5mm in diameter.

In a blind, third-party study of pathology-proven cancers, ClearRead CT detected 89.5% of known cancers. Cancers were both comprised of solid, mixed and ground glass. The average false positive rate per normal patient was 0.7469 false positives per CT series. For emphasis, it is noted that ClearRead CT and the radiologist will not necessarily detect the same nodules.

#### 7.2: ROI Markers

ClearRead CT uses the segmented contour on the center slice with ellipses on +/- one slice to indicate a region of interest. The circles are drawn on the image as white circles with a gray outline (if the burned in option is chosen). This provides visibility of the circle in both lucent and dense regions of the image.

The device allows for configuration of the CAD marker display. It is possible to display the CAD markers on both series: the original and the vessel suppressed. Alternatively, the system can be configured to display the CAD markers on the vessel suppressed volume only.
7.3: ROI CHARACTERISTICS

ClearRead CT computes four measurements related to each ROI - volume, maximum diameter, minimum diameter and average density. The ROI characteristics and related information is displayed as an overlay in the bottom left corner of the center slice, and +/- one slice to the center slice of the ROI. This provides visibility of the ROI and its associated characteristic information without obscuring the underlying or surrounding tissues.

The device allows for configuration of the ROI characteristics display. It is possible to display the ROI information either in the bottom left corner or in the top left corner of the image. Alternatively, the user can choose not to display the computed ROI characteristic information.

7.4: TRUE POSITIVE AND FALSE POSITIVE MARKER TYPES

A ClearRead CT true positive is a case in which ClearRead CT correctly detects a nodule. It may direct the radiologist to an area of the CT containing a previously unidentified lesion. True positive detections are the goal of ClearRead CT, while minimizing the number of false positives.

A ClearRead CT false positive is a case where ClearRead CT marks a region and there is no lung nodule. The following are the predominant sources of false positives:

Benign Pathologies:
- Scars
- Mucous plugs
- Pleural plaques

Other Pathologies:
- Tuberculosis (TB)
- Pneumonia
- Presence of other lung diseases such as Emphysema, Pulmonary Embolism, etc.

Normal Anatomy:
- Residual vessel
- Bronchial structures
- Protrusions on the pleural surface
8: Using ClearRead CT

8.1: Interpreting a Case

The radiologist reviews a chest CT concurrently with the vessel suppressed volume. The radiologist reviews the marked regions using the original images and determines whether any action is required. Although the ClearRead CT marker is typically centered on the region of interest, it is possible some markers will not be perfectly centered.

8.2: Detection Errors vs. Interpretation Errors

There are two types of errors in cancer detection:

- In an oversight error, the radiologist fails to see a nodule.
- In an interpretation error, the radiologist sees a nodule but decides it is not actionable.

Computer-aided detection (CAD) helps decrease oversight errors. In this process, the computer aids the radiologist in reducing oversight error.

8.3: How to Respond to ClearRead CT Markers

If upon review of the ROI, a nodule or other abnormality is observed, the radiologist should proceed according to their usual protocol for the type of abnormality observed.

When ClearRead CT has marked a finding that the radiologist can see but determines it is likely benign, the criteria for ordering further evaluation should be the same as if the radiologist noticed the finding without the use of the ClearRead CT system.

If there is no clear explanation for the cause of the marked ROI, the radiologist should dismiss the region as a false positive.

8.4: Potential Effects of ClearRead CT False Negatives

A ClearRead CT false negative is a case in which the computer fails to mark a true lung nodule. As previously indicated, the device will not mark all nodules. Therefore, the clinical action should never be reversed based on the absence of a ClearRead CT marker.
9: Configurability: Selective Processing

ClearRead CT has the ability to filter images using Boolean logic operations on any of the fields in the DICOM header. This filter allows ClearRead CT to distinguish chest CT volumes from other incorrect modalities or anatomy. Thus, it is important that your images contain DICOM headers that are properly populated according to the DICOM standard and that accurately reflect the acquisition and anatomical properties of the image. In addition to selecting only chest CT series, the filter may be extended to control demographic or other characteristics of the images sent to ClearRead CT. For example, the filter can be used to exclude pediatric exams, or to reject images from a particular modality.

10: Contraindications

There are no contraindications for use of the device.

11: Adverse Effects

There are no known direct risks to the health or safety of the patient from the physical use of the ClearRead CT system. This is a post-processing application and does not require additional radiation dose to the patient.

Possible indirect risks are:

- The physician may be dissuaded from working up an earlier finding if the device fails to mark that site, thus missing a possible nodule.
- The physician may be misled into working up a benign finding that would not otherwise have been acted upon.

12: Conformance to Standards

The ClearRead CT system conforms to the DICOM standards for digital communications of medical information.

13: Connectivity

The modality-acquired CT series can be sent to ClearRead CT directly from the modality or from a PACS, where the source of the series is a CT device.
ClearRead CT receives images according to DICOM® protocol\(^2\) (via a standard IEEE 802.3 network connection), processes the chest CT, and outputs the resulting information and/or images through the same 802.3 network connection using the DICOM protocol. Image inputs are limited to Computed Tomography (CT). The output results are sent for physicians to review on one or more devices that conform to the ClearRead CT DICOM Conformance Statement.

The workflow in which ClearRead CT can receive images to process is shown in Figure 3. In one realization of this workflow, ClearRead CT receives the image directly from any of the modalities. In this mode of operation, ClearRead CT receives the input image from the modality, processes the image, and sends the image on to the PACS. ClearRead CT populates the DICOM header of the derived ClearRead CT objects so that it is stored as part of the same study as the original chest CT exam.

In another realization of this workflow, ClearRead CT receives images directly from the PACS. In this mode of operation, ClearRead CT receives the input image from the PACS, processes the image, and sends the ClearRead CT image back to the PACS. ClearRead CT populates the DICOM header of the derived ClearRead CT objects so that it is stored as part of the same study as the original chest CT exam.

![Figure 3 - ClearRead CT Workflow: Receiving Images from Modality or PACS](image)

**14: Examples of ClearRead CT Detection**

The following figures provide typical outputs from ClearRead CT. ROIs are displayed as overlays with computed characteristics - avg density (HU), max diameter (mm), min diameter (mm) and volume (mm\(^3\)), shown in the bottom right corner. The ROI contour and its associated computed characteristic information can also be burned in to the image depending on the

---

\(^2\) DICOM is the registered trademark of the National Electrical Manufacturers Association for its standards publications relating to digital communications of medical information.
configuration setting. In the following examples of ClearRead CT detections, note the following:

- Some examples show the full image so as to place the ROI in context, others show a magnified view of the ROIs for clarity.
- In each example, the ROI is indicated by an overlay. Note that if a burn-in option is chosen, the white circle and black outline are both required to clearly see the contour on light and dark portions of the image.
- In some examples, more than one ROI is visible.

The following examples are provided:

- Examples 1 to 6: True positive detections. In these examples, ClearRead CT detected truth confirmed nodules.
- Example 7: True positive and false positive mark on the same image.
- Example 8: Image with the most common false positives explained.
- Examples 9-10: Images with the most common false negatives explained.
- Examples 11-12: Images where the nodules are under segmented.

**EXAMPLE 1: TRUE POSITIVE DETECTION**

![CT slice with marked nodule](image)

Shown here is a CT slice containing large nodule (left), vessel suppressed CT slice with the segmented contour and the associated characteristics as produced by the CAD engine (right). For quick reference, the mark number is indicated along with the ROI contour. Note, the associated ROI mark number and CAD engine computed characteristics are shown in the bottom right corner.
**Example 2: True Positive Detection**

Shown above is a small nodule as marked by the CAD engine. Other nodule marked by the CAD engine can also be seen on the same slice. For quick reference, the mark number is indicated along with the ROI contour. When more than one nodule is present on the same slice, the ROI characteristic information is displayed in a tabular format as shown. Note that depending on the configuration setting, the ROI characteristic information can be displayed either in the bottom right corner (default) or in the top right corner of the image. Note, the small pleural nodule above the two indicated was not marked due to the rank limit of five.
**EXAMPLE 3: TRUE POSITIVE DETECTION**

This example shows a cavitated nodule as marked by the CAD engine.

**EXAMPLE 4: TRUE POSITIVE DETECTION**

This example shows a small nodule as marked by the CAD engine. Note that ClearRead CT has been designed to detect nodules greater than or equal to 5mm in size. However, ClearRead CT may detect some nodules smaller than 5mm in diameter.
**EXAMPLE 5: TRUE POSITIVE DETECTION**

This example shows a ground glass nodule marked by the CAD engine.

**EXAMPLE 6: TRUE POSITIVE DETECTION**

This example shows a sub-solid nodule marked by the CAD engine. Note the spurious ground glass content that is not marked by the CAD.
**EXAMPLE 7: TRUE POSITIVE & FALSE POSITIVES**

This example shows a sub-solid nodule marked by the CAD engine. Note the false positive residual in the left lung in the vessel suppressed series.

**EXAMPLE 8: FALSE POSITIVES**
This example shows a false positive from vessel branching marked by the CAD engine.

**EXAMPLE 9: FALSE NEGATIVE**

This example shows a nodule not marked by the CAD engine. This CT series has more than 5 nodules. However, ranking leads to loss of TPs as the maximum number of cad marks is limited to 5. Note the clear visibility of the nodule in the vessel suppressed series.
**EXAMPLE 10: FALSE NEGATIVE**

This example shows a false negative due to vessel merger.

**EXAMPLE 11: NODULE UNDER SEGMENTED**

This example shows a peripheral nodule marked by the CAD engine. The segmented contour shows that the nodule is under segmented due to proximity to the lung border and bone structures.
**Example 12: Nodule Under Segmented**

This example shows a nodule marked by the CAD engine. Note that the vessel nodule merging leads to inaccurate segmentation.

15: Possible Error Messages

If the ClearRead CT system is unable to process an image, you will see the text “Image processing unsuccessful” displayed on a blank image.

It is important to note that incorrect DICOM headers can cause ClearRead CT to reject an input image for processing, in which case no result will be returned for viewing. Do not delay reading of the primary image in order to view the ClearRead CT result.
16: ClearRead CT Clinical Study

**INTRODUCTION**

The Arlington Innovation Center for Health Research of Virginia Tech, (Virginia) performed a clinical study of ClearRead CT.

**STUDY SUMMARY**

In a multi-reader multi-case (MRMC) reader study, radiologists interpreted images in order to compare the radiologists’ ability to detect pulmonary nodules when they were aided by the ClearRead CT application. The reader study’s primary test metric was the difference in the partial area under the curve (pAUC) derived from the localization receiver operating characteristic (LROC) curve when using ClearRead CT relative to the unaided reads. Additionally, radiologist’s interpretation time when using ClearRead CT relative to unaided interpretations was measured. These results along with other secondary measures are captured below.

**STUDY DATA DESCRIPTION**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2-3.0 mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40 – 357 mA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5-20mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt; -800 HU to ≤ 200 HU</td>
</tr>
</tbody>
</table>
**READER STUDY**

Twelve radiologists participated in each of the three reader arms. The readers had no prior knowledge of the cases, interpreted the lung CT series either with or without the aid of the ClearRead CT aids and were instructed to report actionable nodules along with a degree of suspicion for marked areas. Readers could record up to 5 locations corresponding to actionable nodules greater than or equal to 5mm. In the first reader arm (Reader Arm 1), readers were provided only the original CT series. After a washout period (minimum of 37 days), readers read concurrently with the ClearRead CT application (the vessel suppressed series along with CAD markings and characterizations) using the same CT cases. This is referred to as Reader Arm 2. Case order was re-randomized for each reader in Reader Arm 2. In the third reader arm (Reader Arm 3), true positive cases and normal cases were equally split according to a pre-specified criteria. Once split, readers were randomly assigned to read one of the two blocks with ClearRead CT and the other block without ClearRead CT. Data from all three reader arms was pooled and analyzed based on established test hypotheses.

The results are summarized in the following tables, with lower and upper 95% confidence limits:
LROC curves for all 12 radiologists combined for cancer cases vs. normals combining the results of the 12 observer radiologists comparing all reads Unaided and Aided.

The overall ability of ClearRead CT to detect cancer cases is superior (i.e. statistically significantly better than) to unaided reads.

As shown below, the aided reader detected approximate 11.34% more cancers, or equivalently, reduced missed cancers by approximately 28%. Using the same two groups of nodules as in the LROC AUC analysis above, sensitivity, specificity, PPV and NPV were estimated by modality and tested for equality.
using the linear mixed model setting. The tables below present the summary of prediction measures within each modality and the difference between modes for cancer versus normal cases and all nodules versus normal, respectively. For sensitivity, there is a statistically significant improvement in reads using CRCT versus unaided for detecting cancer nodules and for detecting any nodules in general. However, specificity is significantly lower in the CRCT reads for both cancer nodules only and combined benign/cancer nodules.

<table>
<thead>
<tr>
<th>Predictive Measure</th>
<th>Read</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Difference</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>CRCT</td>
<td>0.7140</td>
<td>0.0176</td>
<td>0.1134</td>
<td>&lt;0.0001</td>
<td>0.0707</td>
<td>0.1560</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.6006</td>
<td>0.0176</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>CRCT</td>
<td>0.7470</td>
<td>0.0168</td>
<td>-0.0820</td>
<td>0.0003</td>
<td>-0.1235</td>
<td>-0.0405</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.8290</td>
<td>0.0168</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>CRCT</td>
<td>0.6404</td>
<td>0.0192</td>
<td>-0.0768</td>
<td>0.0037</td>
<td>-0.1267</td>
<td>-0.0269</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.7172</td>
<td>0.0192</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>CRCT</td>
<td>0.8112</td>
<td>0.0079</td>
<td>0.0472</td>
<td>&lt;0.0001</td>
<td>0.0291</td>
<td>0.0652</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.7640</td>
<td>0.0079</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Estimates of sensitivity, specificity, PPV, NPV and the associated 95% CIs, across modality for all cancer and normal cases

<table>
<thead>
<tr>
<th>Predictive Measure</th>
<th>Read</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Difference</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>CRCT</td>
<td>0.7206</td>
<td>0.0172</td>
<td>0.1182</td>
<td>&lt;0.0001</td>
<td>0.0773</td>
<td>0.1590</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.6024</td>
<td>0.0172</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>CRCT</td>
<td>0.7284</td>
<td>0.0182</td>
<td>-0.0860</td>
<td>0.0003</td>
<td>-0.1292</td>
<td>-0.0427</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.8143</td>
<td>0.0182</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>CRCT</td>
<td>0.6543</td>
<td>0.0192</td>
<td>-0.0734</td>
<td>0.0033</td>
<td>-0.1206</td>
<td>-0.0262</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.7278</td>
<td>0.0192</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Estimates of sensitivity, specificity, PPV, NPV and the associated 95% CIs, across modality for all actionable nodules and normal cases

Read Times:
As the distribution of read times in seconds within each modality were skewed, a log transformation was applied to the time data in order to generate more symmetric distribution of times (i.e. to meet normality assumption). Given the analysis was performed to obtain the difference in the times on the log scale, the back-transformed values are the estimate and 95% CI on the LS mean for each modality separately were calculated and transformed into seconds from milliseconds. The table below provides the estimated LS mean reading times by modality, back-transformed to the original scale. The reduction in average read time from UA to CRCT was almost half a minute per case (mean differences of 29.0 and 28.4 seconds, respectively).

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>LS Mean Times (back-transformed to seconds)</th>
<th>CRCT-UA (calculated from back-transformed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimate</td>
<td>95% Lower CL</td>
</tr>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>84.4</td>
<td>76.5</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.4</td>
<td>102.7</td>
</tr>
<tr>
<td></td>
<td>CRCT</td>
<td>85.1</td>
<td>77.4</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.5</td>
<td>103.2</td>
</tr>
</tbody>
</table>

Table 16.18 Read time model results, back-transformed to original scale (seconds)*

*Note: As the 95% confidence interval of difference in reading time (log(milliseconds)) for CRCT- UA falls completely below “0”, superiority can be concluded.

It can be concluded that ClearRead read times are lower than unaided read times and that this difference in read times is statistically significant. This is demonstrated in both all read times and in the subset of read times within 3 standard deviations of the mean read time. This equates to a 26% reduction in read time when using CRCT as compared to the unaided read when using all data.
**MACHINE TEST**

Using the clinical data and machine only results, the free response operating characteristic (FROC) curve was derived. The free-response operating characteristic curve is a plot of the sensitivity (proportion of nodules correctly marked) versus the false positive rate per patient in the normal (non-nodule) cases. At the clinical operating point, the sensitivity is 0.8947 and 0.8202 for cancers and all nodules, respectively. The corresponding false positive rate per patient or per case was 0.7469 as illustrated by the dashed lines, in the below.

FROC curve for CRCT on clinical data. This chart displays the CRCT FROC curves of stand-alone machine performance for true positive detection of cancer nodules alone and combined cancers and all combined nodules.
Innovative solutions for improved clinical outcomes
# Table of Contents

1  Introduction ........................................................................................................... 3  
   1.1  Definitions...................................................................................................... 3  
   1.2  Contacting Riverain™ Technologies ......................................................... 3  
   1.3  Overview....................................................................................................... 3  
   1.4  Computer Assembly .................................................................................... 4  
   1.5  Software Description .................................................................................. 4  
   1.6  Remote Access for Technical Service ....................................................... 6  

2  Installing the Riverain System .................................................................................. 6  
   2.1  Windows Updates, Third-Party Software, and Domain Membership ........... 6  
   2.2  Initial Installation of Software-Only Riverain Systems ............................ 7  
   2.3  Installing Riverain Software on the Customer’s Operating System .......... 7  

3  Configuring the Riverain System After Installation ........................................... 9  
   3.1  Opening the ClearRead CT™ Administration Console .............................. 10  
   3.2  ClearRead CT™ Administration Console.................................................. 10  
   3.3  Device Details.............................................................................................. 11  
   3.4  Settings - Image Input ................................................................................. 14  
   3.5  Settings - Image Output .............................................................................. 15  
   3.6  Settings - Hosted DICOM Services ............................................................ 17  
   3.7  Settings - Maintenance .............................................................................. 18  
   3.8  Data Interchange ......................................................................................... 21  
   3.9  Image Workflow .......................................................................................... 27  
   3.10 Device Logs ................................................................................................ 39  
   3.11 Testing the Riverain System After Installation .......................................... 45  
   3.12 Testing the Basic Network Connection ..................................................... 45  
   3.13 Performing a System Self-Test ................................................................... 45  

4  Servicing the Riverain System On-Site ............................................................ 46  
   4.1  Before Servicing the Riverain System ....................................................... 46  
   4.2  Updating and Upgrading Windows ............................................................. 46  

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
4.3 Licensing ................................................................. 47
4.4 Configuring the “Hospital” User Password ......................... 48
4.5 Device Log Files ....................................................... 48
4.6 Other System Diagnostic Activities .................................. 48
4.7 Dell PowerEdge Server ............................................... 49
4.8 Backing Up Files and Settings ...................................... 51
4.9 Deleting Files Prior to Shipment .................................... 51
4.10 Replacing the Hardware ............................................. 52
4.11 Restoring Backed-up Files and Settings ......................... 53
4.12 Dell DVD-ROM Drive Assembly .................................. 53
4.13 Dell HD Drive Assembly ............................................ 54
4.14 System Software .................................................... 56
4.15 Dell Power Supply Assembly ...................................... 56
4.16 HASP Micro Key (Dongle) ........................................ 56
4.17 Replacing the HASP Micro Key .................................. 57
4.18 Troubleshooting for System Administrators .................... 57
1 Introduction

1.1 DEFINITIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Application Entity: A software process that implements DICOM</td>
</tr>
<tr>
<td>AE Title</td>
<td>Used to identify an AE</td>
</tr>
<tr>
<td>ARTIM</td>
<td>Association Request/Reject/Release Timer: Time limit for open associations between DICOM applications</td>
</tr>
<tr>
<td>CAD</td>
<td>Computer-Aided Detection</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
</tr>
<tr>
<td>FRU</td>
<td>Field Replaceable Unit</td>
</tr>
<tr>
<td>GSPS</td>
<td>Grayscale Softcopy Presentation State</td>
</tr>
<tr>
<td>HTTP</td>
<td>Hypertext Transfer Protocol</td>
</tr>
<tr>
<td>HTTPS</td>
<td>Hypertext Transfer Protocol Secure</td>
</tr>
<tr>
<td>PACS</td>
<td>Picture Archiving and Communication System</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>SC</td>
<td>Secondary Capture</td>
</tr>
<tr>
<td>SCP</td>
<td>Service Class Provider: In DICOM, a server application. Services can include storage, printing, etc.</td>
</tr>
<tr>
<td>SCU</td>
<td>Service Class User: In DICOM, a client application</td>
</tr>
<tr>
<td>SSL</td>
<td>Secure Sockets Layer</td>
</tr>
<tr>
<td>UID</td>
<td>Unique Identifier</td>
</tr>
</tbody>
</table>

1.2 CONTACTING RIVERAIN™ TECHNOLOGIES

You can call the Riverain Technologies Customer Care Hotline at +1.800.914.1446 or +1.937.425.6950. You can also reach us by fax at 937-425-6493 or by e-mail at support@riveraintech.com.

1.3 OVERVIEW

This manual describes on-site installation, configuration, and servicing procedures. It is intended for field engineers who install and service the ClearRead CT™ device.

Chapter 2 of this manual contains complete instructions for installing the Riverain system on-site.

Chapter 3 of this manual contains configuration instructions post installation.

Chapter 4 of this manual contains instructions for servicing the Riverain system on site. While not every possible problem can be handled on site or covered in this document, this section covers basic procedures for testing and servicing. Riverain provides the ClearRead CT medical device as turn-key Dell PowerEdge
T110 II server or in a software-media format for installation on customer-provided hardware. In the software-media format, the customer is responsible for obtaining hardware servicing instructions.

1.4 COMPUTER ASSEMBLY

<table>
<thead>
<tr>
<th>Server</th>
<th>Recommended specifications:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Intel processor, at least 2.4 GHz; 4 available cores</td>
</tr>
<tr>
<td></td>
<td>• 6 GB Random Access Memory (RAM)</td>
</tr>
<tr>
<td></td>
<td>• 100 GB hard disk (available storage)</td>
</tr>
<tr>
<td></td>
<td>• 1 Gbit/sec Ethernet controller</td>
</tr>
<tr>
<td></td>
<td>• USB 2.0 or greater</td>
</tr>
</tbody>
</table>

| Operating System | Windows 7 Professional/Enterprise/Ultimate 64-bit |
|                 | Windows 8.1 Professional/Enterprise 64-bit |
|                 | Windows 2008 R2 Server 64-bit |
|                 | Windows 2012 R2 Server 64-bit |

Operating System

Windows is a registered trademark of Microsoft Corporation in the United States and other countries.

<table>
<thead>
<tr>
<th>Web Browser</th>
<th>Microsoft Internet Explorer 10 or better, with cookies and Javascript enabled</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Software Protection Key</th>
<th>The HASP-HL key requires a continuous power supply from the USB port of up to 900mA.</th>
</tr>
</thead>
</table>

1.5 SOFTWARE DESCRIPTION

ClearRead CT™ Vessel Suppression produces a vessel suppressed chest CT series derived from a primary chest CT series.

ClearRead CT™ CAD is a system that aids radiologists in the detection of ROIs within a chest CT series.

The Riverain system receives images according to DICOM® protocol1 (via a standard IEEE 802.3 network connection), processes the images, and outputs the resulting information and/or images through the same DICOM network connection. Image inputs must be Computed Tomography (CT). The output results are sent for radiologists to review on one or more devices that conform to the system’s DICOM Conformance Statement.

The major functions of the device – receiving original images, processing images through Riverain devices, and sending Riverain output objects - are

1 DICOM is the registered trademark of the National Electrical Manufacturers Association for its standards publications relating to digital communications of medical information.
implemented as a Windows Service. It is started when the device boots up and runs continuously.

The system software is incorporated into a DICOM network as shown in Figure 1. Figure 2 shows a representative clinical workflow in which imaging modalities send images to a DICOM archive (or storage server) and to ClearRead CT™. The software processes each chest CT series received and generates licensed derived output. The results are sent to a destination device that conforms to the system’s DICOM Conformance Statement, such as a storage archive.

![Diagram of the Riverain system in a DICOM network environment](image)

**Figure 1: Integration of the Riverain system in a DICOM network environment**

![Diagram of a representative clinical workflow using the Riverain system](image)

**Figure 2: Diagram of a representative clinical workflow using the Riverain system**

In this workflow, the Riverain system receives and sends data to the network without human intervention.
1.6 REMOTE ACCESS FOR TECHNICAL SERVICE

Riverain Technical Services Department uses TeamViewer to perform many service tasks remotely.

Riverain Technologies always informs hospital staff prior to making changes via remote access, in order to ensure that the hospital workflow is not interrupted. TeamViewer uses port 80, 443, or 5938. Changing port settings should be coordinated with Riverain Technical Services.

To test remote access connectivity, see Section 4.6.2 Testing the Remote Access Connection, page 49.

**WARNING:** This system is a medical device. It should be used only as described in the accompanying Riverain Technologies manuals. Other activities, such as web browsing, email, or installation of third-party software without specific authorization from Riverain Technologies, are prohibited. Software authorized by Riverain Technologies should be scanned with anti-virus software before installation.

2 Installing the Riverain System

Systems are provided by Riverain as a software-only format for installation on customer-provided hardware. To perform installation, see Section 2.2 Initial Installation of Software-Only Riverain Systems, page 7.

**NOTE:** When updating the Riverain software or the Windows operating system, test the Riverain software by running a self-test and by processing input images through each Riverain device licensed on the system. See Section 3.11 Testing the Riverain System After Installation, page 45.

2.1 WINDOWS UPDATES, THIRD-PARTY SOFTWARE, AND DOMAIN MEMBERSHIP

Riverain does not recommend enabling Automatic Updates for Windows on devices with the ClearRead CT™ software installed.

**WARNING:** This system is a medical device. It should be used only as described in the accompanying Riverain Technologies manuals. Other activities, such as web browsing, email, or installation of third-party software without specific authorization from Riverain Technologies, are prohibited. Software authorized by Riverain Technologies should be scanned with anti-virus software before installation.

If anti-malware software is used to scan the Riverain system, the installation folder should be excluded from the scan.
Your organization might choose to add the Riverain system to a domain. Please note that doing so can cause group policies and/or updates to be pushed automatically to the Riverain system from the domain. If you do add the Riverain system to a domain, make sure that this does not lead to unauthorized Windows updates or third-party software installations, as described above.

### 2.2 Initial Installation of Software-Only Riverain Systems

This section describes how to install a system provided by Riverain in a software-only format on customer-provided hardware.

Riverain Technologies has shipped you an installation kit that has everything you need. The installation kit contains:

- This manual
- ClearRead CT™ 2.0 Software Installation CD, Riverain part number -0348-20
- HASP Micro key, programmed for your site, Riverain P/N -0717-01 or HASP-SL Software key, programmed for your site, Riverain P/N -0721-01
- (Optional) Remote Access Software CD, Riverain part number -0330-35 TeamViewer Installation CD and associated instructions LB-1144

If any of these items are missing, please contact the Riverain Technologies Customer Care Hotline at +1.800.914.1446 or +1.937.425.6950.

If any of the following steps returns an unexpected result:

- Stop working on the procedure.
- Write a note at the relevant step, including the unexpected result.
- Report the event to the Riverain Technologies Customer Care Hotline.

**NOTE:** It is advised not to lock the Riverain software with Windows AppLocker and not to enable Windows BitLocker.

Riverain software can be installed directly on the customer’s operating system and hardware

### 2.3 Installing Riverain Software on the Customer’s Operating System

1. **NOTE:** The installation of the software requires Administrator privileges.
2. **NOTE:** All settings configured during installation can be changed at a later date through the administrative console.
3. **NOTE:** The advanced power option for “USB selective suspend” should be changed to Disabled.

4. **NOTE:** The advanced power option for the “Sleep” should be set to Never.

5. Run the ClearRead CT™ software installer


7. The screen displays the License Agreement. Select I accept this agreement, and then press [Next>].

8. Select the location to install the software. This location must be a local hard drive. Press [Next>] to continue. Press [Next>].


   - **Maximum cache size limits** the size of the image cache in gigabytes. The default for this setting is 100GB.

   - The available free space setting limits the amount of free disk space in gigabytes that the system must have available, otherwise image services will be stopped. The default is 10GB.


   - The port is the TCP/IP port that will host the administrative console web interface. The default port is 8104.

   - If “Allow remote access to administrative web interface” is checked, then the administrative web interface will allow access from web browsers hosted on remote computers.

   - If “Enable SSL using a self-signed certificate (https)” is checked, then the administrative web interface will use the HTTPS protocol for access to the administrative web interface.

11. Accept the default Start menu program group by pressing [Next>].

12. The Ready to Install screen is displayed. Press [Install] to continue and perform the installation.

   - The installation may take several minutes depending on the hardware. Please wait until complete.

13. When the installation is complete, the screen displays the message: “Click Finish to exit setup.” Click [Finish].

14. If Remote Access software is to be installed, please refer to LB-1144 as included in your installation kit.
When using Windows Firewall, a new inbound rule allowing the clearreadct.exe program needs to be added. Clearreadct.exe is installed into C:\Program Files\Riverain\ClearReadCt by default. It is recommended to apply this rule to All Windows network profiles.

After adding the rule in Windows Firewall with Advanced Security under Administrative Tools, the service clearreadct.exe (Riverain ClearRead CT) needs to be restarted in Services under Administrative Tools.

Note: If you are using a third party firewall, please refer to that vendor's documentation to allow an inbound rule for clearreadct.exe.

<table>
<thead>
<tr>
<th>Windows Network Profile Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain</td>
<td>Use this profile when the computer is a member of the same domain and authenticated to the same domain controller as the other connected network interfaces.</td>
</tr>
<tr>
<td>Private</td>
<td>Use this profile when at least one interface is connected to a private network location and the other connected network interfaces are either authenticated to a domain controller or on a private network.</td>
</tr>
<tr>
<td>Public</td>
<td>Use this profile when the private or domain profiles do not apply.</td>
</tr>
</tbody>
</table>

3 Configuring the Riverain System After Installation

As part of installing the Riverain system, you must perform a number of configuration procedures.

Go through this entire section in order, and perform all of the configuration procedures that are required, in the order that they are presented here.

**NOTE:** Some of these tasks might involve changing port settings. Because TeamViewer uses port 80, 443, or 5938, any changes to port settings on the Riverain system must be communicated to Riverain Technical Services as soon as they are implemented. See Section 4.6.2 Testing the Remote Access Connection, page 49.
3.1 OPENING THE CLEARREAD CT™ ADMINISTRATION CONSOLE

The ClearRead CT™ Administration Console can be launched from the Start menu. The default Start menu group is Riverain\ClearRead CT and the shortcut menu name is Admin Console. If default settings were used during installation, the URL is http://localhost:8104. The console requires a password to access the site. The default password is admin.

3.2 CLEARREAD CT™ ADMINISTRATION CONSOLE

![ClearRead CT™ Administration Console](image)

Figure 3. ClearRead CT Administration Console

The ClearRead CT™ Administration Console is made up of the following sections:

1. Title panel - Provides access to user actions such as logout and change password and applying of saved changes.
2. Navigation panel - Provides navigation of the configuration sections of the system.
3. Details panel - The currently selected configuration section.

Setting changes made in the administration console requires a two-step process. Setting changes must first be saved. Saved settings are NOT immediately applied to the device. Once all intended setting changes have been made, apply pending changes by pressing [Applying Pending Changes] in the title panel. This button will be enabled anytime the device detects modified settings. Pending saved settings can also be applied by restarting the device.
3.3 DEVICE DETAILS

The Device Details screen contains version information, license information and configuration backup and restore actions. The Device Details screen also indicates the current status of the ClearRead CT™ state. The status can be Testing, Started or Stopped.

![ClearRead CT™ Image Lookup](image)

The status of ClearRead CT™ can be changed by selecting the down arrow on the status indicator unless the system is Testing. This status does not reflect the state of the Windows service but the internal activities of the ClearRead CT™ application.

The Version tab contains the software component version installed on the system including the ClearRead CT™ device version and the Unique Device Identifier (UDI).

The License tab contains information pertaining to the license status and content availability based on the installed license.

The Backup tab allows for configuration backup and restoration.

3.3.1 GENERATING A SYSTEM ID FOR HASP-SL KEY

If you purchased a system that will be licensed using the HASP-SL Software key, a system ID must be generated before the HASP-SL key can be provided. If the HASP-HL USB key was supplied, please skip this section.

To generate a system ID:

1. Navigate to Device Details and select the License tab.
2. Press [Export System ID]. You may be prompted to Open or Save the file, select [Save]. The default file name generated will be the server’s hostname followed by an “.id” file extension.

3. Email the saved file to licensing@riveraintech.com to request a software license.

You will receive an email containing a .hasp file which will be your HASP-SL Software key.

To install the HASP-SL key:

1. Navigate to Device Details and select the License tab.
2. Press [Import License]. When prompted, browse to the .hasp file and select [Import]. This operation may take several seconds to complete.
3. Once the license import is complete, a message will appear indicating that the license was successfully imported and the license details screen will update.

3.3.2 IMPORT A LICENSE

To install a license:

1. Navigate to Device Details and select the License tab.
2. Press [Import License]. When prompted, browse to the Riverain supplied file and select [Import]. This operation may take several seconds to complete.
3. Once the license import is complete, a message will appear indicating that the license was successfully imported and the license details screen will update.

3.3.3 EXPORTING LICENSE DETAILS

The device license details can be exported from the device for reporting purposes only. This operation does not remove the license from the device and the resultant exported file cannot be re-imported to any device.

1. Navigate to Device Details and select the License tab.
2. Press [Export License]. The system will generate a text file and you may be prompted by your web browser to open or save the file. Select [Save].
3.3.4 MODALITY LIMITED AND MODALITY LIMIT

Modality Limits is a licensing mechanism used to constrain image processing to specific acquisition devices. When Modality Limited displays “Yes”, the device will only process images acquired from the number of modalities specified.

When the device is licensed, the modality limit is set at the time the license is created. As needed, additional modality licenses can be purchased from Riverain Technologies.

For site licenses, the modality limit is assigned to prevent the device from being used beyond a single physical location. Facilities with a large number of CT acquisition devices at a single physical location may need the Modality Limit adjusted by Riverain Technical Services.

Pressing the ‘Request licensed modalities reset’ will cause the ClearRead CT™ server to reset its modality device database. Doing so will prevent the server from image processing for 15 minutes. There are very few circumstances beyond replacing a CT modality that would require the use of this action; it is recommended to consult with Riverain Technical Services before performing this action.

3.3.5 BACKING UP AND RESTORING CONFIGURATION SETTINGS

A configuration backup is recommended after the initial device setup and after configuration changes. Configuration backups may only be restored to a device at the same software version level, therefore a backup should be performed after upgrades.

To back up the device’s configuration settings:

1. Navigate to Device Details and select the Backup tab.
2. Press [Backup]. You may be prompted by your web browser to open or save the file. Select [Save].

To restore a configuration backup:

1. Navigate to Device Details and select the Backup tab.
2. Press [Restore]. When prompted, browse to an earlier generated backup file and select [Restore]. This operation may take several seconds to complete.
3. Once the configuration restore is complete, a message will appear indicating that the operation succeeded.

3.4 SETTINGS - IMAGE INPUT

The Image Input Preferences page allows for inbound image configuration.

3.4.1 DICOM INBOUND GATEWAYS

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DICOM service port</td>
<td>Listening port for DICOM C-STORE SCP purposes</td>
<td>104</td>
</tr>
<tr>
<td>Maximum number of concurrent DICOM associations</td>
<td>The maximum number of simultaneous DICOM associations supported for all hosted DICOM services.</td>
<td>20</td>
</tr>
<tr>
<td>CT series acquisition inactivity timeout</td>
<td>The number of seconds required to start processing a CT series when using the folder gateway or when transmitting a single frame per association.</td>
<td>60</td>
</tr>
</tbody>
</table>

**NOTE:** If you change the DICOM service port number, you must also reconfigure the hospital’s devices so that they send input images to the correct port number on the Riverain system.

3.4.2 INBOX GATEWAYS

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polling interval for inbox folders (seconds)</td>
<td>The interval at which file system input folders, if configured, are checked for new content</td>
<td>5</td>
</tr>
<tr>
<td>Perform DICOM file signature check</td>
<td>Checks DICOM files for embedded DICOM signature. Recommended.</td>
<td>Checked</td>
</tr>
<tr>
<td>Minimum inbox image size (MB)</td>
<td>The minimum DICOM image size allowed in MB</td>
<td>.1</td>
</tr>
<tr>
<td>Maximum inbox image size (MB)</td>
<td>The maximum DICOM image size allowed in MB</td>
<td>2</td>
</tr>
</tbody>
</table>
### 3.4.3 Acquisition Delay Filtering

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enable acquisition time delay filtering</td>
<td>Useful for addressing external DICOM routers that infrequently hang causing delayed image transfers. By default, this setting is not enabled. If enabled, the system will check the acquisition time of the image against the current system time and discard images older than the configured value in minutes.</td>
<td>Unchecked</td>
</tr>
<tr>
<td>Maximum delay (minutes)</td>
<td>The maximum allowed time delay from image acquisition time to current time for image acceptance.</td>
<td>25</td>
</tr>
</tbody>
</table>

**NOTE:** To ensure that the acquisition time filter is operating as intended, all date and time settings should be synchronized across all devices. If needed, individual DICOM image collection endpoints can be excluded from acquisition time filtering. Refer to the Data Interchange settings for details.

### 3.4.4 Minimum Age Filter

To define a minimum patient age for image processing, select the check box to enable minimum age filter for any content, and then type the minimum patient age in years.

**NOTE:** The DICOM Image Filter detailed in a later section permits a more generalized age filtering option such that any image can be excluded by age for all processing regardless of product.

<table>
<thead>
<tr>
<th>Product</th>
<th>Default setting for Enable minimum age filter</th>
<th>Default Minimum patient age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel Suppression</td>
<td>Unchecked</td>
<td>18</td>
</tr>
<tr>
<td>CAD</td>
<td>Unchecked</td>
<td>45</td>
</tr>
</tbody>
</table>

### 3.5 Settings - Image Output

The Image Output Preferences page allows for outbound image configuration.

#### 3.5.1 Retry Interval Preferences

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retry intervals</td>
<td>Comma delimited values in seconds. The number of values specified will dictate</td>
<td>10,60,3600</td>
</tr>
</tbody>
</table>
the number and delay for retry attempts.

### 3.5.2 IMAGE ANNOTATIONS

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClearRead CT™ image labels</td>
<td>Suppress ClearRead CT™ brand labeling</td>
<td>Should remain unchecked unless directed by Riverain</td>
</tr>
<tr>
<td>CAD characteristics placement</td>
<td>Defines CAD measurements placement.</td>
<td>Bottom Right</td>
</tr>
<tr>
<td></td>
<td>Options include:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bottom Right</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Top Right</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• None</td>
<td></td>
</tr>
</tbody>
</table>

### 3.5.3 ERROR HANDLING

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not send output in the event of an image processing error</td>
<td>Suppresses DICOM output for processing errors</td>
<td>Unchecked</td>
</tr>
</tbody>
</table>

### 3.5.4 DICOM OUTBOUND GATEWAYS

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use a single DICOM association to deliver all series images</td>
<td>Send all frames of a series as a single association</td>
<td>Should remain checked unless there is a compelling reason otherwise</td>
</tr>
<tr>
<td>Application entity</td>
<td>AE title used by ClearRead CT™ when acting as a C-STORE SCU sending to remote devices</td>
<td>RIVERAIN</td>
</tr>
<tr>
<td>Association timeout</td>
<td>Maximum time ClearRead CT™ will wait during the construction of a DICOM association, in seconds</td>
<td>15</td>
</tr>
<tr>
<td>Read timeout</td>
<td>Maximum time ClearRead CT™ will wait during the READ portion of a DICOM message before timing out, in seconds</td>
<td>45</td>
</tr>
</tbody>
</table>

### 3.5.5 OUTBOX FILE NAMING CONVENTIONS

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outbox file naming conventions</td>
<td>File name format used for saving DICOM objects to configured outbound folders.</td>
</tr>
</tbody>
</table>
### Options include:

{transaction id}_{derived code}_{frame #}.dcm
{transaction id}_{patient id}_{derived code}_{frame #}.dcm

**Default:**

{transaction id}_{derived_code}_{frame #}.dcm

### 3.6 Settings – Hosted DICOM Services

The Hosted DICOM Services page allows for configuration of ClearRead CT™ C-STORE SCP services.

**NOTE:** All DICOM services are available on the port defined on the Image Input Preferences page. The default port is 104.

A new installation of ClearRead CT™ will have the following default DICOM services configured. These services can be edited and deleted. By default, these services are enabled.

<table>
<thead>
<tr>
<th>AE Title</th>
<th>Service</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLEARREAD_STORE</td>
<td>C-STORE</td>
<td>The C-STORE SCP configured for receiving images targeted for ClearRead processing.</td>
</tr>
</tbody>
</table>

**NOTE:** Additional C-STORE services may be configured to allow greater control of what derived objects are created for given systems.

### 3.6.1 Adding a C-STORE Service

To add a C-STORE Service press [Add Storage Service].
**3.7 SETTINGS – MAINTENANCE**

The Device Maintenance page allows for configuration of logging, web administration console settings, storage limits, routine device maintenance.
## Device Maintenance

### Logging preferences

- [ ] enable verbose logging for temporary troubleshooting purposes

### Administration website settings

- Website changes require the ClearRead CT™ Windows service to be restarted manually.
- [ ] enable remote access to web administration site
- [ ] enable SSL (utilizes a self-signed certificate)

#### Hosting port

- Port: 8194

### Weekly device maintenance

#### Weekly maintenance time

- Day: Sunday
- Time: 01:00
- AM/PM: AM

Device will be unavailable for approximately five seconds during maintenance.

### Device storage constraints

- Minimum system free space available (GB): 10
- Maximum storage space permitted (GB): 10

### Housekeeping schedule

- Minimum log retention (minutes): 10800
- Minimum derived output image retention (minutes): 10800
### 3.7.1 Logging Preference

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enable verbose logging for temporary troubleshooting purposes</td>
<td>Enables logging of low level diagnostic messages. This should be unchecked unless troubleshooting.</td>
<td>Not checked</td>
</tr>
</tbody>
</table>

### 3.7.2 Administration Website

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enable remote access to web administration site</td>
<td>Allow web access from a remote computer. SSL is recommended.</td>
<td>Not checked</td>
</tr>
<tr>
<td>Enable SSL (utilizes a self-signed certificate)</td>
<td>Enable SSL for administration web site.</td>
<td>Not checked</td>
</tr>
<tr>
<td>Hosting port</td>
<td>The admin web site listening port.</td>
<td>8104</td>
</tr>
</tbody>
</table>

**NOTE:** Any configuration changes to the administration website settings require the ClearRead Windows service to be restarted in order to take affect.

**NOTE:** For SSL support, a self-signed certificate is generated and used. Because a certificate authority did not sign the certificate, the web browser will warn the user about an untrusted certificate. The untrusted certificate will need to be accepted to proceed to the web site.

### 3.7.3 Weekly Device Maintenance

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly maintenance time</td>
<td>The day of the week and time to perform a periodic restart.</td>
<td>Sunday at 10:00 PM UTC</td>
</tr>
</tbody>
</table>

### 3.7.4 Device Storage Constraints

Storage constraints prevent the device from over utilizing storage resources. All configured storage constraints must be honored in order for the device to operate.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum system free space available (GB)</td>
<td>The minimum remaining free storage space on installed hard drive volume that must exist for the device to operate. This setting ensures the device will never fully exhaust the storage capacity and possibly prevent the server from booting properly.</td>
<td>10</td>
</tr>
<tr>
<td>Maximum storage space permitted (GB)</td>
<td>The maximum allowed storage space on installed hard drive that is used by the device for its image cache.</td>
<td>100</td>
</tr>
</tbody>
</table>
### 3.7.5 HOUSEKEEPING SCHEDULE

Housekeeping allows the device to operate unattended. All housekeeping tasks are checked for execution time at the rate dictated by the sweep interval. Images and device logs are aged and removed from the device based on these settings.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum log retention (minutes)</td>
<td>Elapsed minutes before ERROR, WARN, INFO, and TRACE log level messages are removed from the device.</td>
<td>10080</td>
</tr>
<tr>
<td>Minimum derived output image retention (minutes)</td>
<td>Elapsed minutes before removing derived output image data.</td>
<td>10080</td>
</tr>
</tbody>
</table>

**NOTE:** Minimum derived output image retention must always be less than or equal to the minimum log retention.

### 3.8 DATA INTERCHANGE

Data Interchange defines the source and destination endpoints for exchanging DICOM images. The system can communicate with remote systems using the DICOM protocol or monitor file system folders. The DICOM Network Registry defines external DICOM stations along with any published services that the device can integrate. The Folder Inboxes / Outboxes define folders to be used for image file exchanges.

#### 3.8.1 CONFIGURING DERIVED IMAGE OUTPUT PREFERENCES

Each storage destination, DICOM C-STORE SCP or Folder Outbox, is configured to store specific ClearRead CT™ derived objects. The available derived objects are identified by a derived object code documented in the device DICOM Conformance Statements under the Image Type tag (0008,0008) except for Grayscale Softcopy Presentation State (GSPS). A given destination will receive a configured derived object anytime the object is generated by the device which is dictated by input filtering, licensing and content selection rules.

**NOTE:** Configuring a derived image output preference on a destination does not instruct the device to generate the derived image. The preference only defines the content of interest for storage purposes if it becomes available.

The table below summarizes the derived code storage options:

<table>
<thead>
<tr>
<th>Derived Code</th>
<th>Product(s)</th>
<th>ClearRead CT™ Derived Object Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2001</td>
<td>Vessel Suppressed Series</td>
<td>Vessel Suppressed Series</td>
</tr>
</tbody>
</table>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2002</td>
<td>Vessel Suppressed Series with CAD</td>
<td>Vessel Suppressed Series with CAD marks burned into the images</td>
</tr>
<tr>
<td>C2003</td>
<td>Vessel Suppressed Series with CAD Overlay</td>
<td>Vessel Suppressed Series with CAD overlay object (DICOM 6000)</td>
</tr>
<tr>
<td>C2004</td>
<td>Vessel Suppressed CAD GSPS</td>
<td>CAD results as a Gray Scale Presentation State object(s) referencing Vessel Suppressed Series</td>
</tr>
<tr>
<td>C2012</td>
<td>Primary Series with CAD</td>
<td>Primary Series with CAD marks burned into the images</td>
</tr>
<tr>
<td>C2013</td>
<td>Primary Series with CAD Overlay</td>
<td>Primary Series with CAD overlay object (DICOM 6000)</td>
</tr>
<tr>
<td>C2014</td>
<td>Primary Series CAD GSPS</td>
<td>CAD results as a Gray Scale Presentation State object(s) referencing Primary Series</td>
</tr>
</tbody>
</table>

**NOTE:** This chart can be accessed by clicking the ClearRead CT™ Image Lookup hyperlink at the top of the Details panel.

**NOTE:** Derived Object types C2002 and C2012, due to the nature of the burned in CAD markings, might lead to non-optimal display of the ROI mark in non-axial views.

### 3.8.2 DICOM NETWORK REGISTRY

DICOM Network Registry screen lists the remote DICOM application entities with which the system communicates.

To add a remote DICOM application entity, press [Add Station]. Depending on the capabilities or responsibilities of the remote application entity, it can be configured in multiple ways.

#### 3.8.2.1 DICOM STATION - CONNECTION

All remote application entities must be configured with a valid AE title and IPv4/IPv6 address. The system can also perform network ICMP pings to the remote host using the [ICMP Ping] option.
## Add DICOM Station

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enable application entity</td>
<td>If checked, the device is enabled.</td>
<td>Checked</td>
</tr>
<tr>
<td>Application entity title</td>
<td>The AE title of the remote DICOM station. Lower case letters and hyphen are also supported but are not recommended and should be considered non-standard.</td>
<td>Blank</td>
</tr>
<tr>
<td>Application entity IP address</td>
<td>The IPv4 or IPv6 address of the remote DICOM station. The address can be “0.0.0.0” or “::” for STORE-SCU DICOM stations only (i.e. no SCP services are provided by the device). This is useful for wireless portable acquisition devices with dynamic IP addresses as it permits the assigned application entity title from any IPv4/IPv6 address.</td>
<td>Blank</td>
</tr>
<tr>
<td>Exclude from acquisition time latency filtering</td>
<td>Only applicable if “Acquisition time delay filtering” under the Image Input is enabled. If checked, the images received.</td>
<td>Unchecked</td>
</tr>
</tbody>
</table>
from this device will not be checked by the acquisition time recorded in the DICOM header.

### 3.8.2.2 STORAGE COMMIT

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device accepts storage commit requests from this station</td>
<td>If checked, ClearRead CT™ will respond to DICOM Storage Commit requests from the sending station</td>
<td>Unchecked</td>
</tr>
<tr>
<td>Enabling Storage Commit will cause the following sections to display:</td>
<td>Respond immediately on original storage commit request association</td>
<td>Checked</td>
</tr>
<tr>
<td>Disabling the ‘Respond immediately on the original storage commit request association’ will cause the following sections to display:</td>
<td>Storage Commit SCP port</td>
<td>The port that ClearRead CT™ will connect to send a response to the DICOM Storage Commit request.</td>
</tr>
<tr>
<td>Commit response delay</td>
<td>The number of seconds that the ClearRead CT™ system will wait before sending the Storage Commit response.</td>
<td>0</td>
</tr>
</tbody>
</table>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
3.8.2.3 DICOM STATION – C-STORE

The DICOM station C-STORE properties must be configured if the Riverain system needs to send images to the DICOM station. The system can perform a DICOM C-ECHO from ClearRead CT™ to the target DICOM Station using the [DICOM ping] option provided.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-STORE destination port</td>
<td>The TCP port of the C-STORE SCP. A zero value indicates station does not provide this service.</td>
<td>0</td>
</tr>
</tbody>
</table>

Entering a value for C-Store destination port will cause the following sections to display:

Presented transfer syntaxes
- The transfer syntaxes which will be presented during association/negotiation. If compression is required, choose JPEG Lossless or JPEG 2000 Lossless.
  - Little Endian Implicit
  - Little Endian Explicit

Derived object storage preferences
- The ClearRead CT™ derived objects that will be sent to storage provider.
- Empty
NOTE: 3.9.3 Content Selection page 35 defines the procedure for choosing Riverain derived objects.

### 3.8.3 FOLDER INBOXES / OUTBOXES

The Folder Inbox / Outbox Management page displays the list of configured folder sources and destinations. Before mapping an Inbox or Outbox folder, the directory must exist.

#### 3.8.3.1 CREATING AN INBOX FOLDER

To create an inbox where the ClearRead CT™ system watches for files and imports files for processing, press **[Add Inbox]**.

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enable folder inbox</td>
<td>If checked, the device is enabled.</td>
<td>Checked</td>
</tr>
<tr>
<td>Local folder path</td>
<td>Absolute local folder path on the system where input files should be monitored.</td>
<td>Blank</td>
</tr>
<tr>
<td>File filter</td>
<td>File pattern expression of files to import into the system for processing. Wildcard expression such as * for zero or more characters and ? for one character.</td>
<td>*</td>
</tr>
<tr>
<td>Exclude from acquisition time latency filter</td>
<td>Only applicable if “Acquisition time delay filtering” under the Image Input is enabled. If checked, the images received from this device will not be checked by the acquisition time recorded in the DICOM header.</td>
<td>Unchecked</td>
</tr>
</tbody>
</table>
3.8.3.2 Creating an Outbox Folder

To create an outbox where the ClearRead CT™ system delivers derived DICOM content, press [Add Outbox].

<table>
<thead>
<tr>
<th>Setting</th>
<th>Description</th>
<th>Default Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enable folder outbox</td>
<td>If checked, the device is enabled.</td>
<td>Checked</td>
</tr>
<tr>
<td>Local Folder Path</td>
<td>The location where derived output images are deposited</td>
<td>Blank</td>
</tr>
<tr>
<td>Output transfer syntax</td>
<td>The transfer syntax of the derived object saved to the outbox location.</td>
<td>JPEG Lossless</td>
</tr>
<tr>
<td>Derived Object Storage</td>
<td>The Riverain derived objects that will be save to the outbox destination.</td>
<td>Empty</td>
</tr>
</tbody>
</table>

NOTE: 3.9.3 Content Selection page 35 defines the procedure for choosing Riverain derived objects.

3.9 Image Workflow

The Image Workflow settings manage the workflow configuration of the image processing pipeline. Each image that is sent to the device must undergo a series of processing steps as it progresses through the image processing pipeline. These workflow steps are arranged under the Image Workflow navigation menu in the order executed by the device.

The Image Workflow processing steps include:

1. DICOM Image Filter - responsible for discarding DICOM objects not intended to be processed by the device
2. Priority Selection - responsible for assigning a processing priority to a Source image. Images are processed in priority order and then order received.
3. Content Selection - responsible for choosing the specific ClearRead content produced for a given source image.
4. Patch - responsible for customizing the ClearRead derived object DICOM header, if needed, to aid with custom integration scenarios.

The workflow steps share a common user interface configuration approach. The workflow areas have specific actions available that define what the device can perform as the image passes through each workflow step.

Each workflow area is composed of two screens: a screen which summarizes all the actions defined for a given workflow area and a details screen that is displayed when an existing action is selected for editing or a new action is added.
The action summary screen lists a description assigned to each action along with its active status. A few of the workflow areas will have additional attributes to denote the action is a read-only system provided action that is not modifiable and/or a priority attribute if the order in which the actions are performed are significant. Unless noted in the specific workflow section below, all active rule actions will be evaluated.

Any workflow action can be conditionally performed based on DICOM header tag values and image transport related metadata such as association application entity titles or file names.

By default, when an action is added to a workflow area, it is defined to be performed unconditionally. An example action for the DICOM Image Filter is depicted below.

Clicking the small down arrow to the left of the action will present menu options for conditionally applying the action.

The [Add a new comparison condition] option builds a conditional statement based on the value of a data element found in either the DICOM header or transport metadata. Elements of the condition statement can be selected and edited by clicking the hyperlinked words in the statement. The associated action will only be performed when the specified conditions are satisfied.
Once a data element of interest is identified, a comparison operation can be chosen.

A comparison is performed against a literal text or numeric value. The [in] and [not in] comparison operations permit comparison against one or more pipe delimited values as depicted below.

More than one condition can be applied to an action. The [any] and [all] predicate determines if all conditions must be satisfied before the action is performed or if only one condition must be satisfied. The [any] predicate is equivalent to a logical OR operation and the [all] predicate is equivalent to a logical AND operation.
Nested conditions can be created by choosing the [Open a bracket] option.

The rule below illustrates a condition built with three predicate brackets consisting of an outer [all] and nested [any] predicates.

The predicate brackets provide a means of parenthetical grouping of logical operations such that the evaluation order and logical combination of conditions can be prescribed to achieve fairly complex conditions.

The arrow menu to the right of the condition statements provide a deletion option.
The following sections will detail the actions unique to each workflow area. The ability to conditionally perform any action just described applies to any action in any workflow area documented below.

Whenever an action or condition needs to refer to a specific ClearRead derived object, a Derived Code documented in the device’s DICOM Conformance Statements will be used for identification purposes. The derived object codes and their description are summarized in section 3.8.1 Configuring Derived Image Output Preferences on page 21.

3.9.1 DICOM IMAGE FILTER

The DICOM Image Filter is used to restrict the DICOM images the device will process. The ClearRead CT products are intended to process only adult chest computed tomography cross-sectional series acquired with the gantry perpendicular to the patient table. A default discard ruleset is shipped with the product and should be reviewed and modified as needed for the site.

The summary screen provides commands for resetting the rules to installation defaults and adding a new image discard rule.

The device rules [ignore images missing pixel information] and [ignore images with decubitus left or right patient position (0018,5100)] are required and cannot be edited or deleted as these values are critical for image processing purposes.
The dropdown [Enabled] box may be used to enable or disable all filtering rules at once. Unless there is a compelling reason, DICOM Image Filter should be Enabled at all times.

A checkmark next to a filtering rule indicates that it is active. If there is no checkmark then it is disabled and ignored by the device.

Click 💾 next to a filtering rule to view its detailed conditions. For example, the rule for [Ignore images missing pixel information] is as below

<table>
<thead>
<tr>
<th>Description</th>
<th>Active</th>
<th>Read-only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ignore images missing pixel information</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore images with ducutus lett or right patient position (0018,5100)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore Riverain derived images (0008,0070)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore images without rescale intercept (0028,1052) or rescale slope (0028,1053)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore images other than chest, lung or thorax</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore images which are not CT modality (0008,0060)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore scout images where image type (0008,0008) contains LOCALIZER</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore scout images by series description (0008,103e)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore images where gantry is tilted (0018,1120)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore unsupported SOP classes (0008,0016)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore unsupported transfer syntaxes (0002,0010)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore pediatric images</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ignore scout images where rows or columns are less than or equal to 64 pixel</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
This screen allows you to:

- Modify or add a rule **description** used for identification and logging purposes.
- Enable or disable rule.
- Define execution conditions.
- Set the logging level of the rule to **error**, **warn**, **info** or **trace**. The default level is **info**.

To enable or disable a filtering rule, click ✅ next to a filtering rule, and then select or deselect **Enable Rule**.

**NOTE:** Rules can only be defined to reject input images.

To create an entirely new rule, click ⬅️ **Add Rule**. New rules are created using the same screens described above.

To delete a rule click ⭕️ next to the filtering rule.

**NOTE:** A warning message is displayed before the rule is deleted. This operation cannot be undone.

Rules with the read-only, ⛔️, symbol cannot be deleted.

Click ⬛️ **Reset Rules** to apply the factory default settings for DICOM header filtering. A warning is displayed: “Are you sure you want to reset DICOM Image Filter rules?” Click **OK** to apply the factory default settings, or **CANCEL** to retain the current rules. Reset rules will delete any existing custom rules.

### 3.9.2 Priority Selection

The Priority Selection screen displays any rules that manipulate the ClearRead processing priority. Input images are normally queued by the device for image processing based on arrival time. If needed, the processing priority in the queue can raised or lowered based on DICOM header values or transport metadata.

The following priority levels, in descending priority order, can be assigned during this workflow step:

1. Stat
2. Urgent
3. Routine (default level)
4. Elective
A checkmark next to a processing priority rule indicates that it is active. If there is no checkmark then it is disabled and ignored by the device.

Click □ next to a processing priority rule to view its detailed conditions:

To create an entirely new rule, click + Add Rule. The below screen shows an example processing priority rule.

This screen allows you to:
- Modify or add a rule **description** used for identification and logging purposes.
- Enable or disable rule.
- Define execution conditions.
- Set the processing priority of the study to **stat, urgent, routine** or **elective**. The default processing priority is **routine**.

To enable or disable a processing priority rule, click  next to a process rule, and then select or deselect **Enable Rule**.

**NOTE:** Clicking the advanced button will enable manual writing of the rule and syntax checking. This is not recommended without advanced knowledge of allowable processing parameters.

To delete a rule click  next to the input image purpose rule.

**NOTE:** A warning message is displayed before a custom input image purpose rule is deleted. This action cannot be undone.

### 3.9.3 Content Selection

The Content Selection screen defines which derived objects should be generated by the device. The content selection rules can be as simple as always generating a bone suppressed image for any input image to tailoring the derived image generated based on a value found in the calling AE title or DICOM header.

**NOTE:** Content selection rules define under which conditions licensed derived objects are generated and become available in the image cache. For automated image distribution, a storage destination must be configured along with its derived object storage preferences.

A checkmark next to a content selection rule indicates that it is active. If there is no checkmark then it is disabled and ignored by the device.

Click  next to a content selection rule to view its detailed conditions:

To create an entirely new rule, click **Add Rule**.
This screen allows you to:

- Modify or add a rule description used for identification and logging purposes.
- Enable or disable rule.
- Configure the derived object to be generated by its Derived Code.
- Define execution conditions.

To enable or disable a derived content selection rule, click the pen icon next to a derived content selection rule, and then select or deselect Enable Rule.

To delete a rule click the trash icon next to the derived content selection rule.

**NOTE:** A warning message is displayed before a custom derived content selection rule is deleted. This action cannot be undone.

### 3.9.4 Patch

The Patch screen configures instructions for modifying the generated derived image DICOM header. Derived image DICOM header patches can be used to fix hanging protocol issues, which usually only become apparent after on-site installation. Derived Image DICOM header patch rules manipulate DICOM tags during derived image fabrication.

**NOTE:** Derived Image DICOM header patching can create nonconforming DICOM messages.
By default, there are no derived image DICOM header patch rules and the corresponding screen is empty as shown below:

A checkmark next to a patch rule indicates that it is active. If there is no checkmark then it is disabled and ignored by the device.

Click next to a patch rule to view its detailed conditions:

To create a new rule, click . A new screen with categories of patch action rules that can be added appears.

The following patch actions are supported:

1. Assign literal value to derived DICOM element - assigns a constant literal text or numeric value to a specified DICOM header element.
2. Assign numeric expression to derived DICOM element - select a numeric DICOM tag from either the source or prior DICOM header and perform addition or subtraction with a literal numeric value before assigning to a specified DICOM header element.
3. Copy a source DICOM element to a derived DICOM element - copy a single DICOM element from either the source or prior image into a specified DICOM header element.
4. Copy an entire DICOM group from a source image - copies an entire DICOM group from either the source or prior image into the derived object. Useful for retaining a vendor’s private DICOM group in derived objects.

5. Remove a DICOM element from a derived image - deletes the specified DICOM header element from the derived object

For example select “Assign literal value to derived DICOM element”.

Patch action conditions provide the additional comparison options [prior] and [derived-code]. These comparison conditions allow a patch action to be optionally constrained by prior DICOM header values and restrict actions to specific derived objects identified by their derived code.

This screen allows you to:
- Modify or add a rule **description** used for identification and logging purposes.
- Enable or disable rule.
- Assign execution priority.
- Specify parameters for various patch actions.

**NOTE:** If you define a condition for a multi-valued tag, do not specify a higher value position than the highest one available in the DICOM header. For example, if there are currently two values for the multi-valued tag (0008,0008), you can specify (0008,0008)[0] and (0008,0008)[1], but not (0008,0008)[2].

- Define execution conditions.

To enable or disable a derived image DICOM header patch rule, click  next to a patch rule, and then select or deselect **Enable Rule**.

Click on advanced to view the detail conditions as a formula:

To delete a rule click  next to the DICOM header patch rule.

**NOTE:** A warning message is displayed before a custom derived image DICOM header patch rule is deleted. This action cannot be undone.

The derived image fabrication process applies the patch rules in the order that they are prioritized in the list of rules. To change this order click the  by any rule, and then click on the new updated execution priority level.

### 3.10 DEVICE LOGS

Riverain ClearRead CT™ provides a unified logging system to help diagnose issues encountered during receiving, processing and sending of images. A typical device log screen is shown below
There are five log levels that may be recorded. These include SYSTEM, INFO, WARN, ERROR and TRACE. The first four are always available; the last level, Trace, is only available if verbose logging is enabled in the system settings.

**NOTE:** Verbose logging should only be enabled for temporary troubleshooting.

The device log files can be filtered by entering criteria in the search textbox and pressing the search button to perform the search. Searchable fields are level, source, id and message fields. Without search keys, only the message data is selected for criteria matching. To search by the other fields, the keywords level, source and id followed by a colon and the search term must be entered.

**EXAMPLE:** To search by id 6 and derived object C0001, enter the following in the search field:
To undo the filter, press the search button with no criteria selected.

3.10.1 Viewing Transactional Logs

Transactional logs can be viewed by selecting the ID hyperlink in the ID column in the device logs. The transaction allows for viewing processing status, metadata, derived objects and logs.
### Transaction #1

#### Transaction Details

- **Id**: 1
- **Created Date**: 2016-07-29 16:46:06
- **Completed Date**: 2016-07-29 16:52:54
- **Status**: Completed

#### Derived Objects

<table>
<thead>
<tr>
<th>Derived Code</th>
<th>Status</th>
<th>Created Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C200</td>
<td>Success</td>
<td>2016-07-29 16:46:06</td>
<td>Vessel suppressed</td>
</tr>
<tr>
<td>C200X</td>
<td>Success</td>
<td>2016-07-29 16:46:06</td>
<td>Vessel suppressed with CAD</td>
</tr>
<tr>
<td>C300</td>
<td>Success</td>
<td>2016-07-29 16:46:06</td>
<td>Vessel suppressed with CAD overlay</td>
</tr>
<tr>
<td>C200X</td>
<td>Success</td>
<td>2016-07-29 16:46:06</td>
<td>Vessel suppressed CAD GSHP</td>
</tr>
<tr>
<td>C201</td>
<td>Success</td>
<td>2016-07-29 16:46:06</td>
<td>Primary volume with CAD</td>
</tr>
<tr>
<td>C201X</td>
<td>Success</td>
<td>2016-07-29 16:46:06</td>
<td>Primary volume with CAD overlay</td>
</tr>
<tr>
<td>C201X</td>
<td>Success</td>
<td>2016-07-29 16:46:06</td>
<td>Primary volume CAD GSHP</td>
</tr>
</tbody>
</table>

#### Metadata

- **asession**: 281949762494126
- **derived-series-instance-uid-root**: 1.3.6.1.4.1.11177.120203.123.4916152362610157
- **dcm-getway.series-set**: CLEARREAD_STORE
- **dcm-getway.series-set**: STOREDCU
- **dcm-getway.series-set**: 127.0.0.1
- **dcm-getway.file-size**: 526006
- **dcm-getway.file-time-stamp**: 2016-07-29 16:46:02.352662Z
- **dcm-getway.patient-id**: [redacted]
- **dcm-getway.series-instance-uid**: 1.3.6.1.4.1.14195.2.1.6279.6001:32790563606491776343487482
- **dcm-getway.scp-instance**: [redacted]
- **dcm-getway.study-instance-uid**: 1.3.6.1.4.1.14195.2.1.6279.6001:234120322390750350050505667
- **dcm-acquisition-time-filter**: false
- **first-frame-index**: 0
- **frame-count**: 23
- **instance-number**: 37
- **inverted**: 0
- **last-frame-index**: 32
- **modality**: CT
- **patient-age**: 71
- **patient-id**: [redacted]
- **priority**: 60
- **requested-derived-objects**: C200X
- **roi-count**: 5
- **sdx-invoked**: true
- **series-instance-uid**: 1.3.6.1.4.1.14195.2.1.6279.6001:32790563606491776343487482
- **series-number**: 3000061
- **scp-axiss-uid**: 1.2.240.1000.0.1.4.1.2
- **scp-instance-uid**: 1.3.6.1.4.1.14195.2.1.6279.6001:491527530687632772137333509657
- **station-name**: [redacted]
- **study-date**: 2000-01-01T00:00:00.000000Z
- **study-instance-uid**: 1.3.6.1.4.1.14195.2.1.6279.6001:234120322390750350050505667
- **timezone**: -0400
- **transaction-id**: 1

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
3.10.1.1 OVERVIEW

The transaction details displays the processing status, creation data, completion date and processing metadata. If the transaction has not been removed from the cache by system maintenance, then derived objects will be listed and available in the DICOM tab. Otherwise, the deleted date will be displayed and no derived objects will be available to view or download.

If derived objects are still available, they can be manually sent to configured DICOM C-STORE and folder destinations by selecting the drop-down to the right of the listed object and selecting the destination. Alternatively, the derived object can also be downloaded through the web browser by selecting download from the same drop-down list.

3.10.1.2 DICOM

The DICOM tab displays the DICOM header and thumbnail for each DICOM object related to the transaction including the source and derived objects. Each DICOM object can be viewed by navigating with the pager control at the top of the page.
Once selected, the DICOM header will be available to view. The DICOM image as a thumbnail can also be viewed by hovering over the picture icon located in the top right corner of the DICOM header details. The DICOM tab cannot be
selected for viewing, if the corresponding images are deleted from the system cache due to house keeping.

### 3.10.1.3 Logs

The Log tab displays related log messages to the transaction once the file has been staged in the ClearRead CT™ application for processing. All details about the origination of the source image will not be displayed. For this information, please refer to the full log details.

### 3.11 Testing the Riverain System After Installation

Once the Riverain system has been configured, check the following:

- Is the server properly connected to the network?
- Is the system software functioning properly? This procedure is performed separately for the ClearRead Bone Suppression, +Detect, +Compare, +Confirm, and Enhanced systems.

### 3.12 Testing the Basic Network Connection

Perform this procedure for all Riverain systems.

1. Make sure that you have the correct gateway IP address, and that the gateway will respond to pings.
2. Double-click the Command Prompt on the desktop.
3. In the Command Prompt screen, type `Ping <gateway IP address>`, and then press ENTER. (Type the actual gateway IP address, without the corner brackets.)
4. Verify that the Command Prompt screen displays the expected ping response with 0% packet loss.
5. If the ping command fails, obtain an alternate address from a responsible administrator at the installation site and repeat the test.
6. Close the Command Prompt screen.

### 3.13 Performing a System Self-Test

1. Open the ClearRead CT™ Administration Console from the Start menu. (Start>Riverain>ClearRead CT>Admin Console)
2. Enter password to access the ClearRead CT™ Administration Console.
3. Click on Device Details
4. Click on the Started button and select Self Test.
5. A message will display indicating the Self Test has started.
6. During the test the Testing status button will be displayed.
7. A message will display that the Device self-test succeeded and the status will change back to Started.
Report any failure event to the Riverain Technologies Customer Care Hotline at +1.800.914.1446 or +1.937.425.6950.

4 Servicing the Riverain System On-Site

The following table lists the hardware FRUs and part numbers (P/N) included in servers provided by Riverain. For systems provided by Riverain in a software-only format, the only FRU is the HASP Micro Key, whose replacement is described on p. 56.

<table>
<thead>
<tr>
<th>Description</th>
<th>Riverain P/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dell T110 Power Supply Assembly</td>
<td>-0716-03</td>
</tr>
<tr>
<td>Dell T610 DVD-ROM Drive Assembly²</td>
<td>-0223-02</td>
</tr>
<tr>
<td>HASP Micro Key</td>
<td>-0717-01</td>
</tr>
<tr>
<td>HASP SL Key</td>
<td>-0721-01</td>
</tr>
<tr>
<td>Riverain programmed HD Drive</td>
<td>-0225</td>
</tr>
<tr>
<td>Riverain T110 Subassembly</td>
<td>-0916</td>
</tr>
</tbody>
</table>

This manual includes testing and replacement procedures for hardware components. To replace software components, replace the entire HD Drive Assembly with a pre-programmed replacement HD Drive Assembly, as described in Section Replacing the HD Drive Assembly, p. 55.

4.1 BEFORE SERVICING THE RIVERAIN SYSTEM

Prior to the date of service, call the responsible administrator at the installation site to make sure that a keyboard, monitor, and mouse are connected to the server.

4.2 UPDATING AND UPGRADING WINDOWS

Riverain does not recommend Automatic Updates for Windows be enabled.

WARNING: This system is a medical device. It should be used only as described in the accompanying Riverain Technologies manuals. Other activities (such as web browsing, email, or installation of third-party software without specific authorization from Riverain Technologies) are prohibited. Software authorized by Riverain Technologies should be scanned with anti-virus software before use.

² The Dell T610 DVD-ROM Drive Assembly can also be used for the Dell T110.
4.3 LICENSING

4.3.1 IMPORTING A LICENSE FILE

Your system has either a USB-based HASP license key or a HASP-SL license key that defines the number of DICOM origin devices that can be configured for each Riverain device. This number is sometimes referred to as the number of “ports” or “modalities.”

You might be provided with a new license file in order to change the number of licensed devices, or to replace a damaged license file. The new license file might be provided on a USB memory stick, or as an attachment to an e-mail, or via some other media.

To import a new license file:

1. Copy the license file onto the Windows desktop.
2. The license file name is in the format nn-xxxx.ini, where nn-xxxx indicates the unit serial number.
   Make sure that the serial number in the license file name matches the serial number printed on top of the server.
3. Open the ClearRead CT™ Administration Console from the Start menu.
   (Start>Riverain>ClearRead CT>Admin Console)
4. Enter password to access the ClearRead CT™ Administration Console.
5. Click on Device Details
6. Click on License
7. Click on Import License
8. The Import License File window will pop-up with a message to Select a license file to install or update.
9. Click Import
4. Select the license file, and then click Open.
5. After a successful import a message will display, “Successfully imported license.”
12. Delete the license file from the Windows desktop and empty the Recycle Bin.
13. To test the new license file, see 3.11 Testing the Riverain System After Installation page 45.

4.3.2 EXPORTING LICENSE DETAILS

This function exports certain license information to a file. To export the information:

1. Open the ClearRead CT™ Administration Console from the Start menu.
   (Start>Riverain>ClearRead CT>Admin Console)
2. Enter password to access the ClearRead CT™ Administration Console.
3. Click on Device Details
4. Click Export License
5. Save dialog box will appear at the bottom of the browser window.

6. Click the drop down selection arrow next to Save and select Save As to choose the location for your exported license file.

4.4 CONFIGURING THE “HOSPITAL” USER PASSWORD

Servers provided by Riverain have three users defined under Windows: “Administrator,” “RMService,” and “Hospital.”

- All hospital system administrators who administer the Riverain system must log in as “Hospital.”
- If you are logging in as a Riverain employee or distributor, log in as “RMService.”

The Riverain system is initially configured with a user password for “Hospital” that is either requested by, or provided to, the installation site. You can change the user password as needed. Note that these users are not defined for systems provided by Riverain in a software-only format for installation on customer-provided hardware.

4.5 DEVICE LOG FILES

The Riverain system includes the device logs in the ClearRead CT™ Administration Console. For more details on logging, please refer to section 3.10 Device Logs on page 39.

4.6 OTHER SYSTEM DIAGNOSTIC ACTIVITIES

4.6.1 WORKING WITH WINDOWS SERVICES

The major functions of the device – receiving original images, receiving queried prior images, processing images through Riverain devices, and sending Riverain output objects – are implemented through a Windows service. It is started when the Riverain system boots up and run continuously. The Riverain Windows service that starts automatically is:

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riverain ClearRead CT™</td>
<td>Provides Riverain ClearRead CT image processing</td>
</tr>
</tbody>
</table>

Note that Riverain Windows service is defined as Automatic, meaning that it starts automatically while other Windows services that are defined as Automatic are starting. If you restart Windows, launch the ClearRead CT™ Admin Console and confirm that the status is Started.

You can restart all Windows Services using any of these methods:
- Restarting the Riverain ClearRead CT service through the Windows Service Control Manager by accessing Administrative Tools -> Services.
- Restarting Windows on the server

**4.6.2 Testing the Remote Access Connection**

**NOTE:** If the installation site does not allow remote access to TeamViewer, you cannot test the remote connection.

To check if TeamViewer has successfully connected to the cloud services, hover the mouse over the TeamViewer icon in the system tray, left click and a panel opens:

![TeamViewer Icon](image)

If the ‘Ready to connect (secure connection)’ is available and the X’s are replaced with an ID number, the system is available for remote access via TeamViewer. If the system is not ‘Ready to connect’, please have the local system administrator or information services team check that the port you are using (80, 443, or 5938) is available and open for outbound communication.

**4.7 Dell PowerEdge Server**

**4.7.1 Testing the Server**

To test the Server:

1. If the monitor displays the Windows desktop, the Server is operational.
2. If the monitor does not display the Windows desktop, use this flowchart:
Refer to the following Dell T110 front panel image for the location of the system health indicator.

![Dell T110 front panel image with power button and system health indicator highlighted.](image)

3. If resetting the server does not solve the problem, select one of these actions:
   - If you determine that there is a general hardware failure, replace the server as described in the next section.
   - If you determine that there is a specific failure of the HD Drive Assembly, see Section Replacing the HD Drive Assembly, p. 55.

### 4.7.2 Replacing the Server

**CAUTION:** Because of the size and weight of the server, never attempt to lift it by yourself.
Before you replace the entire server, consider the possibility of a HD Drive Assembly failure. If you determine that there is a failure of the HD Drive Assembly, see Section Replacing the HD Drive Assembly, p. 55.

Also, note that the following instructions include steps for backing up and restoring system configuration files, backing up and restoring TCP/IP settings, and deleting files prior to shipment. Depending on the extent to which the server is defective, this might not be possible.

4.8 BACKING UP FILES AND SETTINGS

To back up files and settings:

1. If the unit is not currently logged on to Windows, log on with the user name **RMService**.

   **NOTE:** This user name is not defined for systems provided by Riverain in a software-only format for installation on customer-provided hardware.

2. Open the ClearRead CT™ Administration Console from the Start menu. (Start>Riverain>ClearRead CT>Admin Console)

3. Enter password to access the ClearRead CT™ Administration Console.

4. Click **Device Details**.

5. Click Backup tab.

6. Click **Backup** button.

7. Insert a USB memory stick into the server.

8. Save dialog box will appear at the bottom of the web browser.

9. Click the drop down selection arrow next to **Save** and select **Save As** to choose the location for your backup.

10. Browse to the USB memory stick and save .bak file.

11. Close all open windows. Remove the USB memory stick from the server and retain for later use.

12. If the USB memory stick has a write protection tab, use it to protect your data.

4.9 DELETING FILES PRIOR TO SHIPMENT

To delete files prior to shipment:

1. Open the ClearRead CT™ Administration Console from the Start menu. (Start>Riverain>ClearRead CT>Admin Console)

2. Enter password to access the ClearRead CT™ Administration Console.
3. Click Data Interchange -> Folder Inboxes/Outboxes
4. Note the Folder Locations.

![Folder Inbox / Outbox Management](image)

5. Close the ClearRead CT™ Administration Console.
6. Go to Start>Riverain>ClearRead CT>Uninstall
7. Click ‘Yes’ to remove ClearRead CT.
8. Using Windows Explorer delete the Inbox and Outbox folders.

### 4.10 REPLACING THE HARDWARE

To replace the currently installed server:

1. Shut down Windows.
2. Make sure that the power on all components is off.
3. Unpack the replacement server. Make sure that the replacement server is the **same model** (i.e., Dell T110) as the currently installed server.
4. Detach the LAN cable that connects the rear of the currently installed server to the local network.
5. Detach the HASP Micro key, if available, from the currently installed server and connect it to the replacement server. The replacement server will not function without the HASP key.

   **NOTE:** It is recommended that you store the HASP key in a labeled plastic bag whenever you have to keep the HASP key separate from the server. The HASP key itself has no identifying marks.

6. Detach the currently installed server from the monitor.
7. Detach the currently installed server from the electrical outlets.
8. Pack the **removed** server for shipping.
9. Connect the power socket on the server to electrical power, using the power cable.

   **NOTE:** Connecting the power cable establishes grounding connections for the Riverain system. As soon as you connect the server to the electrical outlet, the server will immediately turn on.
10. Attach the LAN cable from the local network to the network port labeled “1” on the rear of the server.
11. Connect the monitor to the blue video port on the rear of the replacement server, using the video cable.
12. Connect the keyboard to a USB port on the rear of the replacement server.
13. Connect the mouse to a USB port on the rear of the replacement server.
14. Turn on the monitor and the replacement server.
15. Repeat the procedure on p. 49 for testing the server.

You should have been provided with a new license file in order to assign your existing licenses to the replacement server. The new license file might be provided on a USB memory stick, as an attachment to an e-mail, or via some other media.

To install the new license file, see Section Licensing, p. 47.

4.11 RESTORING BACKED-UP FILES AND SETTINGS

To restore backed-up files and settings:

1. Insert the USB memory stick into the server with the .bak file.
2. Open the ClearRead CT™ Administration Console from the Start menu. (Start>Riverain>ClearRect CT>Admin Console)
3. Enter password to access the ClearRead CT™ Administration Console.

4. Click Device Details.
5. Click Backup tab.
6. Click Restore button.
7. Restore Configuration Backup windows pops-up. Select a configuration backup file to restore by clicking Choose File...
8. Click Open
9. Click Restore
10. After a successful restore this message will display: Device configuration successfully restored.
11. Remove the USB memory stick from the server.

4.12 DELL DVD-ROM DRIVE ASSEMBLY

4.12.1 TESTING THE DVD-ROM DRIVE ASSEMBLY

The DVD-ROM drive is used to install and reinstall software, as well as to transfer files to the Riverain system from systems that are not connected to the DICOM network.

To test the DVD-ROM Drive Assembly:
1. Make sure that the power for the server is on and that Windows has fully started.
2. Test the DVD-ROM Drive Assembly according to this flowchart:

   Insert a DVD-ROM into the DVD-ROM drive of the server assembly
   Using Windows Explorer, view the contents of the DVD-ROM
   DVD-ROM content viewable?
   Yes
   DVD-ROM drive assembly is operational
   No
   DVD-ROM drive assembly is defective

3. If the DVD-ROM Drive Assembly is defective, replace it as described in the next section.

4.12.2 REPLACING THE DVD-ROM DRIVE ASSEMBLY

To replace the currently installed DVD-ROM Drive Assembly, follow the instructions in the Dell Hardware Owner’s Manual, which has been provided to you on the CD labeled “Riverain User and Installation Manuals.”

Make sure that the replacement DVD-ROM Drive Assembly is for the same model (i.e., Dell T110) as the server. Pack the removed DVD-ROM Drive Assembly for shipping to Riverain Technologies.

After you replace the DVD-ROM Drive Assembly, repeat the procedure above for testing the DVD-ROM Drive Assembly.

4.13 DELL HD DRIVE ASSEMBLY

4.13.1 TESTING THE HD DRIVE ASSEMBLY

To test the HD Drive Assembly:

1. Make sure that the power for the server is on and that Windows has fully started.
2. If the Computer icon is displayed on the Windows desktop, double-click it. If the Computer icon is not displayed, click the Start button, and then click Computer.
3. In the Computer screen, right-click the C: drive and select Properties from the popup menu.
4. In the Properties screen, click the Tools tab.
5. In the Tools tab, in the Error Checking panel, click Check Now.
6. In the Check Disk screen, clear the Automatically fix file system errors check box and check the Scan for and attempt recovery of bad sectors check box.
7. Click Start.
8. A message is displayed: “Do you want to check for hard disk errors the next time you start your computer?” Click Schedule Disk Check.
9. Click **Start**, and then **Shut Down**. Select **Restart** from the drop-down list, and then click **OK**.

10. If the HD Drive Assembly is defective, replace with a pre-programmed replacement HD Drive Assembly as described in the next section.

### 4.13.2 REPLACING THE HD DRIVE ASSEMBLY

The replacement part must be the programmed HD Drive listed in the Field Replaceable Unit (FRU) List on p. 46 (Riverain P/N -0225).

The following instructions include steps for backing up and restoring system configuration files, backing up and restoring TCP/IP settings, and deleting files prior to shipment. Depending on the extent to which the HD Drive Assembly is defective, this might not be possible.

To replace the currently installed HD Drive Assembly:

1. Follow the instructions in Section Backing Up Files and Settings, p. 51.
2. Follow the instructions in Section Deleting Files Prior to Shipment, p. 51.
3. Unpack the pre-programmed **replacement** HD drive assembly. Save the shipping materials for use with the currently installed HD drive assembly to be shipped back to Riverain Technologies.
4. Write down the serial number of the pre-programmed **replacement** Dell HD drive assembly on the Service Report (QU-1041A).
5. To replace the currently installed HD Drive Assembly, follow the instructions in the Dell Hardware Owner’s Manual, which has been provided to you on the CD labeled “Riverain User and Installation Manuals.” In some cases, you might need to remove the hard drive from its bracket with a screwdriver.

<table>
<thead>
<tr>
<th>CAUTION: The surface of the HD Drive Assembly may be hot. Use caution when removing it from the server.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Write down the serial number of the <strong>removed</strong> Dell HD drive assembly on the Service Report (QU-1041A).</td>
</tr>
<tr>
<td>7. Pack the <strong>removed</strong> HD Drive Assembly for shipping to Riverain Technologies.</td>
</tr>
<tr>
<td>8. Turn on the server and log on with the user name <strong>RMSERVICE</strong>.</td>
</tr>
<tr>
<td><strong>NOTE:</strong> This user name is not defined for systems provided by Riverain in a software-only format for installation on customer-provided hardware.</td>
</tr>
<tr>
<td>9. Repeat the procedure on p. 54 for Testing the HD Drive Assembly.</td>
</tr>
</tbody>
</table>

To restore backed-up files and settings after replacing the HD Drive Assembly, and to restore the computer name:
1. Follow the instructions in Section Testing the HD Drive Assembly, p. 54.
2. Follow the instructions in Section Restoring Backed-up Files and Settings, p. 53.
3. Click Start, and then Settings, and then Control Panel. In the Control Panel, double-click System.
4. In the System Properties screen, click the Computer Name tab.
10. Make sure that the Computer Name matches the Riverain Device serial number as printed on top of the server.
11. Close all open windows.
7. Close all open windows.

4.14 SYSTEM SOFTWARE
Software components should be replaced by replacing the currently installed HD Drive Assembly with a pre-programmed replacement HD Drive Assembly, as described in Section Replacing the HD Drive Assembly.

4.15 DELL POWER SUPPLY ASSEMBLY
The Dell T110 server Assembly has a single Power Supply Assembly. Do not shut down Windows or shut off power to the Riverain system before testing the Power Supply Assemblies.

To replace a defective Power Supply Assembly, follow the instructions in the Dell Hardware Owner’s Manual, which has been provided to you on the CD labeled “Riverain User and Installation Manuals.”

CAUTION: The surface of the Power Supply Assembly may be hot. Use caution when removing it from the server.

4.16 HASP MICRO KEY (DONGLE)
The software is protected from unauthorized duplication and usage by either a HASP Micro key or HASP-SL software key. The Riverain system will not operate unless the HASP key attached to the server is programmed for that specific server. The HASP Micro key has the word “HASP” imprinted on one side.

NOTE: The HASP Micro key can require up to 900mA power. If you attach additional accessories to USB ports that share power with the USB port used for the HASP key, excessive power draw by those additional accessories can prevent the HASP key from functioning normally.
4.17 REPLACING THE HASP MICRO KEY
The currently installed HASP key is connected to a USB port on the front of the server. To replace the currently installed HASP key:

1. Shut down Windows.
2. Make sure that the power on all components is off.
3. Inspect the HASP key shipping envelope for damage. If damaged, report this to your supervisor before continuing.
4. Open the shipping envelope. Remove the pre-addressed return envelope and the replacement HASP key (inside a zipper plastic bag) from the shipping envelope.

**NOTE:** Do not remove the replacement HASP key from the zipper plastic bag until you have completed the following step.

5. The label on the zipper plastic bag specifies the server serial number. Verify that this information is correct.
6. Remove the replacement HASP key from the zipper plastic bag and place it on top of the server.

**NOTE:** At this stage, do not connect the replacement HASP key to the Server.

7. Remove the currently installed HASP key from the USB port on the front of the server and place it in the zipper plastic bag.
8. Use a black ink pen to write Returned on the HASP key bag label.
9. Place the zipper plastic bag with the removed HASP key in the pre-addressed return envelope and seal the return envelope.
10. Insert the replacement HASP key into a USB port on the front of the server.
11. Turn on the server.
12. Ship the removed HASP key in the pre-addressed return envelope to Riverain Technologies.

4.18 TROUBLESHOOTING FOR SYSTEM ADMINISTRATORS
The Riverain ClearRead CT™ system should be serviced only by an authorized service technician. However, before you contact Riverain Technologies for servicing, there are a number of test procedures that can clarify or even solve the problem you are experiencing.

Before troubleshooting the Riverain ClearRead CT™ system, verify that the monitor, keyboard, and mouse connections are correct.

**NOTE:** One alternative to using a monitor, keyboard, and mouse is to connect the Server to a KVM (keyboard/video/mouse) switch.
Since the Riverain system receives and sends data to the network without human intervention, there are normally only three indications of a system malfunction:

- For the Dell T110, the system health indicator blinks amber rather than continual green.
- A network error message from an origin device indicating that it could not send an image to the ClearRead CT™ system
- The failure of an expected image to arrive at a destination device from the ClearRead CT™ system

Following is a list of possible causes and their testing procedures and responses. If you complete this list and the problem persists, report the test procedures and results to the Riverain Technologies Customer Care Hotline at +1.800.914.1446 or +1.937.425.6950.

**Step 1. Is the Server turned on?**

If the Server is turned on, continue with the next step.

**For T110 servers provided by Riverain,** these indicate that the Server is turned on:

- The Server fan is audible.
- The system health indicator is lit continuous green or blinking amber.

![System health indicator](image)

**Step 2. Is the Server connected to the network?**

To test whether the Server is properly connected to the network:

a) Make sure that you have the correct gateway IP address, and that the gateway will respond to pings.

b) Double-click the Command Prompt on the desktop.

c) In the Command Prompt screen, type **Ping <gateway IP address>**, and then press ENTER. (Type the actual gateway IP address, without the corner brackets.)

d) Verify that the Command Prompt screen displays the expected ping response with 0% packet loss.

e) Close the Command Prompt screen.
f) If the Command Prompt screen did not display the expected ping response with 0% packet loss, report the test procedures and results to Riverain Technologies. Otherwise, continue with the next step.

Step 3. Restart Windows

If the Server is turned on and properly connected to the network, restart Windows. If the problem persists, continue with the following test procedures.

Step 4. Is the HASP® key plugged in?

Verify that the HASP key is fully plugged into a USB port on the front of the Server.

**NOTE:** The HASP key can require up to 900mA power. If you attach additional accessories to USB ports that share power with the USB port used for the HASP key, excessive power draw by those additional accessories can prevent the HASP key from functioning normally.

Step 5. Does the origin image fit the required parameters?

Verify these input image parameters:
- Digital file format (CT)
- Chest study
- Proper chest view (Not a scout, decubitus, or tilted acquisition)

Step 6. Is the origin device functioning properly?

If the origin device is capturing images, proceed to Step 7; if not, refer to origin device service provider.

Step 7. Is the origin device connected to the network?

If you have to reconfigure the origin device’s network connections, restart the origin device’s operating system before you continue troubleshooting.

Step 8. Is the origin device configured to send images to the Riverain ClearRead CT™ system?

If you have to reconfigure the origin device to send images to the Riverain system, restart the origin device’s operating system before you continue troubleshooting. See also section 3.9.1 DICOM Image Filter on page 31 for information about certain required DICOM attribute settings.

Step 9. Is the Riverain ClearRead CT™ system configured to receive images from the origin device?

See section 3.8.2.1 DICOM Station - Connection on page 22.

Step 10. Is the Riverain system configured to respond to pings from the origin device?
See section 3.8.2.1 DICOM Station - Connection on page 22 for pinging a remote AE station.

**Step 11. Is the Riverain ClearRead CT™ system configured to send images to the destination device?**

See section 3.8.2.1 DICOM Station - Connection on page 22 for configuring and performing a dicom C-ECHO.

**Step 12. Is the destination device functioning properly?**

Is the destination device receiving images from the modalities? If so, do the ClearRead CT™ transfer attempts show in the destination device logs? If not proceed to **Step 13**; otherwise, reconfigure devices to match expectations.

**Step 13. Is the destination device connected to the network?**

If you have to reconfigure the destination device’s network connections, restart the destination device’s operating system before you continue troubleshooting.

**Step 14. Is the destination device configured to receive images from the Riverain ClearRead CT™ system?**

If you have to reconfigure the destination device to receive images from the Riverain ClearRead CT™ system, restart the destination device’s operating system.

If you complete this list and the problem persists, report the test procedures and results to Riverain Technologies.

**Step 15. Is there a network routing or configuration issue?**

Check the configuration of any hospital network components, in order to ensure a clear path between the PACS, the various modalities, and the Riverain system.
Riverain Technologies
3020 South Tech Blvd.
Miamisburg, OH 45342-4860 U.S.A.
Phone: +1.937.425.6811
www.riveraintech.com

EMERGO EUROPE
Molenstraat 15
2513 BH, The Hague
The Netherlands
Phone: +31.70.345.8570
Fax: +31.70.346.7299

© 2002-2015 Riverain Technologies
ClearRead CT

DICOM Conformance Statement

Riverain Technologies
3020 South Tech Blvd.
Miamisburg, OH 45342-4860 U.S.A.
Phone: +1.937.425.6811
www.riveraintech.com

EMERGO EUROPE
Molenstraat 15
2513 BH, The Hague
The Netherlands
Phone: +31.70.345.8570
Fax: +31.70.346.7299

Document #LB-1176-05, DCN-draft, draft
Design Control Information

1: Introduction ...................................................................................................................................... 2
2: Design Control Process .................................................................................................................. 3
3: Device Risk Analysis ..................................................................................................................... 16
4: Project Plan ..................................................................................................................................... 25
5: Architecture Design Chart ............................................................................................................ 32
6: ClearRead CT Common Platform Software Requirements Specification (SRS) .......................... 33
7: ClearRead CT Algorithm Software Requirements Specification (SRS) ........................................ 42
8: ClearRead CT Software Design Specification (SDS) ................................................................... 46
9: Verification and Validation Activities .......................................................................................... 68
   9:1: Test Plan ................................................................................................................................... 68
   9:2: Traceability Matrix .................................................................................................................. 75
   9:3: Test Report ............................................................................................................................... 89
   9:4: Test Protocols .......................................................................................................................... 95
   9:5: Validation of Characterization Measurements .......................................................................... 218
   9:6: In House Algorithm Performance Testing .............................................................................. 230
10: Revision Level History ............................................................................................................... 235
11: Unresolved Anomalies (Bugs or Defects) .................................................................................. 237
1: Introduction

This appendix initially describes the Design Control Process that was used in the design and
development of ClearRead CT™, including:

- Design and Development Planning
- Design Input
- Design Output
- Design Review
- Design Verification
- Design Validation
- Design Transfer
- Design Changes
- Design History File

The rest of the appendix is comprised of the design and development records that were generated for ClearRead CT using the Design Control Process, including:

- Device Risk Analysis
- Project Plan
- Architecture Design Chart
- Software Requirement Specifications (SRS)
- Software Design Specification (SDS)
- Verification and Validation Documentation including Traceability
- Revision Level History
- Unresolved Anomalies (Bugs or Defects)
ROI Feature Descriptions

(b)(4)
# Clinical Information

1: Clinical Protocol ........................................................................................................................................... 2

<table>
<thead>
<tr>
<th>(b)(4)</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>47</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>52</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>56</th>
<th></th>
</tr>
</thead>
</table>

2: Clinical Report ..................................................................................................................................... 70

<table>
<thead>
<tr>
<th>(b)(4)</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>215</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>219</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>222</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>245</th>
<th></th>
</tr>
</thead>
</table>

| 286    | |
A Retrospective, Multi-Reader, Multi-Case, Reader study using ClearRead CT InSight

Clinical Study Protocol

Protocol Number: *(b)(4)*

Study Sponsor

Riverain Technologies, LLC

3020 South Tech Boulevard
Miamisburg, OH 45342-4860 USA

Phone (937) 425-6811
Fax: (937) 425-6493

March 30, 2015

Confidential
syngo LungCARE CT and syngo Lung CAD

syngo® LungCARE CT is designed to support the physicians in conforming the presence or absence of lung lesions, regular-size ground glass nodules (GGN), and small-size ground glass opacities (GGO). It allows for volumetric analysis of pulmonary lesions, aiding the user to assess nodule changes in their growth.

syngo LungCARE CT offers:

- Computer-guided localization of pre-marked lesion
- Close-up inspection of suspected lesion with the rotating MPR mode
- Automatic segmentation and volumetry measurements of lung lesions
- Visualization of the segmented lesions with perspective VRT displays or MPR techniques
- Dedicated and flexible reporting of all findings

The syngo LungCAD device is a computer-aided detection (CAD) tool designed to assist radiologists in the detection of solid pulmonary nodules.

* Only available on syngo MultiModal®y Workplace and on SOMATOM® Definition

syngo LungCARE CT and syngo Lung CAD

Computer-aided detection and follow-up support of pulmonary nodules

Answers for life.
Prerequisites

A contiguous high resolution volume dataset acquired with low dose technique.

Image Display

• 4-segment screen layout with:
  - 3D slab display for cine mode in MPR, MIP or VRT technique
  - Slice reference image
  - MPR slab reference image
  - Volume-of-Interest display for the selected nodule

Workflow

• Identification of lesions in the 3D slab segment by scrolling through the data with cine mode
• Marking of a lesion with one mouse click
• Close-up inspection of the lesion with a magnified rotating MPR around its axis to distinguish lung nodules from vessels
• Visualization of the segmented nodule in perspective rendering technique together with the original data
• Interactive viewing by rotating and zooming the volume rendered lung nodule
• Automatic calculation of the volume and diameter of the nodule
• Documentation and reporting
• Automated nodule matching in follow-up studies
• Automated dataset synchronization
  - “Get counterpart” functionality
  - History graphs

Quantitative Analysis

• Calculation of
  - Volume
  - Diameter in all three axes
  - Max/Min diameter of the nodule
  - HU histogram of the nodule
  - Average and standard deviation of the density in HU

Documentation and Reports

• Specific details such as the location, morphology, and characteristics of each lesion can be entered together with two images from the screen
• All information entered is saved as DICOM SR data
• Straightforward reporting with different output formats (e.g. PDF and html) and syngo Filming can be used for documentation

**syngo Lung CAD – Computer-aided Detection of Lung Nodules**

• syngo Lung CAD is an enhancement to the syngo LungCARE software package that supports the physician by providing an automated workflow

It is Designed

• Second reader tool for thoracic CT
• To increase diagnostic confidence by automatically displaying markers on pre-identified pulmonary lesions

It Offers

• Low-dose, high resolution CT imaging of suspicious pulmonary nodules
• Automated nodule segmentation
• DICOM compatible structured report functionality
• Computer-aided detection of lung nodules

* Only available on **syngo MultiModality Workspace** and on **SOMATOM Definition**

---

**Global Siemens Headquarters**

Siemens AG

Wittelsbacherplatz 2

80333 München

Germany

**www.siemens.com/healthcare**

---

**Legal Manufacturer**

Siemens AG

Wittelsbacherplatz 2

DE-80333 München

Germany

© 07.2009, Siemens AG

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Siemens AG Medical Solutions  
% James Kuhn Jr.  
Senior Regulatory Submissions Manager  
20 Valley Stream Parkway  
MALVERN PA  19355  

Re: K143196  
Trade/Device Name: syngo.CT Lung CAD  
Regulation Number: 21 CFR 892.2050  
Regulation Name: Picture archiving and communications system  
Regulatory Class: II  
Product Code: OEB  
Dated: April 20, 2015  
Received: April 22, 2015  

Dear Mr. Kuhn:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act’s requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.
If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, “Misbranding by reference to premarket notification” (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH’s Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Robert Ochs, Ph.D.
Acting Director
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure
Appendix E. Predicate Device Labeling

Indications for Use

510(k) Number *(if known)*

k143196

Device Name

syngo.CT Lung CAD

Indications for Use *(Describe)*

The syngo.CT Lung CAD device is a computer-aided detection (CAD) tool designed to assist radiologists in the detection of solid pulmonary nodules during review of multi-detector computed tomography (MDCT) examinations of the chest. The software is an adjunctive tool to alert the radiologist to regions of interest (ROI) that may have been initially overlooked. The syngo.CT Lung CAD device is intended to be used as a second reader after the radiologist has completed his/her initial read.

Type of Use *(Select one or both, as applicable)*

- [x] Prescription Use *(Part 21 CFR 801 Subpart D)*
- [] Over-The-Counter Use *(21 CFR 801 Subpart C)*

*CONTINUE ON A SEPARATE PAGE IF NEEDED.*

This section applies only to requirements of the Paperwork Reduction Act of 1995.

*DOS NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASstaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."
510(k) Summary

This summary of 510(k) safety and effectiveness is provided in accordance with the requirements of SMDA 1990 and 21 CFR §807.92

Date Prepared: May 11th, 2015

General Information

Legal Manufacturer

Siemens AG
Medical Solutions
Henkestrasse 127
91052 Erlangen
Germany

Manufacturing Location

Siemens Medical Solutions USA, Inc.
20 Valley Stream Parkway
Malvern PA. 19355

Establishment Registration Number: 3002808157

Contact Person

James E. Kuhn Jr.
Senior Regulatory Submissions Manager
Phone: (610) 448-3006  Fax: (610) 448-4274
Email: james.kuhn@siemens.com

Device Name and Classification

Trade Name: syngo.CT Lung CAD
Classification Name: Lung computed tomography system, computer-aided detection
CFR Section: 21 CFR §892. 2050
Device Class: Class II
Product Code: OEB
Safety and Effectiveness Information Supporting the Substantial Equivalence Determination

Device Description

syngo.CT Lung CAD is a medical device that is designed to perform CAD processing in thoracic CT examinations for the detection of solid pulmonary nodules ≥ 3 mm in size. The device processes images acquired with Siemens multi-detector CT scanners with 4 or more detector rows.

The syngo.CT Lung CAD device supports the full range of nodule locations (central, peripheral) and contours (round, irregular). The detection performance of the syngo.CT Lung CAD device is optimized for nodules between 3 mm and 10 mm in size. Additionally, the syngo.CT Lung CAD device can be used in scans with or without contrast enhancement.

The device receives images via an input data interface, performs CAD processing and provides locations of suspected nodules as an output. Specific visualization applications, such as the syngo PET&CT Oncology application (K093621) or equivalent Siemens products, should be used (but are not part of this clearance) to display the CAD marks. The syngo.CT Lung CAD device is intended to be used as a second reader only after the initial read is completed.

Intended Use

The syngo.CT Lung CAD device is a computer-aided detection (CAD) tool designed to assist radiologists in the detection of solid pulmonary nodules during review of multi-detector computed tomography (MDCT) examinations of the chest. The software is an adjunctive tool to alert the radiologist to regions of interest (ROI) that may have been initially overlooked. The syngo.CT Lung CAD device is intended to be used as a second reader after the radiologist has completed his/her initial read.

Safety and Effectiveness Information

Software design description, hazard analysis, and technical and safety information have also been completed and provided in support of this device. Risk management is ensured via the hazard analysis, which is used to identify potential hazards. These potential hazards are controlled during the development, verification/validation testing, and adherence to recognized and established industry practices and standards.

The device has no patient contacting materials and is utilized only by trained professionals. The output of the device is evaluated by trained professionals as a second reader. Use of this device does not impact the quality or status of the original acquired data.

Substantial Equivalence

The syngo.CT Lung CAD is substantially equivalent, both in intended use and technical characteristics to the following device:

<table>
<thead>
<tr>
<th>Company</th>
<th>Product – Trade Name</th>
<th>510(k) #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siemens</td>
<td>syngo Lung CAD</td>
<td>K063877</td>
</tr>
</tbody>
</table>
In summary, Siemens is of the opinion that the *syngo* CT Lung CAD software, as described within this document, does not pose any unmitigated potential safety risks and is substantially equivalent to and performs as well as the predicate device.

The difference between the predicate device *syngo* Lung CAD and *syngo*.CT Lung CAD are minor in nature and both devices have the same characteristics and functionalities. The comparison table below summarizes the differences and similarities between the two devices.

<table>
<thead>
<tr>
<th>Subject Device</th>
<th><em>syngo</em> Lung CAD 510(k) (K063877)</th>
<th><em>syngo</em>.CT Lung CAD new version</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device name</td>
<td><em>syngo</em> Lung CAD</td>
<td><em>syngo</em>.CT Lung CAD</td>
</tr>
<tr>
<td>Platform</td>
<td><em>syngo</em> classic</td>
<td><em>syngo</em>.via</td>
</tr>
<tr>
<td>Similarities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workflow</td>
<td>Second reader tool</td>
<td>Second reader tool</td>
</tr>
<tr>
<td>Detection target</td>
<td>Solid pulmonary nodules in diagnostic chest CT exams</td>
<td>Solid pulmonary nodules in diagnostic chest CT exams</td>
</tr>
<tr>
<td>Indications For Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The <em>syngo</em> Lung CAD device is a computer-aided detection (CAD) tool designed to assist radiologists in the detection of solid pulmonary nodules during review of multi-detector computed tomography (MDCT) examinations of the chest. The software is an adjunctive tool to alert the radiologist to regions of interest (ROI) that may have been initially overlooked. The <em>syngo</em> Lung CAD device is intended to be used as a second reader after the radiologist has completed his/her initial read.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The <em>syngo</em>.CT Lung CAD device is a computer-aided detection (CAD) tool designed to assist radiologists in the detection of solid pulmonary nodules during review of multi-detector computed tomography (MDCT) examinations of the chest. The software is an adjunctive tool to alert the radiologist to regions of interest (ROI) that may have been initially overlooked. The <em>syngo</em>.CT Lung CAD device is intended to be used as a second reader after the radiologist has completed his/her initial read.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Non-clinical Performance Testing Summary**

Non-clinical tests were conducted for the device *syngo*.CT Lung CAD during product development. The modifications described in this Premarket Notification were supported with verification and validation testing.

Siemens claims conformance to the following standards:

Software Verification and Validation

Testing, including standalone performance testing, were conducted to assess the new syngo.CT Lung CAD device and compare it to the predicate device with respect to false positives, sensitivity, and the dismissibility of false positives. The results of these tests support the substantial equivalence of this device.

The Risk Analysis was completed and risk control implemented to mitigate identified hazards. The testing results support that all the software specifications have met the acceptance criteria. Testing for verification and validation for the device was found acceptable to support the claims of substantial equivalence.

Software documentation for a Moderate Level of Concern software per FDA’s Guidance Document “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices” issued on May 11, 2005 is included as part of this submission. The performance data demonstrates that the subject device conforms to the special controls for medical devices containing software.

Summary
Performance tests were conducted to test the functionality of the device syngo.CT Lung CAD. Results of all conducted testing were found acceptable in supporting the claim of substantial equivalence.
Siemens syngo.PET&CT Oncology
510(k) Premarket Notification

510(k) Summary
as required by 21 CFR Part 807.87(h)

Identification of the Submitter

Submitter: M. Alaine Medio, RAC
PET and PCS Regulatory Projects Manager
Siemens Medical Solutions USA, Inc.
Molecular Imaging
810 Innovation Drive
Knoxville, TN 37932

Telephone Number: (865)218-2703
Fax Number: (865)218-3019

Name / Address of Manufacturer
Siemens Medical Solutions USA, Inc
Molecular Imaging
2501 N. Barrington Road
Hoffman Estates, IL 60192
USA

Date of Submission: November 20, 2009

Identification of the Product

Device Proprietary Name: syngo.PET&CT Oncology
Common Name: Image Processing Software
Classification Name: Picture Archiving and Communication System per 21 CFR 892.2050
Product Code: LLZ
Classification Panel: Radiology
Device Class: Class II
# Appendix E. Predicate Device Labeling

## Marketed Devices to which Equivalence is claimed

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>510(k) Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>syngo.x (syngo.via)</td>
<td>Siemens AG, Medical Solutions</td>
<td>K092519</td>
</tr>
<tr>
<td>True D</td>
<td>Siemens Medical Solutions USA, Inc</td>
<td>K091373</td>
</tr>
<tr>
<td>Syngo Dual Energy</td>
<td>Siemens Medical Solutions USA, Inc.</td>
<td>K073003</td>
</tr>
<tr>
<td>syngoCT Oncology</td>
<td>Siemens Medical Solutions USA, Inc.</td>
<td>K071310</td>
</tr>
</tbody>
</table>

## Device Description:

The syngo.PET&CT Oncology package is a software only medical device which will be delivered on CD-ROM / DVD to be installed onto the commercially available Siemens syngo.via software platform by trained service personnel.

syngo.PET&CT Oncology is a medical diagnostic application for viewing, manipulation, 3D-visualization and comparison of medical images from multiple imaging modalities and/or multiple time-points. The application supports functional data, such as PET or SPECT as well as anatomical datasets, such as CT or MR. The images can be viewed in a number of output formats including MIP and volume rendering.

syngo.PET&CT Oncology enables visualization of information that would otherwise have to be visually compared disjointedly. syngo.PET&CT Oncology provides analytical tools to help the user assess, and document changes in morphological or functional activity at diagnostic and therapy follow-up examinations.

syngo.PET&CT Oncology is designed to support the oncological workflow including interpretation and evaluation of examinations, and follow up documentation of findings.

The syngo.PET&CT Oncology package is similar to the commercially available TrueD software (K091373), syngoCT Oncology (K071310) and syngo Dual Energy software (K073003) in functionality and usage. syngo.PET&CT Oncology is intended to be run on the Siemens syngo.via software platform (K092519) either alone or with other advanced commercially cleared applications.
Safety and Effectiveness:

The device labeling contains instructions for use and any necessary cautions and warnings to provide for safe and effective use of the device.

Risk Management is ensured via a risk analysis in compliance with ISO 14971:2007 to identify and provide mitigation to potential hazards beginning early in the design cycle and continuing throughout the development of the product. Siemens Medical Solutions, USA Inc. adheres to recognized and established industry standards for development.

Indications for Use:

syno.PET&CT Oncology is a medical diagnostic application for viewing, manipulation, 3D-visualization and comparison of medical images from multiple imaging modalities and/or multiple time-points. The application supports functional data, such as PET or SPECT as well as anatomical datasets, such as CT or MR.

syno.PET&CT Oncology enables visualization of information that would otherwise have to be visually compared disjointedly. syno.PET&CT Oncology provides analytical tools to help the user assess, and document changes in morphological or functional activity at diagnostic and therapy follow-up examinations.

syno.PET&CT Oncology is designed to support the oncological workflow including interpretation and evaluation of examinations, and follow up documentation of findings.

Note: The clinician retains the ultimate responsibility for making the pertinent diagnosis based on their standard practices and visual comparison of the separate unregistered images. syno.PET&CT Oncology is a complement to these standard procedures.
Ms. Alaine Medio, RAC  
PET and PCS Regulatory Projects Manager  
Siemens Medical Solutions USA, Inc.  
810 Innovation Drive  
KNOXVILLE TN 37932-2751

Re: K093621  
Trade/Device Name: syno PET&CT Oncology  
Regulation Number: 21 CFR 892.2050  
Regulation Name: Picture archiving and communications system  
Regulatory Class: II  
Product Code: LLZ  
Dated: November 20, 2009  
Received: November 23, 2009

Dear Ms. Medio:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act’s requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of...
medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH’s Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Donald J. St.Pierre
Acting Director
Division of Radiological Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure
INDICATIONS FOR USE

510(k) Number (if known): K093621

Device Name: syno.PET&CT Oncology

Indications for Use:

syno.PET&CT Oncology is a medical diagnostic application for viewing, manipulation, 3D-visualization and comparison of medical images from multiple imaging modalities and/or multiple time-points. The application supports functional data, such as PET or SPECT as well as anatomical datasets, such as CT or MR.

syno.PET&CT Oncology enables visualization of information that would otherwise have to be visually compared disjointedly. syno.PET&CT Oncology provides analytical tools to help the user assess, and document changes in morphological or functional activity at diagnostic and therapy follow-up examinations.

syno.PET&CT Oncology is designed to support the oncological workflow including interpretation and evaluation of examinations, and follow up documentation of findings.

Note: The clinician retains the ultimate responsibility for making the pertinent diagnosis based on their standard practices and visual comparison of the separate unregistered images. syno.PET&CT Oncology is a complement to these standard procedures.

Prescription Use X OR Over the Counter Use (21 CFR 801 Subpart C)

(Please do not write below this line – continue on another page if needed)

Concurrence of CDRH, Office of Device Evaluation (ODE)

(Division Sign-Off)
Division of Radiological Devices
Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) Number K093621
Ms. Jennifer Vetter  
Director-Regulatory and Quality Assurance  
Riverain Medical Group, LLC  
3020 South Tech Blvd.  
MIAMISBURG OH 45342  

Re: K092363  
Trade/Device Name: Softview™  
Regulation Number: 21 CFR 892.2050  
Regulation Name: Picture archiving and communications system  
Regulatory Class: II  
Product Code: LLZ  
Dated: February 5, 2010  
Received: February 12, 2010  

Dear Ms. Vetter:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act’s requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of...
medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/Reportaproblem/default.htm for the CDRH’s Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Donald J. St.Pierre
Acting Director
Division of Radiological Devices
Office of In Vitro Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure
2.0 INDICATIONS FOR USE STATEMENT

Device Name: SoftView™

Indications for Use:

SoftView is intended to generate an enhanced, secondary digital radiographic image of the chest. The enhanced AP or PA image of the chest provides improved visibility of the lung parenchyma through bone suppression and tissue equalization, and may facilitate discerning the presence or absence of nodules. The SoftView image provides adjunctive information and is not a substitute for the original PA/AP image. This device is intended to be used by trained professionals, such as physicians, radiologists, and technicians on patients with risk of having lung nodules and is not intended to be used on pediatric patients.

Prescription Use _X__ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON ANOTHER PAGE OF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

[Signature]

Division of Radiological Devices
Office of In Vitro Diagnostic Device Evaluation and Safety

Page 1 of
3.0 510(K) SUMMARY

Submission Date: August 4, 2009

Submitter Information:

Company Name: Riverain Medical Group, LLC.
Company Address: 3020 South Tech Blvd., Miamisburg, OH 45342-4860
Contact Person: Jennifer Vetter
Director, Regulatory Affairs and Quality Assurance
Riverain Medical
800.990.3387
937.425.6493
jvetter@riverainmedical.com

Device Information:

Trade Name: SoftView™
Regulation Number: 21 CFR §892.2050
Regulation Name: System, Image Processing, Radiological
Regulatory Class: Class II
Product Code: LLZ

Predicate Device: Dual Energy and Tissue Equalization Software Options (K013481)
GE Medical Systems
Class II

Device Description: SoftView is a dedicated post-processing application which suppresses bone structures from digital radiographic images of the chest.

Intended Use: SoftView is intended to generate a bone-suppressed image from a original PA/AP chest radiograph.

Indications for Use: SoftView is intended to generate an enhanced, secondary digital radiographic image of the chest. The enhanced AP or PA image of the chest provides improved visibility of the lung parenchyma through bone suppression and tissue equalization, and may facilitate discerning the presence or absence of nodules. The SoftView image provides adjunctive information and is not a substitute for the original PA/AP image. This device is intended to be used by trained professionals, such as physicians, radiologists,
and technicians on patients with risk of having lung nodules and is not intended to be used on pediatric patients.

Comparison to Predicate Device:

SoftView is substantially equivalent to the cited predicate device. Differences in the design and performance from the cited predicate device do not affect either the safety or effectiveness of SoftView for its intended use.

Conclusion:

SoftView is a mathematical model of a DES system that operates on a standard chest X-ray. It is an accurate representation of the soft tissue image produced by the predicate device’s hardware/software process. The model is built from DES data by using simple image features extracted from the standard PA, along with target values derived from a DES soft tissue image. Thus, although SoftView does not generate the soft tissue image based on two exposures to the patient in real time, it is an accurate mathematical model of the process. The result of SoftView processing is a soft tissue image of the patient, consistent with that produced by a DES device but without requiring any additional radiation dose to the patient. Effectiveness of this model was demonstrated both by a reader study and by a comparative analysis of the contrast-to-noise ratio (CNR) of the residual bone in the predicate device’s images in the soft tissue rib and clavicle regions, relative to the subject device.

Reader Study Results:

A reader study was conducted to assess the benefit of SoftView to a radiologist for detecting actionable lung nodules. Reader performance was quantified by the area under the Localization Receiver-Operating Characteristic (LROC) curve which measures the conjoint ability to detect and correctly localize a true positive location on the radiograph. The difference in the average area under the LROC curve with and without the aid of SoftView was used to assess performance. The mean difference in the area under the curves was -0.098 (95% CI: -0.116 to -0.080), a statistically significant improvement. Sensitivity was 49.5% (95% CI: 45.9-53.0) without SoftView and 66.3% (95% CI: 63.1-69.7) with the addition of the SoftView image. Specificity was 96.1% (95% CI: 95.0-97.1) with the standard image and 91.8% (95% CI: 89.5-93.5) with the SoftView image.
Substantial Equivalence: To establish substantial equivalence, a comparative analysis of the contrast-to-noise ratio (CNR) of the residual bone in the predicate device’s soft tissue images versus the subject device was performed. A CNR analysis was performed for both the GE and Fuji dual energy subtraction (DES) soft tissue images.

Analysis of scatter plots of the contrast-to-noise ratio (CNR) for the residual rib objects for an independent dataset was used to compare the SoftView correlative relationship relative to DES. Statistical hypothesis tests were also performed on the independent dataset. Two series of tests were performed, equivalency and non-inferiority tests. Data were stratified across modality, CR (Fuji DES), DR (GE DES), and lung regions, i.e., pleural, mid-lung, and hilum.

For the indicated strata of the data, it was demonstrated that SoftView is equivalent to the DES soft tissue images. The exception was the middle area of the lung for the DR modality (GE DES). SoftView was found to be better in this region based on an “ideal” CNR of the residual ribs in the soft tissue image being 0.0. Furthermore, a non-inferiority test demonstrated that SoftView was non-inferior to the DR and CR dual energy devices soft tissue images across all strata. Descriptive statistics of the means and standard deviations of the CNRs across the different modalities and regions of the lungs were in agreement.
Reference Material

1: Adaptive floating search methods in feature selection ................................................................. 1

2: The Lung Image Database Consortium (LIDC) and Image Database Resource Initiative (IDRI): A Completed Reference Database of Lung Nodules on CT Scans ........................................................................................................ 8

3: A Comparison of Decision Tree Ensemble Creation Techniques .................................................... 25

4: Lung Cancer Screening in the NELSON Trial Balancing Harms and Benefits. .............................. 34
Adaptive floating search methods in feature selection

P. Somol a,b,c,*, P. Pudil a,c, J. Novovičová a,c, P. Paclík a,c

a Department of Pattern Recognition, Institute of Information Theory and Automation, Academy of Sciences of the Czech Republic, 182 08 Prague 8, Czech Republic
b Faculty of Mathematics and Physics, Charles University, Prague, Czech Republic
c Joint Laboratory of Faculty of Management, University of Economics, Prague and Institute of Information Theory and Automation, Czech Academy of Sciences, Czech Republic

Abstract

A new suboptimal search strategy for feature selection is presented. It represents a more sophisticated version of “classical” floating search algorithms (Pudil et al., 1994), attempts to remove some of their potential deficiencies and facilitates finding a solution even closer to the optimal one. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Pattern recognition; Feature selection; Search methods

1. Introduction

In feature selection, a search problem of finding a subset of \( d \) features from a given set of \( D \) measurements, \( d < D \), has been of interest for a long time. Since the optimal methods (exhaustive search or the Branch-and-Bound method which is restricted to monotonous criteria) are not suitable for high-dimensional problems, research has concentrated on suboptimal search methods. Two well-known basic approaches to the required feature set construction are usually recognized: the “bottom up” and “top down” one.

A number of search methods has been developed, starting with sequential backward selection (SBS) and its “bottom up” counterpart known as sequential forward selection (SFS). Both of them suffer from the so-called “nesting effect”. Attempts to prevent the nesting of feature subsets led to the development of the Plus-l-Minus-r search method by Stearns (1976) and to generalization of SBS, SFS and Plus-l-Minus-r algorithms proposed by Kittler (1978).

According to the comparative study made by Jain and Zongker (1997), probably the most effective known suboptimal methods are currently the sequential floating search methods, proposed by Pudil et al. (1994). In comparison to the Plus-l-Minus-r method, the “floating” search treats the “nesting problem” even better, since there is no need to specify any parameters such as \( l \) or \( r \). The number of forward (adding)/backward (removing) steps is determined dynamically during the method’s run so as to maximize the criterion function (see Fig. 1).

2. Preliminaries

Pudil et al. (1991, 1994) presented the definitions of individual significance of a single feature
with respect to the set and in the set. Before discussing the adaptive floating search algorithms formally, the following generalization of these definitions has to be introduced.

Let \( X_k = \{x_i : 1 \leq i \leq k, \; x_i \in Y\} \) be the set of \( k \) features from the set \( Y = \{y_i : 1 \leq i \leq D\} \) of \( D \) available features. Let \( T_o \) be generally the tuple of \( o \) features. The value \( J(T_o) \) of the feature selection criterion function if only the \( D \) available features. Let \( T_o \) be generally the tuple of \( o \) features. The value \( J(T_o) \) of the feature selection criterion function if only the features \( t_i, \; i = 1, 2, \ldots, o, \; t_i \in T_o \) are used will be called the individual significance \( S_k(T_o) \) of the feature o-tuple.

The significance \( S_{k-o}(T_o) \) of the feature o-tuple \( T_o = \{t_i : 1 \leq i \leq o, \; t_i \in X_k\} \) in the set \( X_k \) is defined by

\[
S_{k-o}(T_o) = J(X_k) - J(X_k \setminus T_o).
\]  

(1)

The significance \( S_{k+o}(U_o) \) of the feature o-tuple \( U_o = \{u_i : 1 \leq i \leq o, \; u_i \in Y \setminus X_k\} \) from the set \( Y \setminus X_k \) with respect to the set \( X_k \) is defined by

\[
S_{k+o}(U_o) = J(X_k \cup U_o) - J(X_k).
\]  

(2)

Denote by \( T_o^i \) the \( i \)th o-tuple belonging to the set of all \( \Theta = \binom{D}{o} \) possible o-tuples from \( X_k \), \( 1 \leq i \leq \Theta \).

We shall say that the feature o-tuple \( T_o^i \) from the set \( X_k \) is:

1. the most significant (best) feature o-tuple in the set \( X_k \) if

\[
S_{k-o}(T_o^i) = \max_{1 \leq i \leq \Theta} S_{k-o}(T_o^i)
\]

\[\Rightarrow J(X_k \setminus T_o^i) = \min_{1 \leq i \leq \Theta} J(X_k \setminus T_o^i);\]  

(3)

2. the least significant (worst) feature o-tuple in the set \( X_k \) if

\[
S_{k-o}(T_o^\ast) = \min_{1 \leq i \leq \Theta} S_{k-o}(T_o^i)
\]

\[\Rightarrow J(X_k \setminus T_o^\ast) = \max_{1 \leq i \leq \Theta} J(X_k \setminus T_o^i).\]  

(4)

We shall say that the feature o-tuple \( U_o^i \) from the set \( Y \setminus X_k \) is:

1. the most significant (best) feature o-tuple with respect to the set \( X_k \) if

\[
S_{k+o}(U_o^i) = \max_{1 \leq i \leq \Psi} S_{k+o}(U_o^i)
\]

\[\Rightarrow J(X_k \cup U_o^i) = \min_{1 \leq i \leq \Psi} J(X_k \cup U_o^i);\]

(5)

where \( \Psi = \binom{D-k}{o} \) is the number of all the possible o-tuples from \( Y \setminus X_k \);

2. the least significant (worst) feature o-tuple with respect to the set \( X_k \) if

\[
S_{k+o}(U_o^\ast) = \min_{1 \leq i \leq \Psi} S_{k+o}(U_o^i)
\]

\[\Rightarrow J(X_k \cup U_o^\ast) = \max_{1 \leq i \leq \Psi} J(X_k \cup U_o^i).\]  

(6)

Remark. For \( o = 1 \) all the terms relating to the feature o-tuple significance coincide with the terms relating to the individual significance of a feature.

3. Adaptive floating search (AFS) properties

For the sake of simplicity, let us denote original floating search methods (SFFS and SBFS) together as “classical floating search” methods and denote them by CFS. CFS methods use only single feature adding or removing, respectively, in the course of the algorithm.

**Fig. 1.** Simplified flow chart of SFFS algorithm.
Our new search strategy aims to utilize the best of both generalized strategies and classical floating strategies. The course of search is similar to that of CFS, but the individual search steps are generalized. However, the new algorithm is by no means just a generalized version of CFS.

The basic generalization of CFS would be to replace the simple SFS or SBS steps inside the CFS procedure by their generalized versions GSFS(o) or GSBS(o), respectively. Unfortunately for a potential user, it is generally not known which value of o to choose to get the best results. Moreover, if the user chooses the value of o too high for his particular problem, this leads to useless increase of computing time.

As opposed to the above mentioned generalized methods, the AFS method does not need the user-specified level of generalization. This level (value of o) is determined dynamically in the course of the search according to the current situation so as to achieve better results. In this sense, AFS brings about a similar improvement in comparison with the generalized search strategies as the CFS search brought about in comparison with simple “non-generalized” strategies (CFS introduced dynamical “floating” of adding/removing steps).

Because of the time-exacting character of generalized steps (especially when used in high-dimensional problems) we introduced a user defined parametric limit \( r_{\text{max}} \), restricting the maximum generalization level which the method can use. The current generalization level, which changes in the course of search, is denoted by o. The AFS is called “adaptive” because of its ability to adjust the limit under which the actual generalization level can be automatically set. Simply said, the nearer the current subset size (k) is to the final one (d), the higher is the generalization limit. This characteristic aims to save computing time by limiting the generalization levels while the current subset is still far from the desired one. Therefore, we introduce the variable \( r \) representing the actual generalization limit for a given dimension.

To summarize, \( r_{\text{max}} \) is a user-specified absolute generalization limit, \( r \) is the actual generalization limit determined adaptively by the algorithm for the current subset (\( r \leq r_{\text{max}} \) always holds), o is the current generalization level depending on the current situation (\( o \leq r \) always holds).

**Remark.** For \( r_{\text{max}} = 1 \) the AFS is identical to classical floating search.

Adaptive determination of \( r \) is done as follows: at the beginning of every forward or backward algorithm phase, respectively:
1. if \( |k - d| < b \), let \( r = r_{\text{max}} \)
2. else if \( |k - d| < b + r_{\text{max}} \), let \( r = r_{\text{max}} + b - |k - d| \)
3. else let \( r = 1 \)

Here \( b \) denotes the neighbourhood of the final dimension, where the highest generalization levels are allowed. Basically it is possible to set \( b = 0 \). The adaptive setting of \( r \) and the meaning of parameter \( b \) is shown in Fig. 2.

Thus, in the generalized course of the AFS algorithm, \( o = 1 \) is used in usual algorithm stages (e.g., in the beginning). Only special algorithm stages (when conditional forward, respectively backward steps brought no improvement) allow increasing of \( o \) and, therefore, a more detailed search.

By setting \( r_{\text{max}} \) or \( b \) to higher values, the user has a possibility to let the algorithm perform a more thorough search with better chances to find the optimal solution, of course at the expense of longer computation time. The setting of these two parameters is not so critical as setting the generalization level in classical GSFS(o), respectively GSBS(o) and Plus-l-Minus-r. Increasing \( r_{\text{max}} \) or \( b \) does not lead to a different search, but to a more detailed search.

![Fig. 2. The meaning of the user parameters \( r_{\text{max}} \) and \( b \) for adjusting the adaptive generalization.](image-url)
Remark. Every AFS algorithm run includes steps identical with CFS ones. Also for this reason we expect the AFS algorithm to find equal or better solutions than CFS. The computer time needed for AFS is expected to be substantially longer (due to the generalization) than for CFS. However, if we constructed the generalized floating search in the simple way, it would consume incomparably more time.

CFS were found to occasionally prefer worse working subsets in the course of search. 1 To describe that case, let us remind the principle of CFS (specifically SFFS) first:
1. Add the most significant feature to the current subset of size $k$. Let $k = k + 1$.
2. Conditionally remove the least significant feature from the current subset.
3. If the current subset is the best subset of size $k - 1$ found so far, let $k = k - 1$ and go to step 2. Else return the conditionally removed feature and go to step 1.

Note that backward steps are conditional. Only backward steps bring improvement are allowed. On the other hand, forward steps cannot be conditional. If they were, the algorithm could lead to finding a subset which is worse than the so-far best one of a given dimension found so far. A less promising “search branch” is thus uselessly followed.

Removal of this problem is simple. If the forward step found a subset worse than the best one known so-far the current one is forgotten and the so-far best one becomes the current one. Note that this “violent” swapping of current subset cannot lead to infinite cycling, as finding of a worse subset by the forward step must have been preceded by finding a better subset in some lower dimension.

Now, having defined the notion and discussed the included principles we can describe the ASFFS and ASBFS algorithms.

4. ASFFS algorithm

The adaptive sequential forward floating search (ASFFS) is basically a “bottom up” procedure.

The algorithm is initialized by setting $k = 0$ and $X_0 = \emptyset$. In order to keep the algorithm description traceable, we did not include all the steps needed to ensure its proper functioning, especially when the current dimension gets near to 0 or $D$. Such steps serve to avoid the algorithm running outside the meaningful dimension boundaries.

Suppose the so-far best values of criterion function $J(X_i)$ are stored as $J_i^{\max}$ for all $i = 1, 2, \ldots, D$. The corresponding so-far best feature subsets $X_i$ are also stored. Initial values of $J_i^{\max}$ for all $i = 1, 2, \ldots, D$ should be set to lowest possible value. Furthermore, suppose $k$ is the size of the current subset.

A. Forward phase

Each phase begins with adaptive setting of $r$. If $|k - d| < b$, let $r = r_{\max}$. Else if $|k - d| < r_{\max} + b$, let $r = r_{\max} + b - |k - d|$. Else let $r = 1$.

Step 1. Let $o = 1$.

Step 2 (Conditional inclusion). Using the basic GSFS($o$) method, select the most significant $o$-tuple $U_o^n$ from the set of available measurements $Y \setminus X_k$ with respect to the set $X_k$, then add it to $X_k$ to form feature set $X_{k+o}$.

Step 3. If $J(X_{k+o}) > J_{k+o}^{\max}$, let $J_{k+o}^{\max} = J(X_{k+o})$, let $k = k + o$ and go to step 6. (The so-far best subset of size $k + o$ was found.)

Step 4 (Conditional increase of generalization step). If $o < r$, set $o = o + 1$ and go to step 2. (The conditionally included features are removed.)

Step 5 (None of the subsets tested in the forward phase were better than the so-far best ones). Forget the current subset $X_k$. Let $k = k + 1$. Now consider the so-far best subset of size $k$ to be the current subset $X_k$.

Step 6 (Testing the terminating condition). If $k \geq d + \Delta$, stop the algorithm.

B. Backward phase

Each phase begins with adaptive setting of $r$. If $|k - d| < b$, let $r = r_{\max}$. Else if $|k - d| < r_{\max} + b$, let $r = r_{\max} + b - |k - d|$. Else let $r = 1$.

Step 7. Let $o = 1$.

---

1 We are grateful for the critical remarks by our colleague Dr. R.P.W. Duin from the Delft University of Technology.
Step 8 (Conditional exclusion). Using the basic GSBS(o) method, select the least significant o-tuple \( T_{l=0} \) in the set \( X_k \), then remove it from \( X_k \) to form feature set \( X_k^{o=0} \).

Step 9. If \( J(X_k^{o=0}) > J_{k-o}^{\text{max}} \), let \( J_{k-o}^{\text{max}} = J(X_k^{o=0}) \), let \( k = k - o \) and go back to the beginning of Backward Phase. (The so-far best subset of size \( k - o \) was found.)

Step 10 (Conditional increase of generalization step). If \( o < r \), let \( o = o + 1 \) and go to step 8. (The conditionally excluded features are returned.)

Step 11 (None of the subsets tested in the backward phase were better than the so-far best ones.) Go to Forward phase.

End. \{ASFFS\}

A simplified flowchart of the ASFFS algorithm is given in Fig. 3. The terminating condition \( k = d + \Delta \) in the flowchart means that in order to fully utilize the potential of the search, we should not stop the algorithm immediately after it reaches for the first time the dimensionality \( d \). By leaving it to float up and down a bit further, the potential of the algorithm is better utilized and a subset of dimensionality \( d \) outperforming the first one is usually found. In practice we can let the algorithm either go up to the original dimensionality \( D \), or, if \( D \) is too large, then the value of \( \Delta \) can be determined heuristically (e.g., according to the value of the maximum number of backtracking steps prior to reaching \( d \) for the first time).

5. ASBFS algorithm

The algorithm is initialized in the same way as ASFFS, except \( k = D \) and \( X_D = Y \). The ASBFS (adaptive sequential backward floating search) is the “top down” counterpart of the ASFFS procedure. Since it is analogous to the forward one, due to the lack of space it is not described here.

6. Experimental results

The performance of adaptive floating search has been compared with that of “classical” floating search on a number of real data. Here we just present the results of ASFFS and SFFS on two sets of data (as both concern two-class problems, in both the cases the Bhattacharyya distance was used as the criterion function; a PC with Pentium II 350 was used):

1. 65-dimensional mammogram data – the dataset was obtained from the Pattern Recognition and

![Fig. 3. Simplified flow chart of ASFFS algorithm.](image-url)
Image Modeling Laboratory (PRIM lab.) at University of California, Irvine.

2. 60-dimensional sonar data – the dataset was obtained from the Machine Learning Database at University of California, Irvine.

From the results we can see that ASFFS yielded better results than classical SFFS. Although in these examples the improvement may seem to be marginal, we have to be aware of the fact that finding a different feature subset with only a marginal increase in the criterion value can cause a better performance of the classifier which may prove to be crucial in certain applications.

Furthermore, more essential than the absolute value of improvement is the fact that the adaptive search is capable of finding a solution closer to the optimal one (of course at the expense of longer computation time as documented, e.g., on Fig. 4 for 25 selected features, where ASFFS found a better subset than SFFS, due to a more thorough search) (see Fig. 5).

7. Conclusion

Two new methods of adaptive floating search have been presented. Owing to a more thorough search than classical floating search, they have a potential of finding a solution even closer to the optimal one. The trade-off between the quality of solution and the computational time can be controlled by user’s setting of certain parameters.

For further reading, see (Devijver and Kittler, 1982; Siedlecki and Sklansky, 1988; Ferri et al., 1994).

Discussion

Gimel’farb: I have two questions. The first question is: How do you avoid the threat of local minima of the criterion function in the search? Because in feature selection, the feature that we add depends on the feature we start with, and this may heavily influence your results. The second question is: How can you explain such non-linear time behaviour?

Somol: Let me answer the second question first. I think that till a certain point, this method does the same kind of search as classical floating search, meaning that it adds or removes only single features. And every time it tries to find a better subset, increasing the criterion function. But at some point it starts using a generalisation step, meaning that it tries groups of two, three or more features at a time. So eventually, the depth of search may reach the generalisation limit, which of course would be accompanied by a sharp increase of the time. As for the time behaviour, the simple reason is that the algorithm is heuristic. However, one possible explanation is in the fact that the generalisation limit is a special function of the dimensionality. This may be the cause that we get different generalisation limits for the same stages.
of the algorithm, when searching subsets of different cardinalities. And for the first question: I would ask my co-author.

Pudil: First, I would like to further comment on the time behaviour, which I would call non-monotonic, rather than non-linear. Obviously, this is data-dependent; with other data, the behaviour may be different and such jumps may happen not at all. At a certain moment, the algorithm switches to deeper search, because it finds that the generalised versions start to find better solutions. But that is at the expense of longer computational time because of the deeper search. And as far as the first question is concerned, obviously as we all know, the sub-optimal methods are heuristic. The method presented here is only an improvement of previous versions, but it cannot guarantee to find the real optimum. However, in most cases when we compared it, for instance with Branch and Bound, it yielded practically always the same solution.

Egmont-Petersen: Have you considered using assessment criteria other than the statistical distance measure you used? With your criterion, you do not need a classifier. However, if you would use, for instance, the error rate, you would need to train a lot of classifiers.

Somol: I have used various distance measures, not only the Bhattacharyya distance, but also the Mahalobis distance, and the behaviour of the algorithm was similar.

Pudil: For classical floating search, we used the apparent error rate, because it does not depend on monotonic criteria like the Branch and Bound method for example. So there we used the error rate.

Acknowledgements

The authors greatly acknowledge the support by research grants from the Czech Grant Agency No.402/97/1242 and the Czech Ministry of Education Nos. VS96063, ME187/98 and Aktion 23b20.

References

The Lung Image Database Consortium (LIDC) and Image Database Resource Initiative (IDRI): A Completed Reference Database of Lung Nodules on CT Scans

Samuel G. Armato III
Department of Radiology, The University of Chicago, 5841 South Maryland Avenue, MC 2026, Chicago, Illinois 60637

Geoffrey McLennan
Department of Internal Medicine, Pulmonary Division, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, Iowa 52242

Luc Bidaut
University of Texas, MD Anderson Cancer Center, Houston, Texas 77030

Michael F. McNitt-Gray
Department of Radiological Sciences, David Geffen School of Medicine at UCLA, 924 Westwood Boulevard, Los Angeles, California 90024

Charles R. Meyer
Department of Radiology, University of Michigan Medical School, 109 Zina Pitcher Place, A522, Ann Arbor, Michigan 48109

Anthony P. Reeves
School of Electrical and Computer Engineering, Cornell University, 392 Rhodes Hall, Ithaca, New York 14853

Binsheng Zhao
Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10065

Denise R. Aberle
Department of Radiological Sciences, David Geffen School of Medicine at UCLA, 924 Westwood Boulevard, Los Angeles, California 90024

Claudia I. Henschke
Department of Radiology, Mount Sinai School of Medicine, 1 Gustave Levy Place, New York, New York 10029

Eric A. Hoffman
Department of Radiology, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, Iowa 52242

Ella A. Kazerooni
Department of Radiology, University of Michigan Health System, Cardiovascular Center Number 5482, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109

Heber MacMahon
Department of Radiology, The University of Chicago, 5841 South Maryland Avenue, MC 2026, Chicago, Illinois 60637

Edwin J. R. van Beek
Department of Radiology, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, Iowa 52242

David Yankelevitz
Department of Radiology, Mount Sinai School of Medicine, 1 Gustave Levy Place, New York, New York 10029

Alberto M. Biancardi
School of Electrical and Computer Engineering, Cornell University, 392 Rhodes Hall, Ithaca, New York 14853

Peyton H. Bland
Department of Radiology, University of Michigan, A502 BSRB, 109 Zina Pitcher Place, Ann Arbor, Michigan 48109

Matthew S. Brown
Department of Radiological Sciences, David Geffen School of Medicine at UCLA, 924 Westwood Boulevard, Los Angeles, California 90024
Purpose: The development of computer-aided diagnostic (CAD) methods for lung nodule detection, classification, and quantitative assessment can be facilitated through a well-characterized repository of computed tomography (CT) scans. The Lung Image Database Consortium (LIDC) and Image Database Resource Initiative (IDRI) completed such a database, establishing a publicly available reference for the medical imaging research community. Initiated by the National Cancer Institute (NCI), further advanced by the Foundation for the National Institutes of Health (FNIH), and accompanied by the Food and Drug Administration (FDA) through active participation, this public-private partnership demonstrates the success of a consortium founded on a consensus-based process.

Methods: Seven academic centers and eight medical imaging companies collaborated to identify, address, and resolve challenging organizational, technical, and clinical issues to provide a solid foundation for a robust database. The LIDC/IDRI Database contains 1018 cases, each of which includes images from a clinical thoracic CT scan and an associated XML file that records the results of a two-phase image annotation process performed by four experienced thoracic radiologists. In the initial blinded-read phase, each radiologist independently reviewed each CT scan and marked lesions belonging to one of three categories (“nodule ≥3 mm,” “nodule <3 mm,” and “non-nodule ≥3 mm”). In the subsequent unblinded-read phase, each radiologist independently reviewed their own marks along with the anonymized marks of the three other radiologists to render
I. INTRODUCTION

Publicly available medical image databases for the development and evaluation of computerized image analysis paradigms have been anticipated for nearly two decades. Although the development of computer-aided diagnostic (CAD) methods has accelerated, access to well-characterized image data remains a common limitation as the task of identifying and collecting appropriate images for any specific research activity is a laborious and expensive process. An organized collection of anonymized clinical images alone would provide a valuable resource and would eliminate database composition as a source of variability that hinders the appropriate comparison of different CAD methods. The utility of an image database would be greatly enhanced through the inclusion of task-specific “truth.” Investigators developing automated detection methods, for example, require the opinion of an experienced radiologist or, more appropriately, a panel of radiologists regarding the location of lesions within the images. Truth for other CAD tasks requires data such as follow-up images to evaluate change over time, pathology reports, or radiologist-drawn lesion outlines. The increasing need for CAD in the clinical practice of radiology lends urgency to the creation of common image databases with established truth to foster the development of CAD methods and enable the direct comparison of different systems.

Publicly available image databases designed to facilitate computerized image analysis research were first introduced in mammography. The most notable of these databases is the Digital Database for Screening Mammography (DDSM), which contains 2620 digitized four-view screening mammograms. Lesions have been annotated by an experienced radiologist to include an American College of Radiology (ACR) keyword description, BI-RADS rating, subtlety score, and a manual outline.

Chest radiography is the most commonly performed radiologic study, and the detection of lung nodules is one of the most important diagnostic challenges in chest radiography. This detection task became an early focus of CAD research in thoracic imaging and the motivation for the Japanese Society of Radiological Technology (JSRT) to create a publicly available database of chest radiographs for education, training, and research. The JSRT database contains 247 digitized posteroanterior chest radiographs with either a solitary pulmonary nodule (n=154) or no nodule (n=93), as confirmed by CT and reviewed by three experienced thoracic radiologists. Each case includes patient information such as age and gender along with nodule size, malignancy status, subtlety rating, coarse anatomic location, and coordinates of the nodule center.

Cornell University in conjunction with the National Cancer Institute (NCI) and funding from the Prevent Cancer Foundation has made publicly available a growing research database of serial CT scans with nodule outlines provided by radiologists. The intent of the Public Image Database is to facilitate the development of computerized methods for the assessment of tumor response to therapy. A set of interactive image viewing tools is provided along with lesion measurements and growth analysis. Databases that allow for the quantitative analysis of serial CT scans are becoming more relevant to radiologic and oncologic research.

The collections of images acquired during comprehensive lung cancer screening trials have the potential to become valuable database resources. One of the first such trials, the Early Lung Cancer Action Program (ELCAP), made available in 2003 the ELCAP Public Lung Image Database. This database consists of 50 documented low-dose CT scans for the performance evaluation of computer-aided detection systems. The National Lung Screening Trial (NLST) randomized 26,724 subjects to the CT screening arm of its two-arm study. From among the 75,133 low-dose thoracic CT scans acquired at the 33 participating institutions according to a strict image-acquisition protocol, 48,547 scans were archived in the CT Image Library (CTIL). Deidentified images were transferred to a central site, which performed quality assurance on the images through confirmation of select digital imaging and communications in medicine (DICOM) fields to ensure accurate transmittal of the correct scan and through visual inspection to ensure image quality. Although the images were not annotated with lesion attributes, demographic and clinical data were maintained for eventual use by researchers once the library becomes publicly available.

The NELSON (Nederlands Leuvenkancer Screeningsonderzoek) trial, a Dutch acronym for “Dutch-Belgian lung cancer screening trial,” has accrued 15,523 participants across four institutions since 2003. Annual CT screening
The development of CAD methods for lung nodule detection, classification, and quantitative assessment can be facilitated and stimulated through the creation of a well-characterized repository of thoracic CT scans. A true reference database, however, would provide an even greater benefit to investigators but would require an even greater commitment of time and resources to create the standards and infrastructure required to capture metadata, such as image annotations and pathologic diagnosis. To this end, the NCI issued a request for applications (RFAs) entitled “Lung Image Database Resource for Imaging Research” in April 2000 to convene a consortium of institutions to develop consensus guidelines for the creation of a CT-based lung nodule reference database.22 Five institutions (Weill Cornell Medical College, University of California, Los Angeles, University of Chicago, University of Iowa, and University of Michigan) were selected to form the Lung Image Database Consortium (LIDC), which has been working since 2001 to develop a web-accessible research resource for the development, training, and evaluation of CAD methods for lung nodules to include (1) an image repository of screening and diagnostic thoracic CT scans, (2) associated metadata such as technical scan parameters (e.g., slice thickness, tube current, and reconstruction algorithm) and patient information (e.g., age, gender, and pathologic diagnosis), and (3) nodule truth information26 based on the subjective assessments of multiple experienced radiologists (e.g., lesion category, nodule outlines, and subtlety ratings).27

Guided by the premise that “public-private partnerships are essential to accelerating scientific discovery for human health” and their successes in this realm,20 the Foundation for the National Institutes of Health (FNIH) created the Image Database Resource Initiative (IDRI) in 2004 to further advance the efforts of the LIDC. The IDRI joined the five LIDC institutions with two additional academic centers (MD Anderson Cancer Center and Memorial Sloan-Kettering Cancer Center) and eight medical imaging companies (AGFA Healthcare, Carestream Health, Inc., Fuji Photo Film Co., GE Healthcare, iCAD, Inc., Philips Healthcare, Riverain Medical, and Siemens Medical Solutions). Through the IDRI, these companies provided additional resources to expand substantially the LIDC database to a targeted 1000 CT scans and to create a complementary database of almost 300 digital chest radiographic images associated with a subset of these CT scans. The experience with chest radiographs will be the subject of a future publication. The IDRI merged the expertise of the academic centers with that of the medical imaging companies. Since the process of database collection, annotation, and curation was exactly the same for the LIDC database and the CT component of the IDRI database, the combined database of thoracic CT scans will be referred to as the LIDC/IDRI Database.

The creation of a reference database through a consensus-based process required careful planning and the proper consideration of fundamental issues such as a governing mission statement, CT scan inclusion criteria, an appropriate definition of target lesions and associated truth requirements, a process model to guide population of the Database, and a framework to direct the application of assessment methodologies by end users. The details of these issues and the evolution of the decisions implemented by the LIDC/IDRI have been reported previously.27,29 The purpose of this paper is to describe the now-completed, publicly available LIDC/IDRI Database of 1018 thoracic CT scans and associated radiologist annotations. A solid understanding of the process through which the Database was created, along with important caveats on its use, is required to ensure that investigators conduct studies that are compatible with valid uses of the Database, while at the same time allowing investigators to take full advantage of the available information. Imparting this knowledge transfers the responsibility for valid use of the Database to individual investigators and to the scientific community so that the peer-review process for grants and publications can function appropriately. Ultimately, the success of the LIDC/IDRI effort will be judged by its impact on the community through the quality of grants awarded, the relevance of derivative publications, and the dissemination of CAD for thoracic CT into clinical practice after successful routing through the regulatory approval process.

II. MATERIALS AND METHODS

II.A. Patient image data

The LIDC/IDRI Database contains a total of 1018 helical thoracic CT scans collected retrospectively, with appropriate local IRB approval, from the picture archiving and communications systems (PACS) of the seven participating academic institutions. Anonymization software was applied to remove all protected health information (PHI) contained within the DICOM headers of the images in accordance with Health Insurance Portability and Accountability Act (HIPAA) guidelines.30 No scan was performed specifically for the purpose of the Database so that a heterogeneous range of scanner models and technical parameters was intentionally represented. The intent was to include only a single scan from any one patient so that scans in the Database would not be correlated. As a result, the LIDC/IDRI Database is not amenable to temporal change analysis research; other publicly available databases, however, such as the NCI’s Reference Image Database to Evaluate Response to therapy in lung cancer12 (RIDER) and Cornell University’s database provide such resources.

Certain inclusion criteria were imposed to ensure relevance of the scans to the development of state-of-the-art CAD systems.27 These criteria evolved from a consensus-based process conducted over numerous telephone confer-
quences and meetings of the twelve-member LIDC Steering Committee, which included radiologists and CAD researchers. Both standard-dose diagnostic CT scans and lower-dose CT scans from lung cancer screening examinations were acceptable. Each scan selected for the Database was required to have a collimation and reconstruction interval no greater than 3 mm (advances in technology forced a reduction from the 5 mm threshold initially published by the LIDC); no requirements with regard to scanner pitch, exposure, tube voltage, or reconstruction algorithm were imposed. Scans were limited to approximately six lung nodules with longest dimension less than 30 mm (consistent with the accepted upper limit of nodule size) and greater than or equal to 3 mm (a lower limit imposed for practical considerations), as determined by a cursory (and nonrecorded) review during case selection at the originating institution; the identification of a greater number of nodules during the subsequent image annotation process, however, was not grounds for case exclusion, and the image annotation process allowed for independent assessments of nodule size. The presence of other pathology, high levels of noise, and streak, motion, or metal artifacts was allowed unless these features compromised nodule interpretation, which was a judgment made by the LIDC radiologist at the originating institution during case selection. A nodule could be primary lung cancer, metastatic disease, a noncancerous process, or indeterminate in nature.

The 1018 CT scans had been acquired from 1010 different patients; it was retrospectively determined that two distinct scans from each of eight patients inadvertently had been included among the 1018 scans. These scans nevertheless were retained in the Database since the effort for image annotation already had been invested; users of the Database may identify these cases by the common patient ID in the respective image headers. A range of scanner manufacturers and models was represented (670 scans from seven different GE Medical Systems LightSpeed scanner models, 74 scans from four different Philips Brilliance scanner models, 205 scans from five different Siemens Definition, Emotion, and Sensation scanner models, and 69 scans from Toshiba Aquilion scanners). (The mention of commercial equipment is intended to specify the conditions of the present study and is not an endorsement by the LIDC/IDRI Research Group of this equipment.) The tube peak potential energies used for scan acquisition were as follows: 120 kV (n=818), 130 kV (n=31), 135 kV (n=69), and 140 kV (n=100). Tube current ranged from 40 to 627 mA (mean: 221.2 mA). Slice thicknesses were 0.6 mm (n=7), 0.75 mm (n=30), 0.9 mm (n=2), 1.0 mm (n=58), 1.25 mm (n=349), 1.5 mm (n=5), 2.0 mm (n=124), 2.5 mm (n=322), 3.0 mm (n=117), 4.0 mm (n=1), and 5.0 mm (n=3). Reconstruction interval ranged from 0.45 to 5.0 mm (mean: 1.74 mm). The in-plane pixel size ranged from 0.461 to 0.977 mm (mean: 0.688 mm). While the convolution kernels used for image reconstruction differ among manufacturers, these convolution kernels may be classified broadly as “soft” (n=67), “standard/nonenhancing” (n=560), “slightly enhancing” (n=264), and “overenhancing” (n=127) (in order of increasing spatial frequencies accentuated by each class).

II.B. Image annotation process

To identify as completely as possible all lung nodules in a scan without requiring forced consensus, a two-phase process was developed for the asynchronous interpretation of CT scans by a thoracic radiologist at each of four different LIDC/IDRI institutions (although five of the seven academic institutions participated in the interpretation process overall, only four institutions contributed to the interpretation of any one scan), as previously reported. A total of 12 radiologists participated in the image annotation process across all five sites over the course of the project. A comprehensive set of written instructions was available to each participating radiologist. These instructions evolved from a consensus-based process conducted over numerous telephone conferences and meetings of the twelve-member LIDC Steering Committee. In summary, the initial “blinded read phase” required each of the four radiologists to independently review a scan using a computer interface and mark lesions they identified as

(1) “nodule ≥ 3 mm” (defined as any lesion considered to be a nodule with greatest in-plane dimension in the range 3–30 mm regardless of presumed histology) [Fig. 1(a)]
(2) “nodule < 3 mm” (defined as any lesion considered to be a nodule with greatest in-plane dimension less than 3 mm that is not clearly benign) [Fig. 1(b)] or,
(3) “non-nodule ≥ 3 mm” (any other pulmonary lesion, such as an apical scar, with greatest in-plane dimension greater than or equal to 3 mm that does not possess features consistent with those of a nodule) [Fig. 1(c)].

Inherent in the definitions of all three lesion categories is the concept of a “nodule,” which was deliberately not defined by the LIDC/IDRI Research Group. In an earlier publication, we recognized that the notion of nodule may not represent a single entity capable of verbal definition, and we suggested that the term nodule is more appropriately applied to a spectrum of abnormalities, which is itself a subset of a broader spectrum of abnormalities that we termed “focal abnormality.” Based on this conceptualization, all nodules are focal abnormalities, but not all focal abnormalities are nodules. The two spectra span a multidimensional space that comprises lesion characteristics such as shape, texture, and margin sharpness. Within this context, each radiologist provided their own interpretation of the “noddleness” of each observed lesion during the image annotation process.

For each “nodule ≥ 3 mm” identified by a radiologist, that radiologist used the computer interface to construct outlines around the nodule in each CT section in which it appeared; for each lesion in one of the other two lesion categories identified by a radiologist, that radiologist used the computer interface to mark the approximate three-dimensional center-of-mass location. Electronic measure-
During the subsequent unblinded read phase, the anonymized blinded read results of all radiologists were revealed to each of the radiologists, who then independently reviewed their marks along with the anonymous marks of their colleagues; a radiologist’s own marks then could be left unchanged, deleted, switched in terms of lesion category, or additional marks could be added. Each radiologist was required to inspect all nodule \( < 3 \) mm and nodule \( \geq 3 \) mm marks placed during the blinded read; this requirement was not imposed on non-nodule \( \geq 3 \) mm marks. For each lesion that a radiologist identified as a nodule \( \geq 3 \) mm after the unblinded read phase, that radiologist independently assessed subjective characteristics of the nodule such as subtlety, internal structure, spiculation, lobulation, shape (sphericity), solidity, margin, and likelihood of malignancy. Each radiologist’s lesion-category designation and associated marks (spatial locations of all points in the outlines constructed for a nodule \( \geq 3 \) mm along with its characteristics and center-of-mass locations for a nodule \( < 3 \) mm and for a non-nodule \( \geq 3 \) mm) for each lesion were stored in a single XML file for each scan after the unblinded read phase (the XML schema is located at http://troll.rad.med.umich.edu/lidc/).

The blinded and unblinded read phases were intended to comprise a single, comprehensive process; therefore, the LIDC/IDRI Database only contains the final set of post-unblinded-read-phase marks in each of the 1018 XML files.

The nodule \( \geq 3 \) mm lesion category was the main focus of the Database; consequently, the research potential of these lesions was enhanced through the inclusion of radiologist outlines to capture spatial extent and the subjective assessment of nodule characteristics. Each outline was meant to be a localizing “outer border” so that, in the opinion of the radiologist, the outline itself did not overlap pixels belonging to the nodule. The radiologists were able to explicitly outline regions of exclusion within a nodule (an air-filled cavity, for example), which were then recorded as such in the XML file (Fig. 2). Three different in-house software systems were used to create nodule outlines and capture subjective nodule characteristic ratings. Each of three institutions used their own software, with which their radiologists were most familiar. The two institutions without in-house software both adopted the same system from another institution. One of these systems allowed for semiautomated creation of nodule outlines, while the other two systems were completely manual. The decision to allow multiple nodule outlining approaches was made after we conducted a study that demonstrated that the variation in nodule outlines derived from different radiologists substantially exceeded variation derived from different software tools. One of the three systems, the one used by three institutions, uses a semiautomated technique based on the Otsu method to compute a threshold for region growing. The system also provides interactive editing tools including region addition, subtraction, and morphological operations. Another system, the SIMBA image marking tool, was used by the Cornell radiologists. This completely web-based tool obtains images from a SIMBA web server. All computer assistance was disabled so that nodule outlines were created manually. The use of different software systems for data ac-

Fig. 1. Examples of lesions considered to satisfy the LIDC/IDRI definition of (a) a nodule \( \geq 3 \) mm, (b) a nodule \( < 3 \) mm, and (c) a non-nodule \( \geq 3 \) mm (reprinted with permission from Ref. 29).

ment tools were available to help the radiologists determine whether a lesion’s dimension exceeded the 3 mm threshold. Only transaxial sections were reviewed; nonaxial reformatted images and maximum-intensity projection images were not available, since such viewing configurations were not standard at all LIDC/IDRI institutions when data collection began. Each CT scan was initially presented at a standard brightness/contrast setting without magnification, but the radiologists were allowed to adjust brightness, contrast, and magnification as appropriate to enable the most complete interpretation of the scan.
I.C. Analysis of lesions

The final marks placed by the four radiologists were reviewed and inventoried retrospectively by each scan, using visual marks indicated by a LIDC/IDRI principal investigator through a computer interface using in-house software. This inventory was conducted for internal LIDC/IDRI assessment purposes. The interface allowed visual distinction among the marks of different radiologists as recorded in the XML file, and the displayed marks of each radiologist were color-coded to allow visual distinction among the marks as recorded in the XML file. Each mark was identified by the radiologist who placed it, and the complete nodule outline created by the radiologist was displayed within the images at the spatial location indicated by the radiologist's marks.

The final marks placed by the four radiologists were reviewed and inventoried retrospectively by each scan, using visual marks indicated by a LIDC/IDRI principal investigator through a computer interface using in-house software. This inventory was conducted for internal LIDC/IDRI assessment purposes. The interface allowed visual distinction among the marks of different radiologists as recorded in the XML file, and the displayed marks of each radiologist were color-coded to allow visual distinction among the marks as recorded in the XML file. Each mark was identified by the radiologist who placed it, and the complete nodule outline created by the radiologist was displayed within the images at the spatial location indicated by the radiologist's marks.

The interface also provided the ability to sequence through the sections of the scan for visual inspection. Each scan was visually reviewed and inventoried retrospectively by each radiologist, and the displayed marks of each radiologist were color-coded to allow visual distinction among the marks as recorded in the XML file. Each mark was identified by the radiologist who placed it, and the complete nodule outline created by the radiologist was displayed within the images at the spatial location indicated by the radiologist's marks.

The interface also provided the ability to sequence through the sections of the scan for visual inspection. Each scan was visually reviewed and inventoried retrospectively by each radiologist, and the displayed marks of each radiologist were color-coded to allow visual distinction among the marks as recorded in the XML file. Each mark was identified by the radiologist who placed it, and the complete nodule outline created by the radiologist was displayed within the images at the spatial location indicated by the radiologist's marks.
II.D. Quality assurance evaluation

Based on the inventory of nodules, a retrospective manual quality assurance (QA) protocol was implemented by a LIDC principal investigator to ensure the integrity of the marks stored in the final XML file of each case. All nodule ≥ 3 mm marks and nodule < 3 mm marks were reviewed visually, along with any non-nodule ≥ 3 mm marks spatially associated with such nodule marks. Seven categories of potential errors were defined, including errant marks on nonpulmonary regions or stray marks within the lungs, marks from multiple lesion categories assigned to the same lesion by the same radiologist, more than a single nodule < 3 mm mark or more than one set of nodule ≥ 3 mm outlines assigned to the same lesion by the same radiologist, nodule ≥ 3 mm outlines for a single lesion that are discontinuous across the CT sections or visually aberrant, lesions marked as nodule ≥ 3 mm by three radiologists that were not assigned any mark at all by the fourth radiologist, and obvious inconsistencies between the physical size of a lesion and the assignment of the nodule < 3 mm or nodule ≥ 3 mm categories. The same radiologist, however, could assign multiple non-nodule ≥ 3 mm marks to the same lesion, since such lesions could be spatially extensive and the non-nodule marks were intended merely to serve as a guide. Potential errors were referred to the responsible radiologist, who either corrected the mark in a manner that resolved the inconsistency or confirmed that the mark was intentional. Since the QA protocol was not designed to provide radiologists with a third evaluation of a scan after the blinded and unblinded read phases, only marks that were identified as belonging to one of the QA categories could be modified by the radiologists at this stage. During the creation of the Database, an automated algorithm was developed to alert radiologists, in real-time during their unblinded read of a case, to potential errors corresponding to QA categories that were amenable to such an algorithm; the intent of this algorithm was to reduce the burden on the subsequent manual, retrospective QA process.

II.E. Database access

The original DICOM images (anonymized and uncompressed) and associated XML files for all 1018 CT scans (which, collectively, comprise the LIDC/IDRI Database) have been uploaded to the National Biomedical Image Archive (NBIA) and are publicly and freely available for download from http://ncia.nci.nih.gov/. Registration is required to access the Database, and a username and password must be created. Once registered, users click on the “search images” button to reach the basic search interface, from which various queries are possible. To access the desired databases, the user selects “LIDC” or “IDRI” (or both) from the “Collections” category and then clicks the “submit” button.

The NBIA uses a “shopping cart” paradigm, where items of interest are identified by a user and added to the “basket.” Note that all images are available free of charge; the shopping cart is just a useful and familiar paradigm. Data may be obtained at any level of granularity—collection, patient, study, series, or image. To obtain all images and XML files for the entire collection, the NBIA provides a “check all” button that causes all series to be selected. The user can then click on the “Add to basket” button, and all checked series will be added to the basket. The user can then “view my basket” to see the series that have been selected. To download the image data (and associated XML files), the user selects “download all items;” the requested files are then compressed into a “.zip” file and downloaded.

The NBIA allows users to query the Database and select subsets of the LIDC/IDRI collections, which may be performed using the query interface provided. Users may also select subsets that have already been created by other users through the use of “shared lists,” which are listed under the “tools” section of the interface. Users can create and share lists of series, so that a consistent training or testing data set can be used by others; however, in the current implementation (December 2010) one must know the exact name of the desired shared list. A few example shared lists have been created. To view these lists, the user can select “Search Shared List” and then enter the exact text “LIDC_thin_slice” or “LIDC_IDRI_thin_slice” (note the underscore character is used rather than spaces between letters) to return all cases with slice thickness < 2 mm in each collection.

Information on the LIDC/IDRI Database is available on the NIH wiki page at https://wiki.nci.nih.gov/display/CIP/LIDC. This page includes information on (a) XML file format, (b) LIDC radiologist instructions, (c) nodule sizes according to a standard metric,37 with a link to a downloadable spreadsheet, (d) a link to software that generates one possible set of distinct nodules based on a spatial grouping of the lesion marks contained in a scan’s XML file and creates nodule probability maps from the radiologists’ nodule outlines,33 (e) the spreadsheet that contains all of the pathology information available for nodules ≥ 3 mm in the Database, and (f) a link to the project that is currently converting the XML files to the caBIG Annotation and Image Markup (AIM) format.

Although all unique identifiers (UIDs) contained within the DICOM fields of each image of a scan and all UIDs that were imported to the corresponding XML file were anonymized initially at the local institution, images and XML files were anonymized again in a consistent manner centrally before submission to the NBIA. The XML file for a scan is organized so that the assigned marks are grouped by radiologist. Each lesion marked by any radiologist is specified by a unique identifier specific to that radiologist’s mark for that specific lesion, but associations of lesions across radiologists are not provided. The relationship among marks and physical lesions will need to be interpreted by Database users based on algorithms that group marks, for example, based on spatial proximity metrics. The marks recorded in the publicly available XML files were not intended to be associated with...
TABLE I. Summary of lesions identified by LIDC/IDRI radiologists across all 1018 CT scans.

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one radiologist assigned either a nodule ≥ 3 mm mark or a nodule &lt; 3 mm mark</td>
<td>7371</td>
</tr>
<tr>
<td>At least one radiologist assigned a nodule ≥ 3 mm mark</td>
<td>2669</td>
</tr>
<tr>
<td>All four radiologists assigned a nodule ≥ 3 mm mark</td>
<td>928</td>
</tr>
<tr>
<td>All four radiologists assigned a nodule ≥ 3 mm mark or all four radiologists assigned a nodule &lt; 3 mm mark</td>
<td>1940</td>
</tr>
<tr>
<td>All four radiologists assigned either a nodule ≥ 3 mm mark or a nodule &lt; 3 mm mark</td>
<td>2562</td>
</tr>
</tbody>
</table>

Given that a lesion is designated a nodule if at least one radiologist assigns to the lesion either a nodule ≥ 3 mm mark or a nodule < 3 mm mark, the Database contains 7371 nodules (as previously mentioned). Figure 4 presents the proportions of these 7371 nodules that were (1) marked as a nodule by different numbers of radiologists or (2) assigned any mark at all (including non-nodule ≥ 3 mm) by different numbers of radiologists. 744 nodules (10.1%) were marked by only a single radiologist and 3396 nodules (46.1%) received marks (regardless of the lesion category) from all four radiologists. Considering specifically nodule marks assigned to these 7371 nodules, 1481 nodules (20.1%) received a single nodule ≥ 3 mm mark or a single nodule < 3 mm mark (irrespective of the number of non-nodule marks that may have been assigned), and 2562 nodules (34.8%) received nodule marks from all four radiologists.

The main focus of the LIDC/IDRI effort was the identification of lesions considered to be nodules ≥ 3 mm. Since these lesions have a greater probability of malignancy than lesions in the other two categories and since these lesions...
receive the greatest attention from CAD developers, radiologist variability in the assessment of such lesions is of most interest. Figure 5 presents the proportions of the 2669 lesions marked by at least one radiologist as a nodule $\geq 3$ mm that were marked as such by different numbers of radiologists. 777 (29.1%) of these 2669 lesions were assigned nodule $\geq 3$ mm marks by only a single radiologist Fig. 6(a), while 928 (34.8%) of these lesions received nodule $\geq 3$ mm marks from all four radiologists Fig. 6(b). Differences of opinion among radiologists regarding lesion category could arise based on the subjective assessment of lesion size and the 3 mm threshold; in an attempt to compensate for such differences, Fig. 7 presents the proportions of the 2669 lesions marked by at least one radiologist as a nodule $\geq 3$ mm that were marked as either a nodule $\geq 3$ mm or a nodule $< 3$ mm by the other radiologists. In this analysis, agreement improves with 1547 such lesions (58.0%) receiving either nodule mark from all four radiologists.

Just as variability exists in the lesion categories assigned by different radiologists to different lesions, so, too, does variability exist in the subjective lesion characteristic assessments of the radiologists who marked a lesion as a nodule $\geq 3$ mm. Variability in radiologists’ assessments of these characteristics for the same physical nodules is a topic for future evaluation.

The QA protocol was an essential component of the LIDC/IDRI process. Of the 1018 cases, 449 cases (44.1%) had QA issues that required further consideration by at least one radiologist. These issues spanned all defined QA categories. In only 25 of these cases did the radiologist intend to assign the mark that flagged the QA issue.

The Database contains 12 nodule $\geq 3$ mm pairs that were considered to be two separate nodules $\geq 3$ mm by at least one radiologist and a single extended nodule $\geq 3$ mm by at least one other radiologist (Fig. 8). One nodule $\geq 3$ mm triplet exists for which three radiologists considered three separate nodules $\geq 3$ mm to be present, while the fourth radiolo-
gist identified a single extended nodule $\geq 3$ mm. Six pairs of lesions exist that are considered a single extended nodule $\geq 3$ mm by at least one radiologist and a nodule $\geq 3$ mm and a separate nodule $< 3$ mm or non-nodule $\geq 3$ mm by at least one other radiologist (Fig. 9). Discrepancy over the assessment of these lesions further demonstrates the variability of radiologist opinion that is captured in the Database.

IV. DISCUSSION

The collection of clinical CT scans with lung nodules from multiple institutions is a worthwhile endeavor that becomes even more relevant with the inclusion of annotations by a radiologist. The LIDC/IDRI sought to further improve on the utility of its database by acquiring and storing the annotations of multiple radiologists (without forced consensus) so that the real-world variability of image interpretation could be captured and incorporated into future studies. The inclusion of serial CT scans, images from complementary modalities, clinical data, and pathologic information would have provided the Database with an even greater level of utility; of these desirable elements, only pathology data are available (although serial CT scans inadvertently exist for eight patients) and only for a subset (26.3%) of cases, with diagnoses captured at the level of individual patients rather than individual lung nodules.

The LIDC/IDRI Database is intended to provide the international medical imaging research community with a reference database. The Database is a research resource with several obvious applications, but with potential utility limited only by the creativity of those who use it. A solid understanding of the process through which the Database was created, along with important caveats on its use, is required (1) to ensure that investigators conduct appropriately designed studies and (2) to allow those engaged in peer review to apply appropriate standards to the methodologies and results of these investigators.

The most immediately apparent use of the Database is in the development of CAD methods for automated lung nodule detection. The reference provided by the Database, however, intentionally reflects the highly tangible variability in radiologists’ identification and classification of lesions according to the three defined categories. Therefore, the challenge for investigators is how to define the detection targets for the
Fig. 9. A lesion identified by one radiologist as a single nodule \( \geq 3 \) mm that was considered to be a nodule \( \geq 3 \) mm (arrowhead) and a separate nodule \(< 3 \) mm (arrow) by another radiologist and a non-nodule \( \geq 3 \) mm (arrowhead) and a separate nodule \(< 3 \) mm (arrow) by two other radiologists.

Training and/or testing of their CAD methods. These targets could range from only those nodules marked as nodule \( \geq 3 \) mm by all four radiologists (\( n=928 \)) (the more conservative approach) to the larger set of nodules marked as nodule \( \geq 3 \) mm by at least one radiologist (\( n=2,669 \)), assuming the investigator is satisfied with a 3-mm lower limit on nodule size. If a larger size threshold is desired, then nodule size must be evaluated from the radiologist outlines, and the impact of size metric, lesion boundary definition, and contour-combining approach across the one to four outlines that might be provided must be considered in the study design and reported in any subsequent publications.

The image annotation process presented the LIDC/IDRI radiologists with a somewhat artificial task that differed from the clinical assessments to which they are accustomed in routine practice. The radiologists’ assignment of a lesion category to a specific lesion required three inherently subjective steps: (1) identification of a lesion (Is the observed structure an abnormality or normal anatomy?), (2) determination of lesion size (Is the longest dimension of the lesion greater than or less than 3 mm? Does the longest dimension exceed 30 mm?), and (3) evaluation of lesion features (Does the lesion represent a “nodule”? If the lesion is less than 3 mm, is it clearly benign?). Any possible combination of the three categories plus the “no mark” option assigned to the same lesion by different radiologists could be considered reasonable due to this inherent subjectivity.

The blinded and unblinded read phases were intended to comprise a single, comprehensive image annotation process. The main purpose of the unblinded read was not to identify lesions previously unmarked by any radiologist during the blinded read (although this certainly was possible and did occur), but rather to give each radiologist a look at the marks placed by the other three radiologists who interpreted the scan (and a second look at their own blinded-read marks) to identify as completely as possible all nodules in a scan without requiring forced consensus. The unblinded read presented each radiologist with the marks placed by all radiologists during the blinded reads; the task for each radiologist then was to assimilate the interpretations of all the radiologists into their own final interpretation. Each radiologist was required to inspect all nodule \(< 3 \) mm and nodule \( \geq 3 \) mm marks placed during the blinded read. The unblinded read effectively eliminated the “identification” component of the subjective process (except that lesions overlooked by all four radiologists during the blinded read would likely remain undetected during the unblinded read) and allowed each radiologist to focus on the relevance of each LIDC/IDRI lesion category to the marks placed during the blinded reads. The marks provided in the LIDC/IDRI Database, therefore, are correlated and do not represent the independent interpretations of the radiologists. Instead, the marks more accurately represent agreement and disagreement in the radiologists’ interpretations of what is a nodule in the context of the LIDC/IDRI lesion categories. A lesion that remains marked as a nodule by only a single radiologist after the unblinded read should not indicate that the other radiologists failed to “detect” the lesion. Rather, since the unblinded read provides each radiologist with an opportunity to review every marked nodule from the blinded read, the other radiologists may be presumed to have specifically chosen not to label the lesion as a nodule because they did not agree that it was a nodule. Rather than forcing consensus, the LIDC/IDRI Research Group deliberately chose to record these differences among readers.

Lesions marked as nodule \( \geq 3 \) mm by more than one radiologist present two more sources of variability due to radiologists’ subjective assessments: nodule characteristics and nodule outlines. Consistency among radiologists’ ratings of the nodule characteristics was not evaluated by the LIDC/IDRI, but such analyses have been reported by other investigators. The rating scheme for the nodule characteristics may be found at http://troll.rad.med.umich.edu/lidc/voi%20array.xsd. One characteristic, “internal structure,” includes the categories “soft tissue,” “fluid,” “fat,” and “air,” and another characteristic, “calcification,” includes five categories of calcification morphology and distribution, if present. The other characteristics allow a single rating on a five-point scale, some of which include descriptive labels for all five points, some have such labels for the two extreme points only, and others also include a label for the middle point. The “likelihood of malignancy” characteristic was especially subjective, since the radiologists were not provided with any clinical information about the patients; as a general guide, likelihood of malignancy was rated under the assumption of a 60-year-old male smoker. When investigators report the selection of lesions used for a study based on these characteristics, the manner in which differences among radiologist ratings were reconciled must be reported.

Differences in nodule outlines and the resulting variance in nodule volume and nodule margin characteristics could be substantial. These differences include variability in the interpretation of in-plane nodule boundaries [Fig. 10(a)], the superior or inferior extents of nodules [Fig. 10(b)], and the perceived connection (or lack thereof) between spatially
similar nodules (see Fig. 8). The LIDC/IDRI QA process identified and corrected visually erratic or inconsistent nodule outlines. Through this manual process, however, outline errors may have been overlooked, and errors in, for example, outline spatial coordinate ordering within an XML file might not have been visually apparent. More subtle errors, such as portions of an outline that encompass zero nodule area based on the outer border definition [Fig. 10(c)], were too tedious to identify manually and would have been too onerous to correct. Lesions marked by a radiologist as nodule $\geq 3$ mm but with outlines constructed by the radiologist that yield a greatest diameter less than 3 mm are possible. An automated method that could have been developed to more completely identify such errors was not explored. It should also be noted that state-of-the-art nodule segmentation algorithms tend to create three-dimensional surfaces rather than creating two-dimensional contours in each of the CT sections, which is the LIDC/IDCR standard against which such algorithms will be compared.

Investigators who use the LIDC/IDRI Database should explicitly indicate the cases used to perform their study when reporting results. Query parameters and inclusion and exclusion criteria should be specified with enough detail to allow others to identify the exact same subset of cases. The use of the “reference list” function provided by NBIA was specifically implemented to allow an explicit listing of cases so that other investigators could evaluate the performance of their algorithms on identical sets of cases. The creation and use of reference lists should be promoted, and investigators should be encouraged to publish their results along with the specific reference lists that were used. The training/testing approach should be fully disclosed along with the manner in which the cases were divided between training and test sets. Investigators also need to specify the metric used to establish “truth” from the LIDC/IDRI Database (e.g., “median” lesion boundary, center-of-mass derived from the union of lesion boundaries present, median boundary error normalized by spatial variance of radiologists, pathologic diagnosis for those cases that contain this information) and the criterion used to indicate agreement between their CAD output and this reference truth (e.g., for the detection task, greater than 50% area overlap between the actual nodule and the detected structure, inclusion of the detected structure’s center-of-mass within the boundary of the actual nodule, less than 5-mm separation between the centers-of-mass of the detected structure and of the actual lesion). Finally, the performance evaluation method (e.g., ROC analysis, FROC analysis, Dice coefficient) must be thoroughly described in the context of the task, the data set used, the training/testing paradigm, the truth metric, and the scoring approach.

The Database intentionally was not configured to allow blinded evaluation of CAD techniques. Through such an approach, the Database would be segregated into dedicated training and test sets; investigators would only have access to designated training cases for the development of their CAD techniques, and the final method would be applied to the test cases, which were not previously available to the investigators. This configuration was not implemented due to the limitations that necessarily would be imposed on investigators’ use of the Database and an inability to anticipate the full range of applications for which investigators might use the Database.

No claim is made that every lesion that could conceivably be considered a nodule has been marked in the Database. We have already reported that fewer lesions would have been marked as nodule $\geq 3$ mm had only three radiologists contributed to the image annotation process; conversely, had a fifth radiologist been involved, additional lesions might have been defined as nodule $\geq 3$ mm. The presence of such additional nodules could result from oversight of the lesion by all four radiologists or from the collective assessment that the observed lesion does not belong to one of the defined lesion categories [for example, it is determined to be less than 3 mm in maximum diameter and clearly benign, it is judged a
nonintraparenchymal lesion (e.g., bronchiolitis, pleural or fissural lesion), or it is interpreted as a normal variant.

The LIDC/IDRI process involved the creation of an image review paradigm, an annotation scheme, a QA protocol to ensure the integrity of the marks, and the specification of a database format, some elements of which have been introduced into, and enhanced by, subsequent initiatives including NCI-funded caBIG Imaging Workspace projects such as the Annotation and Image Markup (AIM) project and the Algorithm Validation Tool (AVT) as well as some aspects of the Radiological Society of North America’s Quantitative Imaging Biomarker Alliance (QIBA) effort. The NCI caBIG Imaging Workspace is currently supporting an effort to convert the data contained in the LIDC/IDRI XML files to the AIM format, which, when completed, will make the LIDC/IDRI data accessible to AIM-enabled visualization and analysis tools.

Most of the limitations of the Database have been previously mentioned, including the availability of patient-based pathologic diagnoses for only a subset of cases, the lack of clinical information, the inability to perform reader studies because the XML files do not maintain radiologist identities or a consistent ordering of radiologist marks, the interpretation of CT scans using only transaxial images, the somewhat artificial nature of the lesion categories relative to clinical practice, the interpretation of every case was not performed by the same four radiologists, and the design of the manual QA process that focused mostly on the visual identification of objective lesion annotation errors and did not analyze, for example, inconsistencies in the subjective nodule characteristic ratings (although the benefit of this QA process to the integrity of the Database should not be understated). The extent of the Database meant that data necessarily were collected over a period of several years, which introduced another limitation: more than a single radiologist typically handled the workload at each of the five LIDC/IDRI institutions that participated in the image interpretation process (although each radiologist was trained by the institution’s primary LIDC/IDRI radiologist to become familiar with the details of the process). During this time an individual radiologist’s interpretation of the lesion categories and image annotation instructions could have drifted. For example, the non-nodule \( \geq 3 \) mm mark was intended for lesions at least 3 mm in maximum in-plane extent, but the Database contains examples of such marks assigned to lesions clearly less than 3 mm in diameter, especially when another radiologist had assigned a nodule \(< 3 \) mm mark to that same lesion during the blinded read. A lesion category for non-nodule lesions less than 3 mm was intentionally not created, but use of the non-nodule \( \geq 3 \) mm category seems to have expanded in the minds of some radiologists to include any non-nodule lesion regardless of size. Differences of opinion regarding the 3-mm threshold certainly contribute to variability in lesion category assignment, in general.

The LIDC/IDRI Research Group has succeeded in the creation of an extensive, publicly available database of annotated thoracic CT scans. The Database, while not without its limitations, represents the culmination of a deliberate and well-reasoned, consensus-based process to develop a high-impact, lasting resource. The process and the lessons learned from this experience are in many ways just as valuable as the database that resulted. A great deal of energy was devoted to harnessing the distinct experiences and divergent opinions of the member institutions and other participating individuals to provide a solid foundation for a robust Database designed to meet the anticipated needs of CAD investigators. Before case collection could begin, considerable time was spent first to identify and then to address a number of critical technical and clinical issues to ensure a focused yet broadly meaningful product; this lengthy but absolutely essential foundation-laying process was evolutionary in nature, as every issue raised generated multiple other issues for consideration. Over the course of many weekly telephone conference calls and regularly scheduled face-to-face meetings during which discordant views gradually gave way to mutual agreement on a common vision and idealized expectations were eventually balanced by practical constraints, a roadmap for the Database unfolded. This roadmap included guidelines for scan inclusion, well-defined lesion categories, a rationale for the information collected from lesions in each category, detailed instructions to the LIDC/IDRI radiologists, a unique image interpretation paradigm, an electronic workflow to transmit images and associated annotations across multiple institutions, a thorough quality assurance protocol, detailed documentation, and an infrastructure for maintaining and distributing the data. Now that such a comprehensive model for database development has been established and implemented, the hope is that other disease states, other imaging modalities, and other radiologic tasks will benefit from future adaptations of the LIDC/IDRI approach.

V. CONCLUSION

The LIDC/IDRI has created a publicly available, freely accessible database of thoracic CT image data along with the annotations of those images by experienced radiologists. The LIDC/IDRI Database of 1018 thoracic CT scans and associated XML-based annotations has been created to stimulate the development of CAD methods for lung nodule detection, classification, and quantitative assessment. Through a consensus-based public-private partnership, seven academic centers and eight medical imaging companies collaborated to identify, address, and resolve challenging organizational, technical, and clinical issues to provide a solid foundation for a robust database. This publicly available database contains 2669 lesions marked as a nodule \( \geq 3 \) mm by at least one of four radiologists and 928 lesions marked as such by all four radiologists. Each radiologist’s annotations for these lesions include nodule outlines and subjective nodule characteristic ratings. The LIDC/IDRI Database is expected to become a powerful resource as a reference database for the international medical imaging research community. A solid understanding of the process through which the Database was created, along with important caveats on its use, is required (1) to ensure that investigators conduct appropriately
ACKNOWLEDGMENTS

This paper is dedicated to the memory of Geoffrey McLennan, M.D., Ph.D., who served as the Chair of the LIDC/IDRI Steering Committee since the inception of the project. Dr. McLennan provided the constant source of motivation, perspective, and determination that moved this database from an idea to reality. His extraordinary scientific and clinical vision, combined with his unfettered perseverance and uncompromising optimism, will be greatly missed by all his co-authors, colleagues, and friends. The authors would like express their sincere appreciation to the late Robert F. Wagner, Ph.D., whose enlightened perspective on computer-aided diagnostic methods, including measurement of nodules. A.P.R. receives research support in the form of grants and contracts from: NCI, American Legacy Foundation for the National Institutes of Health from contributions provided by the medical imaging companies that participated in the IDRI. Disclosure statement: S.G.A. and H.M. receive royalties and licensing fees through the University of Chicago related to computer-aided diagnosis. H.M. is a consultant to Riverain, a company that produces software for lung nodule detection. A.P.R. is a paid consultant of and holds stock in VisionGate, Inc. A.P.R. is a coinventor on a patent and other pending patents owned by Cornell Research Foundation which are non-exclusively licensed to General Electric and are related to technology involving computer-aided diagnostic methods, including measurement of nodules. A.P.R. receives research support in the form of grants and contracts from: NCI, American Legacy Foundation, Flight Attendants’ Medical Research Institute, AstraZeneca, Inc., GlaxoSmithKline and Carestream Health Inc. D.Y. is a named inventor on a number of patents and patent applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF) are non-exclusively licensed to General Electric. As an inventor of these patents, D.Y. is entitled to a share of any compensation which CRF may receive from its commercialization of these patents.

*Author to whom correspondence should be addressed. Fax: 773-702-0371; Electronic mail: s-armato@uic.edu*

*Present address: University of Dundee–Ninewells Hospital and Medical School, Clinical Research Centre (CRC), James Arroitt Drive, Dundee DD1 9SY, Scotland, United Kingdom.*

*Present address: Department of Radiology, Columbia University Medical Center, 710 West 168th Street, NI-B-04H, New York, New York 10032.*

*Previous address: Department of Radiology, Weill Cornell Medical College, New York, New York.*

*Present address: Clinical Research Imaging Centre, Queen’s Medical Research Institute, University of Edinburgh, 47 Little France Crescent, Edinburgh EH16 4TJ, United Kingdom.*


A Comparison of Decision Tree Ensemble Creation Techniques

Robert E. Banfield, Student Member, IEEE, Lawrence O. Hall, Fellow, IEEE, Kevin W. Bowyer, Fellow, IEEE, and W.P. Kegelmeyer, Member, IEEE

Abstract—We experimentally evaluate bagging and seven other randomization-based approaches to creating an ensemble of decision tree classifiers. Statistical tests were performed on experimental results from 57 publicly available data sets. When cross-validation comparisons were tested for statistical significance, the best method was statistically more accurate than bagging only on eight of the 57 data sets. Alternatively, examining the average ranks of the algorithms across the group of data sets, we find that boosting, random forests, and randomized trees are statistically significantly better than bagging. Because our results suggest that using an appropriate ensemble size is important, we introduce an algorithm that decides when a sufficient number of classifiers has been created for an ensemble. Our algorithm uses the out-of-bag error estimate, and is shown to result in an accurate ensemble for those methods that incorporate bagging into the construction of the ensemble.

Index Terms—Classifier ensembles, bagging, boosting, random forests, random subspaces, performance evaluation.

1 INTRODUCTION

Bagging is one of the older, simpler, and better known techniques for creating an ensemble of classifiers [1]. A number of other randomization-based ensemble techniques have been introduced. Some of the more prominent of these include boosting [2], [3], [4], random subspaces [5], random forests [6], and randomized C4.5 [7]. We present the results of an experimental study aimed at determining the extent to which any of these other techniques offer an increase in accuracy over bagging.

This is the largest such experimental study to date, in terms of the number of experimental data sets and the breadth of different techniques considered. We compare boosting, random subspaces, three variations of random forests, and randomized C4.5 against standard bagging. We present experimental results on a total of 57 different data sets. This includes all the data sets used in previous studies on boosting [3], random subspaces [5], random forests [6], and randomized C4.5 [7], plus two additional data sets.

This is also the most rigorous such study to date, looking at statistical significance based on the typical 10-fold cross-validation evaluation method and contrasting this with significance based on the improved 5 × 2-fold cross-validation proposed by Dietterich [8] and modified by Alpaydin [9]. A paired t-test on the results of a 10-fold cross-validation is the typical approach used in the literature when statistical significance is reported. Dietterich notes that the 10-fold cross-validation violates the assumptions of the statistical test, in a way that results in an underestimation of the variance, leading to results being declared statistically significant more frequently than they should. Alpaydin notes that Dietterich’s method can produce instability based on the order of the cross-validations, and corrects for this using an F-test.

In [10], an approach based on average algorithm rank was argued as the best way to evaluate multiple algorithms on multiple data sets. It allows for a summary decision to be made on statistically significant performance differences over the whole group of data sets and we have applied it for that purpose.

This work extends our previous results [11] in several important respects.

1. Results for boosting are now included in our evaluation.
2. The number of data sets used is greatly increased.
3. A much larger ensemble size is considered.
4. The statistical analysis includes the 5 × 2-fold approach, as well as the typical 10-fold cross-validation, and an average rank analysis. These extensions have altered some previous conclusions and made some additional insights possible.
5. A method to determine when to stop adding classifiers to an ensemble is introduced.

2 RANDOMIZATION-BASED ENSEMBLE CREATION TECHNIQUES

We report on an experimental evaluation that looks at bagging as a baseline against which to compare other randomization-based ensemble techniques. The other techniques considered here are boosting, random subspaces, randomized C4.5, and random forests. Bagging, boosting, and random subspaces are general techniques that can be used with any type of base classifier. However, the evaluation reported here focuses on using decision trees as the base classifier.

Bagging creates an ensemble of classifiers by sampling with replacement from the set of training data to create new training sets called “bags” [1]. In the results reported here, as is the case for most work on bagging, the number of items in each bag is the same as the number of items in the set of training data and a separate classifier is trained from each bag. We consider ensembles consisting of up to 1,000 classifiers.

Ho’s random subspace technique selects random subsets of the available features to be used in training the individual classifiers in an ensemble [5]. Ho’s approach randomly selects one half of the available features for each decision tree and creates ensembles of size 100. In one set of experiments, the random subspace technique gave better performance than either bagging or boosting for a single train/test split for four data sets. Another set of experiments involved 14 data sets that were randomly split into halves for training and testing. Ten random splits were done for each of the 14 data sets. For each data set, the minimum and maximum of the 10 accuracies were deleted and the remaining eight values averaged. Qualitatively, it appears that random subspaces resulted in higher accuracy than either bagging or boosting on about five of the 14 data sets. The differences in accuracy were not evaluated for statistical significance. Ho summarized the results as follows: “The subspace method is better in some cases, about the same or worse in other cases when compared to the other two forest building techniques [bagging and boosting]” [5]. One other conclusion was that “the subspace method is best when the data set has a large number of features and samples, and that it is not good when the data set has very few features coupled with a very small number of samples or a large number of classes” [5].

Breiman’s random forest technique blends elements of random subspaces and bagging in a way that is specific to using decision trees as the base classifier [6]. At each node in the tree, a subset of the
available features is randomly selected and the best split available within those features is selected for that node. Also, bagging is used to create the training set of data items for each individual tree. The number of features randomly chosen (from \( n \) total) at each node is a parameter of this approach. Following [6], we considered versions of random forests created with random subsets of size 1, 2, and \( \log_2(n) + 1 \). Breiman reported on experiments with 20 data sets, in which each data set was randomly split 100 times into 90 percent for training and 10 percent for testing. Ensembles of size 50 were created for Adaboost and ensembles of size 100 were created for random forests, except for the zip code data set, for which ensembles of size 200 were created. Accuracy results were averaged over the 100 train-test splits. The random forest with a single attribute randomly chosen at each node was better than AdaBoost on 11 of the 20 data sets. The random forest with \( \log_2(n) + 1 \) attributes was better than AdaBoost on 14 of the 20 data sets. The results were not evaluated for statistical significance.

Dietterich introduced an approach that he termed randomized C4.5 [7]. We will refer to this more generally as random trees. In this approach, at each node in the decision tree, the 20 best tests are determined and one of them is randomly selected for use at that node. With continuous attributes, it is possible that multiple tests from the same attribute will be in the top 20. Dietterich reported on experiments with 33 data sets from the UC Irvine repository. For all but three of the data sets, a 10-fold cross-validation approach was followed. The other three used a train/test split as included in the distribution of the data set. Random tree ensembles were created using both unpruned and pruned (with certainty factor 10) trees, and the better of the two was manually selected for comparison against bagging. Differences in accuracy were tested for statistical significance at the 95 percent level. With this approach, it was found that randomized C4.5 resulted in better accuracy than bagging six times, worse performance three times, and was not statistically significantly different 24 times.

Freund and Schapire introduced a boosting algorithm [3] for incremental refinement of an ensemble by emphasizing hard-to-classify data examples. This algorithm, referred to as AdaBoost.M1, creates classifiers using a training set with weights assigned to every example. Examples that are incorrectly classified by a classifier are given an increased weight for the next iteration. Freund and Schapire showed that boosting was often more accurate than bagging when using a nearest neighbor algorithm as the base classifier, though this margin was significantly diminished when using C4.5. Results were reported for 27 data sets, comparing the performance of boosting with that of bagging using C4.5 as the base classifier. The same ensemble size of 100 was used for boosting and bagging. In general, 10-fold cross-validation was done, repeated for 10 trials, and average error rate reported. For data sets with a defined test set, an average of 20 trials was used with this test set. Boosting resulted in higher accuracy than bagging on 13 of the 27 data sets, bagging resulted in higher accuracy than boosting on 10 data sets, and there were 4 ties. The differences in accuracy were not evaluated for statistical significance.

Table 1 shows a comparative summary of experiments and results of this work with the previously discussed work.

### Table 1: Selected Aspects of This Work Compared with Previous Works

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Datasets</th>
<th>Ensemble Size</th>
<th>Experiments</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho [5], random subspaces</td>
<td>18</td>
<td>100</td>
<td>half-half split, repeat 10 times, average of middle 8</td>
<td>RS better than bagging, boosting in 5 or 6 of 14 data sets; no statistical test</td>
</tr>
<tr>
<td>Breiman [6], random forests</td>
<td>20</td>
<td>RF: 100, boosting: 50</td>
<td>90-10 split, 100 trials</td>
<td>RF better than Adaboost in 11 of 19 data sets, no statistical test</td>
</tr>
<tr>
<td>Dietterich [7], random trees</td>
<td>33</td>
<td>RT: 200 bagging: 200 boosting: 100</td>
<td>10-fold cross-val select pruned or unpruned trees</td>
<td>statistically significantly better in 6 of 33 data sets</td>
</tr>
<tr>
<td>Freund [3], boosting (AdaBoost)</td>
<td>27</td>
<td>100</td>
<td>10-fold cross-val, 10 trials</td>
<td>boosting better than bagging in 12 of 27 data sets, no statistical test</td>
</tr>
<tr>
<td>this work</td>
<td>57</td>
<td>1,000</td>
<td>10-fold cross-val, 5x2-fold cross-val, Friedman-Holm test</td>
<td>no stat. sig. improvement over bagging in 38 of 57 data sets; boosting_1000, RF.1gN best; bagging, random subspaces equiv.</td>
</tr>
</tbody>
</table>

### 3 Experimental Design

In this work, we used the free open source software package “OpenDT” [13] for learning decision trees in parallel. This program has the ability to output trees very similar to C4.5 release 8 [14], but has added functionality for ensemble creation. In OpenDT, like C4.5, a penalty is assessed to the information gain of a continuous attribute with many potential splits. In the event that the attribute set randomly chosen provides a “negative” information gain, our approach is to randomly rechoose attributes until a positive information gain is obtained, or no further split is possible. This enables each test to improve the purity of the resultant leaves. This approach was also used in the WEKA system [15].

As AdaBoost.M1 was designed for binary classes, we use a simple extension to this algorithm called AdaBoost.M1W [2] which modifies the stopping criteria and weight update mechanism to deal with multiple classes and weak learning algorithms. Our boosting algorithm uses a weighted random sampling with replacement from the initial training set, which is different from a boosting-by-weighting approach where the information gain is adjusted according to the weight of the examples. Freund and Schapire used boosting-by-resampling in [3]. There appears to be no accuracy advantage for boosting-by-resampling or boosting-by-reweighting [16], [17], [18] though Breiman reports increased accuracy for boosting-by-resampling when using unpruned trees [19]. We use unpruned trees because of this and, in general, for increased ensemble diversity [20]. Boosting-by-resampling may take longer to converge than boosting-by-reweighting though.

We have made a modification to the randomized C4.5 ensemble creation method in which only the best of the \( \log_2(n) + 1 \) attributes is...
allowed to be among the best set of 20 tests, from which one is randomly chosen. This allows the algorithm to be less prejudiced against discrete attributes when there are a large number of continuous valued attributes. We call it the "random trees B" approach. For this approach, we used a random test from the 20 attributes with maximal information gain.

In the random subspace approach, half \( \left(\frac{d}{n} = \frac{2}{2}\right) \) of the attributes were chosen each time. For the random forest approach, we used a single attribute, two attributes, and \( b \log_2 n + 1 \) attributes (which will be abbreviated as random forests-lg in the following).

Fifty-seven data sets were used, 52 from the UC Irvine repository [21], credit-g from NIAAD (www.liacc.up.pt/ML), phoneme from the ELENA project (ftp.dice.ucl.ac.be/pub/neural-nets/ELENA/databases), and several synthetic data sets from Breiman for which source code may be found with the Delve package (http://www.cs.utoronto.ca/~delve/data/datasets.html). The data sets, described in Table 2, have from 4 to 256 attributes and the attributes are a mixture of continuous and nominal values.

### 3.1 Experiments

For each data set, a stratified 10-fold cross-validation was performed. A stratified \( n \)-fold cross-validation breaks the data set into \( n \) disjoint subsets each with a class distribution approximating that of the original data set. For each of the \( n \) folds, an ensemble is trained using \( n - 1 \) of the subsets, and evaluated on the held out subset. As this creates \( n \) nonoverlapping test sets, it allows for statistical comparisons between approaches to be made.

For each data set, we also performed a set of five stratified two-fold cross-validations. In this methodology, the data set is randomly broken into two halves. One half is used in training and the other in testing and vice versa. This validation is repeated five times, each with a new half/half partition. Dietterich's experiments used a t test to evaluate statistical significance [8]. In Alpaydin's method, the t test is abandoned in favor of an F test for reasons of stability [9]. Specifically, rather than using the difference of only one test set, the difference of each test set is considered in the F test used here.

For each approach we use 1,000 trees in our ensemble, though we examine boosting with both 50 and 1,000 trees. Breiman often used only 50 trees in his research [1], [6], and Schapire has used as many as 1,000 [22].

### 3.2 Statistical Tests

We used three approaches to testing the statistical significance of the observed differences in accuracy. One approach is a t test on the results of a 10-fold cross-validation. This is the most widely used approach for this type of experiment. While the 10 folds of the cross-validation have independent test sets, the training data is highly overlapped across folds, and use of the t test assumes independent trials. Dietterich points out that this results in an elevated level of Type I error, which can be corrected for by his \( \frac{n}{\log n} \) cross-validation. This relies on the idea that learning curves rarely cross for algorithms as training set size varies.

We applied the Bonferroni correction, a calculation which raised the critical value necessary for determining significance, in order to compensate for the number of methods used in our experiments. In the Bonferroni correction, the \( \alpha \) value of an entire set of \( n \) comparisons is adjusted by taking the \( \alpha \) value of each individual test as \( \alpha/n \) [23]. In our experiments, we define \( \alpha = 0.05 \) and \( n = 7 \). In the case of the 10-fold cross-validation, the t-critical value is 3.47 and for the \( \frac{5}{2} \)-fold cross-validation, the F-critical value is 11.66.

A recent paper [10] suggests that the best way to compare multiple algorithms across multiple data sets is to compare their average ranks. In our case, one could rank the algorithm by average accuracy over a cross-validation experiment from 1-the best to 8-the worst.
worst. If, for example, two algorithms tied for third, they would each get a rank of 3.5. After obtaining the average ranks the Friedman test can be applied to determine if there are any statistically significant differences among the algorithms for the data sets. If so, the Holm step-down procedure was used to determine which might be statistically significantly different from bagging. It was argued [10] that this is a stable approach for evaluating many algorithms across many data sets and determining overall statistically significant differences.

### 4 EXPERIMENTAL RESULTS

Table 3 shows the results of our experiments. Statistical wins against bagging are designated by a plus sign and losses by a minus sign. If neither a statistical win nor statistical loss is registered, the table field for that data set is omitted. We separate the results of the 10-fold cross-validation and the 5×2-fold cross-validation with a slash. Table 4 shows a summary of our results.

For 37 of 57 data sets, considering both types of cross-validation, none of the ensemble approaches resulted in a statistically significant improvement over bagging. On one data set, zip, all ensemble techniques showed statistically significant improvement under the 10-fold cross-validation approach. The best ensemble building approaches appear to be boosting-1,000 and random forests-lg. Each scored the most wins against bagging while never losing. For both random subspaces and random forests-1 there were a greater number of statistical losses to bagging than statistical wins. Boosting with only 50 trees and random forests using only two attributes also did well. Random trees-B had a high number of statistical wins in the 10-fold cross-validation but also a high number of losses. Interestingly, in the 5×2-fold cross-validation, it resulted in very few wins and losses.

In comparing the differences between the 10-fold cross-validation and the 5×2-fold cross-validation, the primary difference is the number of statistical wins or losses. Using the 5×2-fold cross-validation method, for only 12 of the 57 data sets was there a greater number of statistical losses to bagging than statistical wins. Boosting with only 50 trees and random forests using only two attributes also did well. Random trees-B had a high number of statistical wins in the 10-fold cross-validation but also a high number of losses. Interestingly, in the 5×2-fold cross-validation, it resulted in very few wins and losses.

The average ranks for the algorithms are shown in Table 4. It was surprising to see that random forests when examining only two randomly chosen attributes had the lowest average rank.
Friedman test followed by the Holm test with a 95 percent confidence level it can be concluded that there was a statistically significant difference between bagging and all approaches except for random subspaces using the average accuracy from a 10-fold cross-validation. Using the $5 \times 2$ cross-validation results, there was a statistically significant difference between bagging and all approaches except for boosting 50 classifiers and random subspaces. The approaches were often not significantly more accurate than bagging on individual data sets. However, they were consistently more accurate than bagging.

5 Discussion

Since many papers compare their approaches with bagging and show improvement, it might be expected that one or more of these approaches would be an unambiguous winner over bagging. This was not the case when the results are looked at in terms of statistically significant increases in accuracy on individual data sets. Of the 57 data sets considered, 37 showed no statistically significant improvement over bagging for any of the other techniques, using either the 10-fold or $5 \times 2$ cross-validation. However, using the Friedman-Holm tests on the average ranks, we can conclude that several approaches perform statistically significantly better than bagging on average across the group of data sets. Informally, we might say that while the gain over bagging is often small, there is a consistent pattern of gain.

There are three data sets, letter, pendigits, and zip, for which nearly everything improves on the accuracy of bagging. Each of these data sets involves character recognition. We conducted experiments that attempt to increase the diversity of an ensemble of bagged classifiers, hypothesizing that the diversity created by bagging on the letter and pendigits data sets was insufficient to increase the accuracy of the ensemble. This was performed by creating bags of a smaller size than the training set, these sizes ranging from 20 percent to 95 percent in 5 percent increments. The highest ensemble accuracy obtained on the letter data set, with 95 percent bags, was only marginally higher than the result with 100 percent bags. This difference was not statistically significant. The pendigits data set showed no improvement at any size. Zip was not tested due to running time constraints.

The raw accuracy numbers show that random subspaces can be up to 44 percent less accurate than bagging on some data sets. Data sets that perform poorly with random subspaces likely have attributes which are both highly uncorrelated and each individually important. One such example is the krk (king-rook-king) data set which stores the position of three chess pieces in row#, column# format. If even one of the attributes is removed from the data set, vital information is lost. If half of the attributes are dismissed (e.g., King at A1, Rook at A7, and King at ??) the algorithm will not have enough information and will be forced to guess randomly at the result of the chess game.

Boosting-by-resampling 1,000 classifiers was substantially better than with 50 classifiers. Sequentially generating more boosted classifiers resulted in both more statistically significant wins and fewer statistically significant losses. If processing time permits additional classifiers to be generated, a larger ensemble wins and fewer statistically significant losses. If processing time boosted classifiers resulted in both more statistically significant improvements. Experimentation with the splice data set resulted in statistically significant wins for random forests-lg and statistically significant losses for random forests-2 with a 6 to 9 percent difference in accuracy. Thus, while testing only two random attributes is likely sufficient, testing additional attributes may prove beneficial on certain data sets. Breiman suggested using out-of-bag accuracy to determine the number of attributes to test [6].

There are other potential benefits aside from increased accuracy. Random forests, by picking only a small number of attributes to test, generates trees very rapidly. Random subspaces, which tests fewer attributes, can use much less memory because only the chosen percentage of attributes needs to be stored. Recall that since random forests may potentially test any attribute, it does not require less memory to store the data set. Since random trees do not need to make and store new training sets, they save a small amount of time and memory over the other methods. Finally, random trees and random forests can only be directly used to create ensembles of decision trees. Bagging, boosting, and random subspaces could be used with other learning algorithms, such as neural networks.

6 An Advantage of Bagging-Based Methods for Ensemble Size

We used an arbitrarily large number of trees for the ensemble in the preceding section. The boosting results, for example, show that an increase in the number of trees provides better accuracy than the smaller ensemble sizes generally used. This suggests a need to know when enough trees have been generated. It also raises the question of whether approaches competitive with boosting-1,000 may (nearly) reach their final accuracy before 1,000 trees are generated. The easiest way of determining when enough trees have been generated would be to use a validation set. This unfortunately results in a loss of data which might otherwise have been used for training.

One advantage of the techniques which use bagging is the ability to test the accuracy of the ensemble without removing data from the training set, as is done with a validation set. Breiman hypothesized that this would be effective [6]. He referred to the error observed when testing each classifier on examples not in its bag as the “out-of-bag” error, and suggested that it might be possible to stop building classifiers once this error no longer decreases as more classifiers are added to the ensemble. The effectiveness of this technique has not yet been fully explored in the literature. In particular, there are several important aspects which are easily overlooked, and are described in the following section.

6.1 Considerations

In bagging, only a subset of examples typically appear in the bag which will be used in training the classifier. Out-of-bag error provides an estimate of the true error by testing on those examples which did not appear in the training set. Formally, given a set $T$ of examples used in training the ensemble, let $t$ be a set of size $|T|$ created by a random sampling of $T$ with replacement, more generally known as a bag. Let $s$ be a set consisting of $T - (T \cap t)$. Since $s$ consists of all those examples not appearing within the bag, it is called the out-of-bag set. A classifier is trained on set $t$ and tested on set $s$. In calculating the voted error of the ensemble, each example in the training set is classified and voted on by only those classifiers which did not include the example in the bag on which that classifier was trained. Because the out-of-bag examples, by definition, were not used in the training set, they can be used to provide an estimate of the true error.

Only a fraction of the trees in the ensemble are eligible to vote on any given item of training data by its being “out-of-bag” relative to them. For example, suppose out-of-bag error was minimized at 150 trees. These 150 trees are most likely an overestimate of the “true number” because for any example in the data set, it would need to be out-of-bag on 100 percent of the bags in order to have all 150 trees classify that example. Therefore, the OOB results most likely lead to a larger ensemble than is truly needed.

Our experimentation with algorithms to predict an adequate number of decision trees is further complicated by the out-of-bag error.
estimate quirks on data sets with a small number of examples. Small data sets (number of examples < 1,000) can often have a very low error estimate with a rather small number of decision trees (50 to 100), but then the addition of more trees results in a greater error rate in both the out-of-bag error and the test set error, as might be shown in a 10-fold cross-validation. This behavior is contrary to many experiments which have shown that test set error steadily decreases with an increasing number of classifiers until it plateaus. We speculate that this is a result of instability in the predictions leading to a “lucky guess” by the ensemble for such data sets. Since the decision to stop building additional classifiers is more effective, in a time-saving sense, for large data sets, we believe it is more important to concentrate on data sets with a larger number of examples. We have developed an algorithm which appears to provide a reasonable solution to the problem of deciding when enough classifiers have been created for an ensemble. It works by first smoothing the out-of-bag error graph with a sliding window in order to reduce the variance. We have chosen a window size of 5 for our experiments. After the smoothing has been completed, the algorithm takes windows of size 20 on the smoothed data points and determines the maximum accuracy within that window. It continues to process windows of size 20 until the maximum accuracy within that window no longer increases. At this point, the stopping criterion has been reached and the algorithm returns the ensemble with the maximum raw accuracy from within that window. The algorithm is shown in Algorithm 1.

Algorithm 1 Algorithm for deciding when to stop building classifiers

1: \( \text{SlideSize} \leftarrow 5 \), \( \text{SlideWindowSize} \leftarrow 5 \), \( \text{BuildSize} \leftarrow 20 \)
2: \( A[n] \leftarrow \text{Raw Ensemble accuracy with n trees} \)
3: \( S[n] \leftarrow \text{Average Ensemble accuracy with n trees over the previous SlideWindowSize trees} \)
4: \( W[n] \leftarrow \text{Maximum smoothed value} \)
5: \( \text{repeat} \)
6: \( \text{Add} (\text{BuildSize}) \text{ more trees to the ensemble} \)
7: \( \text{NumTrees} = \text{NumTrees} + \text{BuildSize} \)
   \( //\text{Update} A[x] \text{ with raw accuracy estimates obtained from out-of-bag error} \)
8: \( \text{for } x \leftarrow \text{NumTrees} - \text{BuildSize} \text{ to NumTrees do} \)
9: \( A[x] \leftarrow \text{VotedAccuracy(Tree1...Treex)} \)
10: \( \text{end for} \)
11: \( \text{for } x \leftarrow \text{NumTrees} - \text{BuildSize} \text{ to NumTrees do} \)
12: \( S[x] \leftarrow \text{Average} (A[x] - \text{SlideSize} \ldots A[x]) \)
13: \( \text{end for} \)
14: \( \text{W[NumTrees/BuildSize – 1]} \leftarrow \max (S[\text{NumTrees} - \text{BuildSize}] \ldots S[\text{NumTrees}]) \)
15: \( \text{until} \ (\text{W[NumTrees/BuildSize – 1]} \leq \text{W[NumTrees/BuildSize – 2]}) \)
16: \( \text{Stop at tree } \arctan (A[\text{J}]j \in \text{NumTrees – 2 * BuildSize} \ldots \text{NumTrees – BuildSize}) \)

6.2 Experiments

We compare the stopping points and the resulting test set accuracy of ensembles built out to 2,000 trees using Random Forests-lg and a 10-fold cross-validation. For this comparison we examine 1) the stopping point of our algorithm, 2) the stopping point by taking the minimum out-of-bag error over all 2,000 trees, and 3) an oracle algorithm which looks at the lowest observed error on the test set over the 2,000 created trees (as trees are added sequentially). Thirteen of the previously used data sets with greater than 1,000 examples are used. The results are shown in Table 5.

For most data sets, the out-of-bag error continues to decrease long into the training stage. This often does not result in any improvement of test set performance. Across all 13 data sets the total gain by using the minimum out-of-bag error rather than our algorithm was only 0.06 percent on average. Comparing our algorithm to the oracle, the accuracy loss is less than 0.25 percent per data set. In comparing the number of trees used, our method uses many fewer trees than the other methods. On average, we use 1,140 fewer trees compared to the minimum out-of-bag error and 755 fewer trees compared to the oracle method. While these numbers are clearly influenced by the maximum number of trees chosen to build, it is also evident that looking at the maximum out-of-bag accuracy causes the algorithm to continue building a large number of trees.

We have also tested this method on the bagged trees without the use of random forests. We generated half (1,000) the number of the trees used in the previous experiment in order to shorten the previously observed large over estimation on the number of trees using the minimum out-of-bag error alone and to reduce the training time. The results for this experiment are shown in Table 5. The use of our algorithm results in an average net loss of 0.12 percent per data set compared to the minimum out-of-bag error, while using 431 fewer trees. Compared to the oracle method, there is a net loss of 0.25 percent per data set (consistent with the previous experiment) while using 442 fewer trees.
Based on these results, we believe it is possible to choose an acceptable stopping point while the ensemble is being built. In experiments with our algorithm, it has not shown itself to be overly sensitive to the parameters of the sliding window size and the building window size. On average, the number of trees built in excess for the purpose of choosing the stopping point in our algorithm, will be half of the building window size.

When bagging a data set, the probability of any particular example being included in the bag is slightly less than two-thirds, meaning only about one-third of the examples are out-of-bag. Put another way, for each example in the training set, only about one-third of the trees in the ensemble vote on that example. Therefore, the number of trees we have chosen to stop at may be as many as three times the amount necessary for equivalent performance on a test set consisting of all unseen examples. For this reason, we include the accuracy results obtained by using a random one-third of the number of trees chosen to stop with in the previous experiments. These results are shown in Table 6.

Looking at the accuracy with one-third of the number of trees shows mixed results. Though there are some data sets unaffected by the change, other data sets, especially the larger sized ones, benefit from the greater number of trees. We believe that our algorithm, which stops at the first window at which accuracy no longer increases, compensates for what might otherwise require three times the number of trees to decide.

### 7 CONCLUSIONS

This paper compares a variant of the randomized C4.5 method introduced by Dietterich [7], random subspaces [5], random forests [6], AdaBoost.M1W [2], and bagging. A 10-fold cross validation and 5 × 2-fold cross validation are used in the comparison. The accuracy of the various ensemble building approaches was compared with bagging using OpenDT to build unpruned trees. The comparison was done on 57 data sets. This is the largest comparison of ensemble techniques that we know of, in terms of number of data sets or number of techniques. This is also the most rigorous comparison, in the sense of employing the cross-validation test suggested by Alpaydin in addition to the standard 10-fold cross-validation and the Friedman-Holm test on the average rank.

We found that some of the well-known ensemble techniques rarely provide a statistically significant advantage over the accuracy achievable with standard bagging on individual data sets. We found that boosting-by-resampling results in better accuracy with a much larger ensemble size than has generally been used.
been used, and that at this larger ensemble size it does offer some performance advantage over bagging. However, the increase in accuracy is statistically significant in only a fraction of the data sets used. Random forests-lg and random forests-2 show some improvement in performance over bagging. The accuracy improvement with these random forests algorithms is perhaps not quite as big as with boosting-1,000, however they have the advantage that the trees can be created in parallel.

An evaluation approach using the average ranking (by cross-validation accuracy) of the algorithms on each data set [10] has recently been argued to be the best approach for comparing many algorithms across many data sets. When we calculated the average ranks and then used the Friedman test followed by the Holm test, boosting 1,000, randomized trees, and random forests were statistically significantly better than bagging using the 5 × 2-fold cross-validation accuracies. With the 10-fold cross-validation accuracies, boosting-50 was also statistically significantly better than bagging. We conclude that for any given data set the statistically significantly better algorithms are likely to be more accurate, just not by a significant amount on that data set. So, performance/accuracy trade-offs may make sense in some cases.

We also showed a way to automatically determine the size of the ensemble. The stopping criteria we presented showed that it is possible to intelligently stop adding classifiers to an ensemble using out-of-bag error, as hypothesized by Breiman. Our experiments show this clearly applies to bagging and random forests-lg, which makes use of bagging. In particular, our results demonstrate that it is possible to stop much earlier than the minimum out-of-bag error would dictate, and still achieve good accuracy from the ensemble.

The raw accuracy results for the 10-fold and the 5 × 2-fold cross-validations are contained in an appendix. The Appendix can be found at http://computer.org/tpami/archives.htm.

ACKNOWLEDGMENTS

This research was partially supported by the US Department of Energy through the ASCI (DVS) Data Discovery Program, Contract number: DE-AC04-76DO00789 and the US National Science Foundation under grant EIA-0130768. The authors would like to thank Remy Losaria for her help with the 5 × 2-fold cross-validation experiments.

REFERENCES


For more information on this or any other computing topic, please visit our Digital Library at www.computer.org/publications/dlib.
Lung cancer screening in the NELSON trial: balancing harms and benefits

Nanda Horeweg
Lung cancer screening in the NELSON trial balancing harms and benefits

Nanda Horeweg
Lung cancer screening in the NELSON trial: balancing harms and benefits

Thesis, Erasmus University Rotterdam, Netherlands

© 2014 Nanda Horeweg
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the author or the copyright-owning journals for previously published chapters.

Cover illustration: Ivanca Horeweg
Lay-out and print: Optima Grafische Communicatie, Rotterdam, The Netherlands

The studies reported in this thesis were funded by The Netherlands Organisation of Health Research and Development (ZonMw), the Dutch Cancer Society (KWF), and the Health Insurance Innovation Foundation (Innovatiefonds Zorgverzekeraars), Health Insurance Innovation Foundation, Siemens Germany, Roche Diagnostics, G. Ph. Verhagen Stichting, Rotterdam Oncologic Thoracic Study (ROTS) group, Erasmus Trust Fund, Stichting tegen Kanker, Vlaamse Liga tegen Kanker, and LOGO Leuven.

This thesis was financially supported by the Department of Public Health, Erasmus MC, Rotterdam.
Lung cancer screening in the NELSON trial: balancing harms and benefits

Longkankerscreening in de NELSON studie: afweging van voor- en nadelen

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam op gezag van rector magnificus

Prof.dr. H.A.P. Pols

en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op dinsdag 25 november 2014 om 9.30 uur

door

Nanda Horeweg

geboren te Spijkenisse
**PROMOTIECOMMISSIE**

**Promotoren:**
- Prof.dr. H.J. de Koning, Erasmus MC Rotterdam, Nederland
- Prof.dr. H.C. Hoogsteden, Erasmus MC Rotterdam, Nederland

**Leescommissie:**
- Prof.dr. M.G.M. Hunick, Erasmus MC Rotterdam, Nederland
- Prof.dr. P.E. Postmus, VUMC Amsterdam, Nederland
- Prof.dr. H. van Swieten, Radboud UMC Nijmegen, Nederland
# TABLE OF CONTENTS

## Part I: Introduction

1. General introduction

## Part II: Evaluation of findings

2. Predictive value of screening test results
   ‘Volumetric computer tomography screening for lung cancer: three rounds of the NELSON trial.’
   *European Respiratory Journal*

3. Characteristics of screen-detected lung cancer
   Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial.
   *American Journal of Respiratory and Critical Care Medicine*

4. Epidemiological evaluation
   ‘Detection of lung cancer through low-dose CT screening: analysis of screening test performance and interval cancers.’
   *Lancet Oncology*

5. Radiological evaluation
   ‘Computed tomographic characteristics of interval and post-screen carcinomas in lung cancer screening.’
   *European Radiology*

## Part III: Optimisation of screening

6. Optimisation of screening protocols
   ‘Lung cancer probability in subjects with CT-detected pulmonary nodules: an analysis of data from the NELSON trial of low-dose CT screening.’
   *Lancet Oncology*

7. Evaluation of bronchoscopy
   ‘The role of conventional bronchoscopy in the work-up of suspicious CT screen-detected pulmonary nodules.’
   *Chest*
8. Evaluation of surgical procedures
   ‘Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial.’
   *European Journal of Cardio-Thoracic Surgery*

**Part IV: Evaluation of effectiveness**

9. Endpoint determination
   ‘Uniform and blinded cause of death verification in a lung cancer CT screening trial.’
   *Lung Cancer*

**Part V: Implications for implementation**

10. State of the art in lung cancer screening
    ‘The importance of screening for lung cancer’
    *Expert Review in Respiratory Medicine*

11. General discussion

12. Summary

13. Samenvatting

**Part VI: Miscellaneous**

14. Dankwoord

15. Curriculum vitae

16. PhD portfolio

17. List of publications
Part I

Introduction
Chapter 1

General introduction
In this thesis, the harms and benefits of lung cancer screening using low-dose computed tomography were investigated. Data of the Dutch-Belgian NELSON trial were used to quantify its harms and benefits and develop strategies to improve the balance between them. If the NELSON trial demonstrates that low-dose CT screening is an effective method to reduce mortality from lung cancer, balance between harms and benefits is a perquisite for the implementation of a lung cancer screening program. Background information on relevant aspects of epidemiology, medical ethics, pulmonary medicine, radiology, and pathology are essential for the interpretation of the studies in this thesis. In this chapter an overview of relevant background information is presented, as well as a description of the design of the NELSON trial.

**AETIOLOGY**

Lung cancer has been studied thoroughly in the past decades, which has given insight in its aetiology. The single most important cause of lung cancer is tobacco smoking.\(^1,3\) Smokers have a 15-fold to 30-fold increased risk of developing lung cancer compared to non-smokers.\(^4\) Other causative factors of lung cancer are: second-hand tobacco smoke exposure,\(^5,6\) ionising radiation,\(^7\) indoor and outdoor air pollution,\(^8\) soot,\(^9\) radon,\(^10-12\) asbestos,\(^13,14\) tar,\(^15\) arsenic,\(^15\) chromium\(^15\) and nickel.\(^15\)

Besides these causative factors, a number of risk indicators have been identified: older age,\(^13,16\) family history of lung cancer,\(^16,17\) acquired lung disease such as COPD,\(^18-21\) HIV infection\(^22\) and occupational exposures such as silica dust.\(^13\) Physical activity and fruit and vegetable intake have consistently shown to be associated with a decreased risk of lung cancer.\(^3\)

**EPIDEMIOLOGY**

Since tobacco smoking is the predominant causative agent of lung cancer, lung cancer incidence is strongly correlated with patterns of smoking prevalence.\(^8,23,24\) The characteristic long latency period of smoking-induced lung cancer, which is the period from the start of smoking to lung cancer diagnosis, causes a delay in lung cancer incidence of 20 to 30 years.\(^8\) In the United States, Australia, New Zealand and many countries in North-West Europe, lung cancer incidence rapidly increased from the 1930’s onwards and peaked in the 1980’s, and has been declining since.\(^8,23\) In contrast, in Southern and Eastern European countries, China, and Japan lung cancer incidence still increases or is stable.\(^8\) Moreover, the lung cancer incidence is predicted to increase substantially throughout Asia and Africa in the future, due to the uptake of western smoking habits.\(^8\) Variations in
lung cancer incidence across countries or between males and females are largely reflected in the differences in the stage and degree of the tobacco epidemic. 

PUBLIC HEALTH

Currently, lung cancer is the second most common cancer; accounting for 14% of all cancer cases in the U.S. in both men and women. Moreover, lung cancer causes most cancer-related deaths; 28% of the cancer related deaths in men and 26% in women. Lung cancer causes more deaths than prostate cancer, breast cancer, colon cancer and pancreatic cancer combined, which makes lung cancer a major public health problem.

DISEASE CHARACTERISTICS

Lung cancer is such a major public health problem because of its high incidence and high case-fatality. The latter is partly caused by the fact that lung cancer often causes no symptoms at early stages of disease. As result, lung cancer is commonly diagnosed at stages wherein disease has advanced to regional (22%) or distant (56%) spread. Hence, only a minority is diagnosed with localised lung cancer, wherein surgical resection of the entire tumour is still feasible. In this group, the chance to be alive five years after diagnosis is 52%. Which is substantially higher than the five-year survival of regionally and distantly metastasised disease; respectively 25% and 4%. At these more advanced stages, surgical resection of the primary tumour is often not curative, and therapy is often only aimed at improving survival and quality of life.

CLINICAL CARE

The advances in treatment of lung cancer have been substantial over the past decades and have improved survival of lung cancer patients. For example: several new chemotherapy regimens have been developed, some specifically directed at histological subtype, and the increased use of chemotherapy as adjuvant therapy. More recently, targeted therapies at somatic mutations in receptors or signal proteins have become available. Further, advances in radiotherapy, such as stereotactic body radiotherapy, contributed to improved survival. The combination of chemotherapy and radiation therapy has evolved from sequential to concomitant, which further improved overall survival. Pre-operative patient selection has improved as result of the use of validated comorbidity indices, multidisciplinary decision-making, and more accurate staging. Finally, bet-
ter adoption to standard care treatment guidelines, and a greater proportion of patients receiving any treatment, contributed to the survival of lung cancer patients.\textsuperscript{37}

Clearly, many improvements in the treatment of lung cancer have been made, but only modest improvement in the survival of lung cancer patients could be observed over the last decades.\textsuperscript{8} In the United States, the overall five-year relative survival of lung cancer patients has improved from 12\% in 1975-1977 to 17\% in 2002-2008.\textsuperscript{23} The overall five-year survival of lung cancer patients in Canada improved from 15.7\% in 1995-1999 to 18.4\% in 2005-2007.\textsuperscript{38} In Australia, an improvement from 13.9\% in 1995-1999 to 17.0\% in 2005-2007 was observed.\textsuperscript{38} The overall five-year survival in Europe improved from 9\% to 11\%, on average.\textsuperscript{39} In the United Kingdom, overall survival was substantially lower, 7.0\% in 1995-1999, as also the improvement in survival; 1.8\% to 8.8\% in 2005-2007.\textsuperscript{38} In North-West Europe, where high-quality registries with national coverage are available, similar small improvements in survival were observed; in the periods from 1995-1999 and 2005-2009 respectively: from 8.0\% to 10.9\% in Denmark, 11.0\% to 14.4\% in Norway, 12.7\% to 16.3\% in Sweden. In the Netherlands, the overall five-year survival increased from 14.8\% in 1989-1993 to 17.4\% in 2009.\textsuperscript{31}

**PREVENTION**

Improvements in the treatment of lung cancer are continued to be made, and will undoubtedly contribute to an improved survival of lung cancer patients in the future. However, the fact that lung cancer is mostly diagnosed at an incurable, advanced stage limits treatment options to improving survival and reducing morbidity. In contrary, prevention may be able to reduce the burden of lung cancer in a different way. As presented in Box 1, three forms of prevention can be distinguished: primary, secondary and tertiary prevention.

**Text box 1. Definitions prevention**

Prevention and clinical care are the main methods in medicine to improve health. Prevention can be sub-classified in primary, secondary and tertiary prevention.
- Primary prevention aims to prevent the occurrence of disease by elimination or reduction of the causes of disease.
- Secondary prevention aims to prevent progression of disease by detecting and treating disease at an early stage.
- Tertiary prevention aims to prevent or limit the unfavorable outcomes of diseases that are already diagnosed.
If these definitions are applied to prevention of lung cancer, the stage of disease plays an important role in the form of prevention applied, which is depicted in Figure 1.

Hence, morbidity and mortality from lung cancer may be reduced by:

I) Primary prevention through reducing the occurrence of lung cancer;
II) Secondary prevention through early detection by screening asymptomatic high-risk subjects;
III) Tertiary prevention through earlier treatment by increasing awareness of the signs and symptoms of lung cancer in the general population.

**Figure 1. Prevention and medical care according to cancer stage**

In time, cancer develops in an individual at risk, from pre-malignant, to malignant, to symptomatic cancer, and after some delay diagnosis is made and the individual receives medical care until death. Primary, secondary and tertiary prevention apply to different stages of disease, but could be offered to any individual receiving medical care.

**Primary prevention**

Primary prevention may improve public health by reducing mortality and morbidity from lung cancer in two different ways. On the one hand, the occurrence of lung cancer can be reduced by protection from the carcinogenic agents that specifically cause lung cancer. On the other hand, the occurrence of lung cancer can be counteracted by the use of specific agents to reverse, suppress, or prevent the process of carcinogenesis.

The latter is called chemoprevention, and many substances, such as aspirin, \( \beta \)-carotene, \( \beta \)-carotene, retinyl palmitate, \( 13 \)-cis-retinoic acid, vitamin E, N-acetylcycteine and selenium have been tested in clinical trials. None of these trials demonstrated any beneficial effect, while some did show harmful effects. Therefore, to date not one agent is recommended for use in the chemoprevention of lung cancer.

Hence, the reduction of exposure of the general population to the causative agents of lung cancer may be a safer and more effective approach to improve public health.
rent knowledge on the aetiology of lung cancer may be used to develop such primary prevention interventions. Since tobacco is responsible for 80-90% of the lung cancer diagnoses,\textsuperscript{3,51} both through smoking\textsuperscript{1-3} and second-hand smoke exposure,\textsuperscript{5} most benefit can be expected from interventions directed at prevention of the initiation of smoking and smoking cessation. The adverse health effects of tobacco smoking became widely apparent in the 1950's,\textsuperscript{52} and many interventions have been implemented since: anti-smoking campaigns, marketing and sales restrictions, federal cigarettes taxes, smoke-free air laws, smoking cessation treatments.\textsuperscript{53,54} These interventions had substantial impact on smoking prevalence, which was reflected in lung cancer incidence and mortality twenty to thirty years later.\textsuperscript{23,54} Millions of premature deaths were prevented by tobacco control interventions; a substantial proportion through prevention of lung cancer deaths.\textsuperscript{55,56} Despite this success of primary prevention, global smoking prevalence was still as high as 23.7\% in 2010.\textsuperscript{57} Moreover, it has been estimated that smoking prevalence will only decrease to 22.0\% in 2030 if no additional tobacco control policies are applied.\textsuperscript{57}

Concluding, primary prevention is inevitable in the fight against lung cancer, and continuous efforts should be made to force back exposure to its causative agents, tobacco smoking in particular. However, primary prevention solely is not expected to be able to reverse the lung cancer epidemic and reduce morbidity and mortality substantially in the next decades.

**Tertiary prevention**

The aim of tertiary prevention is to improve survival and reduce mortality by early treatment in symptomatic lung cancer patients. To be able to treat lung cancer as early as possible, delays between the onset of symptoms and treatment should be minimised. Three types of delay are recognised in the literature:\textsuperscript{58,59}

I) Patient-related delay due to failure to act immediately on suspicious symptoms through fear or lack of knowledge.

II) Doctor-related delay due to misinterpreting symptoms or not referring for diagnostic testing.

III) System-generated delay due to inefficiency or long waiting times of appointments or tests.

Efforts to reduce delay type II and III are embedded in clinical guidelines and performance indicators of health care.\textsuperscript{35,60} Delay type I has been recognised as the most important source of delay between onset of symptoms and start of treatment.\textsuperscript{61}

Several studies on patient-related delay in seeking a cancer diagnosis have been published, but identified different sets of determinants. Corner et al identified comorbidity, misinterpretation of symptoms, lack of knowledge, and difficulties of recognising ill health in elderly as determinants.\textsuperscript{58} While Leydon et al. found that a person's experiences, expectations from health care, family decisions and fear of cancer were important.\textsuperscript{62} In
the study of Ristvedt et al. predisposition to seek help and certain personality traits were identified as determinants of delay.63

Further, the spontaneous awareness of the symptoms of lung cancer is limited; nearly a quarter of the general population cannot mention any symptoms of lung cancer, and those who can mention breathlessness and coughing.64 This information is essential for developing tertiary prevention interventions that reduce patient-related delay, which may address to the poorer survival associated with delay.65 Henceforth, several initiatives to raise awareness of symptoms of lung cancer and to de-stigmatise the disease have been implemented.66-68 The effectiveness of tertiary prevention has been investigated in a limited number of studies; effects on self-reported awareness,69-72 intention to seek care,70,72 health care policy,69,73 referral rates,70 disease incidence70 have been reported. A favourable effect on disease stage at diagnosis was not consistently proven,70,72 moreover none of the studies evaluated the effect on survival or lung cancer mortality.

Despite the fact that the effectiveness of the aforementioned interventions on lung cancer morbidity and mortality has not been demonstrated, and the disease itself is often asymptomatic in early stages, tertiary prevention should not be disregarded. The observation that clinically-diagnosed lung cancer has often already progressed to an advanced stage at diagnosis23 might be not exclusively caused by the biology of the disease; a part of this problem might also result from the social context of the disease.58,74 The general public has low expectations from health care, because lung cancer is considered as an inevitably fatal condition.58,74 Earlier diagnosis in symptomatic patients is scarcely promoted because there is little expected gain.58,74 In addition, patient advocacy movements are disabled by the blame of self-infliction of disease and the relatively small proportion of patients that survive the disease.58,74 The power of tertiary prevention is best demonstrated in breast cancer: by creating awareness, the general public has become educated on the symptoms of the disease and on the benefits of seeking an early diagnosis, and a powerful social movement has arisen.75

Concluding, tertiary prevention has not proven to be able to reduce lung cancer morbidity and mortality. Nonetheless, its effects may reach further than just earlier treatment of symptomatic patients; it may influence the public opinion and professional agendas, which contributes to the development and funding of research, screening, clinical care and aftercare.

Secondary prevention
Lung cancer screening is a form of secondary prevention (Box 1), and aims to reduce mortality by cancer detection at an early and curable stage. As this early stage is often not accompanied by any signs or symptoms, screening is applied to apparently healthy, asymptomatic persons.
Harms and benefits
The benefit asymptomatic high-risk subjects have from an effective screening program is: a reduced probability of dying from lung cancer, and a reduced probability to suffer from advanced disease (Table 1). Unfortunately, the subjects who undergo screening are also exposed to several harms. The harms can be related to the screening test itself; as for example radiation-induced cancer or psychological distress awaiting the test result. But harms can also be related to false positive screenings (e.g. complications of subsequent diagnostic tests) and false negative screenings (e.g. delayed diagnosed due to false reassurance). Further, overdiagnosis is considered to be an important harm of screening. A detailed overview of potential harms and benefits of screening is provided in Table 1.

Medical ethics
The harms and benefits listed in Table 1 represent one of the contradictions in screening. On the one hand, screening aims to improve (public) health by reducing morbidity and mortality from lung cancer, on the other hand, screening unintentionally exposes the screened population to a variety of harms. To be able to perform and interpret research in the field of screening, knowledge on the ethical principles is essential.

Table 1. Benefits and harms of cancer screening

<table>
<thead>
<tr>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less persons dying from lung cancer</td>
</tr>
<tr>
<td>Less persons suffering from advanced lung cancer</td>
</tr>
<tr>
<td>Less persons receiving intensive or mutilating primary treatment</td>
</tr>
<tr>
<td>Possible positive effects on smoking cessation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undergoing screening test and awaiting result - psychological distress</td>
</tr>
<tr>
<td>Radiation-induced cancers - morbidity and mortality</td>
</tr>
<tr>
<td>False positive results - psychological distress, morbidity and mortality due to subsequent diagnostic procedures</td>
</tr>
<tr>
<td>False negative results - false reassurance, delayed diagnosis once symptoms occur</td>
</tr>
<tr>
<td>Overdiagnosis - psychological distress, morbidity and mortality due to overtreatment</td>
</tr>
<tr>
<td>Persons receiving the diagnosis of lung cancer earlier</td>
</tr>
<tr>
<td>Possible negative effects on smoking cessation</td>
</tr>
</tbody>
</table>

Ethical principles
The following four ethical principles are considered most relevant for lung cancer screening:
I) Beneficence: this principle signifies that physicians must help their patients and act in their patients’ best interest.
II) Non-maleficence: this principle signifies that physicians must not harm their patients.

III) Autonomy: this principle signifies that physicians must respect the right of patients to decide over their own medical interventions and treatments.

IV) Justice: this principle signifies that physicians must treat equal patients equally and must consider fair distribution of health care resources.

As these ethical principles are part of the medical oath, physicians involved in screening have a number of responsibilities. According to the principle of beneficence physicians should propose lung cancer screening to those individuals in whom it is beneficial for their health. According to the principle of non-maleficence, physicians should not offer lung cancer screening to those individuals in whom it is not beneficial. Moreover, this principle also implies that physicians have the responsibility to minimise the harms of screening in whom screening is considered beneficial. According to the principle of autonomy, physicians should respect a person's decision to undergo lung cancer screening or not. As informed decision-making is a prerequisite for participation in screening, physicians also have the responsibility to inform screening candidates on benefits and harms of screening. According to the principle of justice, physicians have the responsibility to treat individuals, who are equal with respect to aspects relevant for screening, equally. This, for example, refers to providing care that is accessible and appropriate for the entire target population, or to the fair distribution of limited health care resources.

**Ethical dilemmas**

The responsibilities that result from the ethical principles can be conflicting. As mentioned previously, the most prominent ethical dilemma in lung cancer screening is the conflict between beneficence and non-maleficence. The harms a screening program induces should be weighed against the benefits the program yields. Obviously, it is not ethical to implement a screening program that causes more harm than benefit. In lung cancer screening, harms and benefits are not the same for every individual but depends i.e. on age, smoking history and co-morbidity. Therefore, the ethical dilemma between beneficence and non-maleficence plays an important role in defining the target population for lung cancer screening.

The principle of autonomy can conflict with the principles of beneficence and non-maleficence. Well-informed individuals have the right to decide for themselves whether or not to undergo screening. However, this right can conflict with the principles of beneficence and non-maleficence when the benefits of screening do not outweigh the harms. For example, in case of an individual with a negligible risk of lung cancer who demands to undergo LDCT screening. The principle of autonomy could also conflict with the ethical principle of justice. The right of the individual to undergo screening can
conflict with the responsibility to distribute limited health care resources responsibly to preserve the accessibility of health care.

The significance of the considerations surrounding the ethical principles and dilemmas has been recognised for decades. As a result, screening criteria that encounter these ethical issues have been developed to guide decisions on the implementation of screening programs.

Criteria for screening

In 1968, the World Health Organisation (WHO) commissioned a report from Wilson and Jungner on the “Principles and practice of screening for disease”. This report contains the ‘Wilson and Jungner criteria’ for screening (overview provided in Box 2), which have been regarded as the golden standard in decision-making for a long time.

Although the value of the Wilson and Jungner criteria is still widely recognised, many have suggested adaptations and improvements of the criteria. In 2008, the WHO published ‘Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past years’. In this article, a new set of criteria was presented, based on the suggested improvement of the Wilson and Jungner criteria proposed over the past forty years (Box 3).

Box 2. Criteria for screening by Wilson and Jungner, 1968

| I) | The condition sought should be an important health problem. |
| II) | There should be an accepted treatment for patients with recognized disease. |
| III) | Facilities for diagnosis and treatment should be available. |
| IV) | There should be a recognisable latent or early symptomatic stage. |
| V) | There should be a suitable test or examination. |
| VI) | The test should be acceptable to the population. |
| VII) | The natural history of the condition, including development from latent to declared disease, should be adequately understood. |
| VIII) | There should be an agreed policy on whom to treat as patients. |
| IX) | The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole. |
| X) | Case-finding should be a continuing process and not a “once and for all” project. |
Screening for lung cancer

Lung cancer fulfils a number of the criteria for mass screening (Box 3).\textsuperscript{78} Criterion I: as the burden of lung cancer is high, an effective screening program responds to a recognized need.\textsuperscript{78} Criterion II: the objective of a lung cancer screening program would be to reduce morbidity and mortality from lung cancer.\textsuperscript{78} Current knowledge on the aetiology of lung cancer provides the opportunity to define specific target populations for screening, which is a prerequisite to fulfil criterion III.\textsuperscript{78} Criteria IV to X (Box 3) do not relate to characteristics of the disease itself, but to the screening program’s effectiveness, balance between harms and benefits, and associated costs.\textsuperscript{78}

Box 3. Modern screening criteria proposed by the World Health Organisation

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I)</td>
<td>The screening programme should respond to a recognised need.</td>
</tr>
<tr>
<td>II)</td>
<td>The objectives of screening should be defined at the outset.</td>
</tr>
<tr>
<td>III)</td>
<td>There should be a defined target population.</td>
</tr>
<tr>
<td>IV)</td>
<td>There should be scientific evidence of screening programme effectiveness.</td>
</tr>
<tr>
<td>V)</td>
<td>The programme should integrate education, testing, clinical services and programme management.</td>
</tr>
<tr>
<td>VI)</td>
<td>There should be quality assurance, with mechanisms to minimise potential risks of screening.</td>
</tr>
<tr>
<td>VII)</td>
<td>The programme should ensure informed choice, confidentiality and respect for autonomy.</td>
</tr>
<tr>
<td>VIII)</td>
<td>The programme should promote equity and access to screening for the entire target population.</td>
</tr>
<tr>
<td>IX)</td>
<td>Programme evaluation should be planned from the outset.</td>
</tr>
<tr>
<td>X)</td>
<td>The overall benefits of screening should outweigh the harm.</td>
</tr>
</tbody>
</table>

Lung cancer screening: cohort studies

Until the 1990s, there has been little role for lung cancer screening because no effective screening test was available.\textsuperscript{85} Screening studies using sputum cytology\textsuperscript{86-88} or chest radiography did not show a significant lung cancer mortality reduction.\textsuperscript{89} In the 1990s, trials using low-dose computed tomography (LDCT) as a screening test were initiated,\textsuperscript{85} and results were encouraging. LDCT appeared to be able to detect more and smaller lung cancers than chest radiography;\textsuperscript{90-92} 61\% to 93\% of lung cancers were diagnosed at stage I.\textsuperscript{90-95} Moreover, survival rates in patients with screen-detected lung cancer were startling: five-year survival in the Japanese ALCA trial\textsuperscript{95} was 64.9\% to 76.2\%, and ten-year survival in the U.S. ELCAP trial was even 80-92\%.\textsuperscript{91,96}
Bias

The survival of patients with screen-detected lung cancer is not the right endpoint to evaluate the effectiveness of a screening program due to three forms of bias:

I) Lead-time bias: by screening asymptomatic individuals, the diagnosis of lung cancer is established earlier than it would have been without screening, which is usually after the onset of symptoms. As survival analyses take the moment of diagnosis as starting point, survival of patients with screen-detected lung cancer will be longer than the survival of patients with clinically diagnosed lung cancer, even when there is no benefit of screening (Figure 2).

II) Length-time bias: as the aforementioned cohort studies analysed survival of patients with screen-detected lung cancer only, this form of bias also plays a role. Lung cancer is a very heterogenic disease, and some subtypes of lung cancer grow slower than other subtypes. The slow-growing cancers have a longer asymptomatic phase than the fast growing cancers. As a result, the likelihood of a slow-growing cancer to be detected by screening is higher than the likelihood of a fast-growing cancer. Hence, screen-detected lung cancers grow slower on average than lung cancer.

---

**Figure 2. Schematic depiction of lead-time bias**

In panel I, calculation of survival is depicted for symptom-detected lung cancer; starting point is the moment of diagnosis and endpoint is the moment of death. In panel II and III, calculation of survival is depicted for screen-detected lung cancer. In both, survival is substantially longer than for symptom-detected lung cancer, as a result of advancing the moment of diagnosis through detection before the onset of symptoms. However, only in panel III survival is truly prolonged by screening. In panel II, the moment of diagnosis is advanced but the moment of death is at the same moment as when lung cancer was diagnosed through symptoms.

---
cancers not detected by screening. Since slow-growing cancers are associated with longer survival and lower case-fatality, the survival of screen-detected cancers is better than the survival of lung cancers not detected by screening. As the survival analyses of the cohort studies only included the screen-detected lung cancers, the result is biased. Therefore, the survival of both screen-detected lung cancers and the lung cancers not detected by screening should be included in the analysis. The latter requires the availability of high-quality cancer registries or thorough follow-up of study participants.

III) Overdiagnosis: is inseparable from screening and means the detection of cancers which would have never had led to symptoms or death (Figure 3). At the time the ALCA and ELCAP study were conducted, almost all individuals who were diagnosed with screen-detected lung cancer also underwent surgery. As a result, it is not possible to determine how many individuals had a lung cancer that would not have been fatal if left untreated; the overdiagnosed cancers. Subsequently, it’s not possible to determine to what extend overall survival is biased by overdiagnosis.

**Figure 3. Schematic depiction of overdiagnosis**

Figure 3 describes a population with a constant lung cancer incidence, that underwent three low-dose computed tomography screening rounds. In panel I, an hypothetical lung cancer screening program that did not lead to any overdiagnosis is depicted. Through earlier detection of lung cancer the cumulative incidence of lung cancer increases faster during screening compared to no screening. However, after screening has stopped and the ‘wash-out period’ of screening has passed, the cumulative lung cancer incidence is as high as in the situation without screening. Hence, there is no overdiagnosis. Note: in practice, due to concurring mortality, there will always be overdiagnosis. In contrary to panel II, where in the cumulative lung cancer incidence remains higher than in the situation without screening. The difference in lung cancer cases between the two lines are the overdiagnosed lung cancers.
To avoid these three forms of bias, the primary endpoint of screening studies should be disease-specific mortality reduction. Ideally, the effect of screening on lung cancer mortality is determined in a trial wherein participants are randomised between screening and no screening. Next, both groups should be followed up simultaneously for a sufficiently long period of time after screening has stopped. Just one of the aforementioned cohort studies assessed lung cancer mortality reduction; the Mayo Lung Project compared lung cancer mortality between the screened cohort and a historical cohort; analysis showed no significant lung cancer mortality reduction.94

Lung cancer screening: randomised trials
The encouraging results of the LDCT cohort studies led to the initiation of several randomised controlled trials (Table 2).97-104 Although design of the trials varies notably, the primary endpoint of all these trials was lung cancer mortality. Four of the seven randomised trials have currently reported their results. The largest trial, the U.S. National Lung Screening Trial (NLST), reported a statistically significant lung cancer mortality reduction of 20.0% (95% CI 6.8-26.7%) after 6.5 years of follow-up.76 In the NLST, screen-

Table 2. Characteristics of randomised controlled trials on LDCT screening for lung cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Initiation</th>
<th>Design</th>
<th>Screenings</th>
<th>Characteristics participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST97,138</td>
<td>53,439</td>
<td>2002</td>
<td>LDCT vs. CXR</td>
<td>3 M/F</td>
<td>55-74 ≥30 py &lt;15 yrs</td>
</tr>
<tr>
<td>NELSON108,139</td>
<td>15,822</td>
<td>2004</td>
<td>LDCT vs. no screening</td>
<td>4 M/F</td>
<td>50-75 ≥15/day for 25 yrs or ≥10/day for 30 yrs ≤10 yrs</td>
</tr>
<tr>
<td>DLST99</td>
<td>4,104</td>
<td>2004</td>
<td>LDCT vs. no screening</td>
<td>5 M/F</td>
<td>50-70 ≥20 py &lt;10 yrs</td>
</tr>
<tr>
<td>MILD100</td>
<td>4,099</td>
<td>2005</td>
<td>LDCT vs. no screening</td>
<td>5/10 M/F</td>
<td>≥49 ≥20 py &lt;10 yrs</td>
</tr>
<tr>
<td>LUSI101</td>
<td>4,052</td>
<td>2007</td>
<td>LDCT vs. no screening</td>
<td>4 M/F</td>
<td>50-70 ≥15/day for 25 yrs or ≥10/day for 30 yrs ≤10 yrs</td>
</tr>
<tr>
<td>UKLS102,140</td>
<td>4,000</td>
<td>2011</td>
<td>LDCT vs. no screening</td>
<td>1 M/F</td>
<td>50-75 ≥5% risk of lung cancer in 5 yrs</td>
</tr>
<tr>
<td>ITALUNG103</td>
<td>3,206</td>
<td>2004</td>
<td>LDCT vs. no screening</td>
<td>4 M/F</td>
<td>55-70 ≥20 py &lt;10 yrs</td>
</tr>
<tr>
<td>DANTE104</td>
<td>2,472</td>
<td>2001</td>
<td>Initial CXR, followed by LDCT vs. no screening</td>
<td>4 M</td>
<td>60-75 ≥20 py &lt;10 yrs</td>
</tr>
</tbody>
</table>

Definition of abbreviations: LDCT = low-dose computed tomography; CXR = chest x-ray; M = male; F = female; py = pack-years; yrs = years.
* Age range up to, but not including upper limit.
ing using LDCT was compared to screening using chest radiography\textsuperscript{2} which does not affect lung cancer mortality.\textsuperscript{89} Moreover, screening using LDCT reduced significantly all-cause mortality with 6.7\% (95\% CI 1.2-13.6\%).\textsuperscript{76} When lung cancer mortality was not included in all-cause mortality analysis, the all-cause mortality reduction dropped to 3.2\%, and was not statistically significant anymore.\textsuperscript{76}

Three smaller trials in Europe, the Danish screening trial, and the Italian DANTE and ITALUNG trials, reported no significant lung cancer or all-cause mortality reduction.\textsuperscript{100,105,106} An overview of the outcomes of the trials is presented in Table 3.\textsuperscript{107} Pooled estimates of the relative risks of death of the four trials combined were not published. Possibly because the estimates were partly based on interim analyses or absolute number life-years were not provided for the Italian studies, or differences in design of the included trials. Our calculation of the pooled relative risk, based on the published data, suggested that LDCT screening has significantly reduced the risk lung cancer mortality.\textsuperscript{53}

### Table 3. Effect of LDCT screening on lung cancer and all-cause mortality

<table>
<thead>
<tr>
<th>Trial*</th>
<th>Quality</th>
<th>Lung cancer deaths</th>
<th>All deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>per 100,000 py\textsuperscript{107}</td>
<td>Relative risk\textsuperscript{107}</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>NLST76</td>
<td>Good</td>
<td>247</td>
<td>309</td>
</tr>
<tr>
<td>DLST105</td>
<td>Fair\textsuperscript{†}</td>
<td>154</td>
<td>112</td>
</tr>
<tr>
<td>MILD100</td>
<td>Poor\textsuperscript{‡}</td>
<td>216</td>
<td>109</td>
</tr>
<tr>
<td>DANTE106</td>
<td>Fair\textsuperscript{¶}</td>
<td>527</td>
<td>637</td>
</tr>
</tbody>
</table>

*Trials included with results published before January 2014.

†Unclear allocation, differential follow-up.

‡Inadequate randomization, differences in baseline demographic characteristics, differential follow-up.

¶Unclear allocation, differences in baseline demographic characteristics, differential follow-up.

Concluding, efficacy of LDCT screening for lung cancer has been demonstrated by the NLST.\textsuperscript{76} However, the high survival rates in earlier cohort studies created high expectations from LDCT screening.\textsuperscript{91,95,96} As a result, the 20\% mortality reduction might not be as high as hoped. Nonetheless, there have been no other interventions so far, besides primary prevention, that have proven to be as successful as LDCT screening in reducing lung cancer mortality.

Currently, the Dutch-Belgian (NELSON), German and British lung cancer screening trial are still ongoing.\textsuperscript{101,102,108} As soon as enough follow-up time has accrued and data becomes available, final mortality analyses are expected from these studies. Updated pooled analyses also including these trials will provide a definitive conclusion on the effectiveness of LDCT screening.
THE NELSON TRIAL

Design
The NELSON trial is a randomised controlled trial on the efficacy of screening using low-dose computed tomography. The trial was conducted in the Netherlands and Belgium. NELSON is the acronym for the Dutch name of the trial: NEderlands-Leuvens longkanker ScreeningsONderzoek.

The NELSON trial was initiated in 2003, after favourable survival of lung cancer patients, who underwent low-dose computed tomography screening, was demonstrated in cohort studies. To determine whether LDCT screening yields not only improved survival but also reduced mortality from lung cancer, screening was compared to no screening. As presented in figure 4, study participants were randomised to no screening, or to four rounds of screening using LDCT; at baseline (first screening round), one year later (second screening round), three years later (third screening round), and five and a half years later (fourth screening round). Both groups of participants are followed up, and the difference in lung cancer mortality between the two groups is determined ten years after randomisation.

Figure 4. Design of the NELSON trial

Endpoints
Primary research objectives of the NELSON trial are:
I) To determine whether LDCT screening yields a reduction of ≥25% in lung cancer mortality.
II) To estimate cost-effectiveness of LDCT screening for lung cancer.
III) Secondary research objectives of the NELSON trial are:
IV) To determine whether LDCT screening yields a reduction in all-cause mortality.
V) To determine the effect of LDCT screening on quality of life.
VI) To determine lung cancer incidence and five-year survival rates.
VII) To determine detection rates and stage distribution per screening round.
VIII) To determine the number, stage distribution and time interval since last screening of interval cancers, and the ratio of the screen-detected cancers and the interval cancers.

IX) To determine the screening algorithm's sensitivity, specificity and positive predictive value.

X) To further define best practices in lung imaging and quality assurance.

XI) To define the molecular dynamics of very early lung cancer.

XII) To further define best practice and quality assurance in nodule evaluation and early stage lung cancer management.

**Hypothesis**

Screening using low-dose computed tomography will yield a lung cancer mortality reduction of ≥25% at ten years of follow-up.

**Recruitment**

The method of recruitment in the NELSON trial was especially designed to maximise the validity of extrapolation of trial results to the population eligible for lung cancer screening. Recruitment strategies based on media advertisements are known to attract health-concerned individuals, who are eager to participate in health and lifestyle interventions. As the population at high risk for developing lung cancer does not typically consist of health-concerned individuals, such an approach should be avoided. To minimize this so-called 'self-selection bias', a population-based recruitment strategy was chosen for the NELSON trial.

Potential trial participants were identified via population registries and were approached by mail. From the second half of 2003 onwards, more than a half million questionnaires on general health, smoking, alcohol consumption, physical exercise, cancer history, family history of lung cancer, body weight and length, education and opinion on screening programs, were sent to all men and women born between 1928 and 1953 in 7 districts in the Netherlands and 14 municipalities around Leuven in Belgium.98 This questionnaire was neither accompanied by information on the minimal requirements for participation, such as smoking history, nor by any other information about the trial, to prevent prejudiced answers.

The information obtained with this questionnaire was used to decide whom to invite for the trial. First, the estimated lung cancer mortality risk of the respondents was estimated using data of the US Cancer Prevention Studies.109,110 Next, the required sample size and the corresponding number of eligible subjects was determined using the same formulas as in the American PLCO (Prostate, Lung, Colorectal and Ovarian) screening trial and the European Randomised Screening Trial on Prostate Cancer.111,112 For this calculation, a 1:1 randomisation, a power of 80%, a one-sided a significance level of 0.05, 95%
compliance in the screen group, 5% contamination in the control group and 10 years of follow-up after randomisation were assumed. Finally, the required participation rate was determined. The most optimal selection scenario, which required a participation rate as low as possible and a required sample size within the ranges of the capacity, was to invite the following population: 50 to 75-year old current or former smokers who had quit less than 10 years ago with a smoking history of at least 15 cigarettes per day for 25 years or at least 10 cigarettes for 30 years.98 Hence, to be able to demonstrate a lung cancer mortality reduction of at least 25% in this study population, the estimated required sample size was 17,300 subjects.98 Therefore, a possible pooling with the Danish lung cancer screening trial was proposed.

In the second phase of recruitment another questionnaire was send, only to the eligible responders, which enclosed questions on smoking habits, smoking cessation, asbestosis exposure and chronic obstructive pulmonary disease, and the trial’s information leaflet and the informed consent. However, subjects with: a moderate or bad self-reported health, the inability to climb 2 flights of stairs, a body weight of 140 kg or more, current or past renal cancer, melanoma or breast cancer, or lung cancer diagnosed less than 5 years ago, or a chest CT examination less than 1 year ago, were excluded.

Eligible subjects without any exclusion criteria, who responded to the second questionnaire and provided written informed consent for participation in the NELSON trial were included and randomised. An overview of inclusion and exclusion criteria is provided in Table 4.

Table 4. Inclusion and exclusion criteria of the NELSON trial

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 - 75 years</td>
</tr>
<tr>
<td>Smoking history</td>
<td>≥ 15 cigarettes per day for 25 years</td>
</tr>
<tr>
<td></td>
<td>≥ 10 cigarettes per day for 30 years</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>≤ 10 years ago</td>
</tr>
<tr>
<td>Self-reported health</td>
<td>moderate or bad</td>
</tr>
<tr>
<td>Ability to climb stairs</td>
<td>≤ 2 flights</td>
</tr>
<tr>
<td>Body weight</td>
<td>≥ 140 kg</td>
</tr>
<tr>
<td>History of lung cancer</td>
<td>still under treatment</td>
</tr>
<tr>
<td></td>
<td>diagnosed &lt; 5 years ago</td>
</tr>
<tr>
<td>History of other cancer</td>
<td>renal cancer</td>
</tr>
<tr>
<td></td>
<td>breast cancer</td>
</tr>
<tr>
<td></td>
<td>melanoma</td>
</tr>
<tr>
<td>History of imaging</td>
<td>Computed tomography of the chest &lt; 1 year ago</td>
</tr>
</tbody>
</table>
Equipment and execution of screening examinations

The participants randomised to the screening group were invited by mail to undergo a LDCT examination of the chest at the nearest of the four screening sites. These were in the Netherlands in University Medical Center Groningen, University Medical Center Utrecht, and Kennemer Gasthuis in Haarlem, and in Belgium in University Hospital Leuven.

The CT scans used were all 16-detector MSCT scanners (MX8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH, USA, or Sensation-16, Siemens Medical Solutions, Forchheim, Germany). All scans were realised in about 12 seconds in spiral mode with 16 mm × 0.75 mm collimation and 15 mm table feed per rotation (pitch = 1.5), in a cranial-caudal scan direction, without intravenous contrast in low-dose setting. Depending on the body weight (less than 50 kg, 50 to 80 kg and more than 80 kg) the kVp settings were respectively 80-90 kVp, 120 kVp and 140 kVp. This corresponds with an effective radiation dose of less than 1.6 mSv. To achieve a CTDIvol of respectively 0.8mGy, 1.6mGy and 3.2 mGy, the mAs settings were adjusted for the machine used. Datasets of the thorax were reconstructed at 1.0 mm slice thickness, with 0.7 mm reconstruction increment and soft kernel (Siemens B30 filter, Siemens Medical Solutions, Forchheim, Germany). To minimise breathing artefacts, scans were performed in inspiration after appropriate instruction of the participants. Data acquisition and scanning conditions were kept standard across the four screening centres for the duration of the trial.

Image reading and volumetric measurements

Images were read on digital workstations (Leonardo, Siemens Medical Solutions) using the Syngo Lungcare software package (Version Somaris/5 VB 10A-W) for multi-dimensional image processing and computer viewing. Lung windows were assessed at a width of 1500 to −650 Hounsfield Units. A nodule was defined as a small approximately spherical, non-linear circumscribed focus of abnormal tissue. Nodules were classified as non-calcified when they did not show a benign pattern of calcification. Transversal, 6 mm thick maximal intensity projections (MIP) reconstructions were used to identify pulmonary nodules. Software to aid radiologist in the detection of pulmonary nodules (Lung-CAD VB10A, Siemens AG Healthcare) was used (Figure 5).

For all non-calcified nodules, the maximum dimensions in x, y and z direction, minimal, maximal and mean diameter, volume, density, location (central versus peripheral, lung segment, slice number) were recorded, as well as nodule surface characteristics (smooth, spiculated or other). The nodule characteristics were uploaded in the NELSON Management System (NMS) immediately after completion of the reading for an unlimited number of evaluated nodules per scan. In case of consecutive CT scans,
nODULES were matched with the same nodules documented on previous scans in order to determine changes in volume and to estimate the volume doubling time (VDT). This could be done either automatically, using a matching algorithm in NMS that provides the most probable match of nodules based on the combination of consistency, size and location, or manually.

Figure 5. Computer-aided detection of pulmonary nodules in the NELSON trial

For solid nodules and for the solid component of part solid nodules, volume was calculated by three-dimensional volumetric computer assessment (Figure 6).

In case of inappropriate segmentation, the radiologist was able to enter manual measurements that overrule the automatically generated volume calculations. For solid pleural based nodules, the diameter perpendicular to the costal pleura was taken to determine nodule size as the volumetric software used was not accurate enough for pleural-based lesions, due to inappropriate segmentation. For non-solid lesions, nodule size was based on two-dimensional manual measurements, namely the average of length and width. Length was measured in the X-Y-axis on a single CT image that showed the maximum
length. Width was defined as the longest diameter perpendicular to length on the same CT image. For part solid lesions, both the volume of the solid part and overall size of the nodule were recorded.

Throughout the study, the definition of growth was kept constant, and was defined as a percentage volume change (PVC) of 25% or more according to the following formula:

$$PVC = 100 \times \left(\frac{V2 - V1}{V2}\right)$$

Wherein PVC represents the percentage of the change in volume; V1 represents the volume of the nodule at the first screening examination, and V2 represents the volume of the nodule at the second screening examination. For nodules with a PVC of 25% or more, the volume doubling time (VDT) was estimated using in following formula:

$$VDT = \frac{\ln 2 \times \Delta t}{\ln \left(\frac{V2}{V1}\right)}$$

Wherein VDT represents the volume doubling time in days, $\Delta t$ represents the time interval between the two screening examinations in days, V1 the volume of the nodule at the first screening examination, and V2 represents the volume of the nodule at the second screening examination. For non-calcified nodules in which only two-dimensional size parameters (dmin or dmean) were available, PVC was not used but volume doubling time was estimated using the following formula:

$$VDT = \frac{\ln 2 \times \Delta t}{3 \ln \left(\frac{D2}{D1}\right)}$$
Wherein VDT represents the volume doubling time in days, Δt represents the time interval between the two screening examinations in days, D1 the two-dimensional measurement of the nodule at the first screening examination, and D2 represents the two-dimensional measurement of the nodule at the second screening examination.\textsuperscript{113}

After the initial reading of the screening examination, the images were made available for a second reading. The second radiologist was unaware of the conclusion of the first radiologist and read the images within 3 weeks.\textsuperscript{113} After the second reading, discrepancies were identified by the NELSON Management System when no auto-matching was achieved or when the second reader disagreed on nodule number, location or volume.\textsuperscript{113} In case of disagreement, an experienced expert radiologist performed a third reading and made the final decision. Finally, the nodule size category and nodule growth category were determined (Table 5).

### Table 5. Nodule size and growth categories in the NELSON trial

<table>
<thead>
<tr>
<th>Nodule size category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NODCAT I</td>
<td>Nodule with benign characteristics such as benign calcification patterns or fat deposition</td>
</tr>
</tbody>
</table>
| NODCAT II            | Solid nodules with volume < 50 mm³  
Pleural-based solid nodules with minimum diameter < 5 mm  
Non solid component part solid nodule with average diameter < 8 mm  
Solid component part solid nodule with volume < 50 mm³  
Non solid nodules with average diameter < 8 mm |
| NODCAT III           | Solid nodules with volume 50 - 500 mm³  
Pleural-based solid nodules with minimum diameter 5 - 10 mm  
Non solid component part solid nodule with average diameter ≥ 8 mm  
Solid component part solid nodule with volume 50 - 500 mm³  
Non solid nodules with average diameter ≥ 8 mm |
| NODCAT IV            | Solid nodules with volume > 500 mm³  
Pleural-based solid nodules with minimum diameter > 10 mm  
Solid component part solid nodule with volume > 500 mm³ |

<table>
<thead>
<tr>
<th>Nodule growth category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>GROWCAT A</td>
<td>Percentage volume change ≥ 25% and VDT &gt; 600 days</td>
</tr>
<tr>
<td>GROWCAT B</td>
<td>Percentage volume change ≥ 25% and VDT 400 - 600 days</td>
</tr>
</tbody>
</table>
| GROWCAT C              | Percentage volume change ≥ 25% and VDT < 400 days  
New solid component in previously non solid nodule |

### Nodule management protocol

After the nodule size category and growth category are assessed, the screening test result and associated actions to be taken are determined according to the NELSON nodule management protocol. A screening test in the NELSON trial could have three different outcomes:
I) Negative: not suspicious of lung cancer, no additional diagnostic tests warranted. The participant only receives an invitation for the next screening round.

II) Indeterminate: abnormalities are identified at the screening examination; it is unclear whether these represent lung cancer. The participant receives an invitation for a follow-up CT examination to determine nodule growth.

III) Positive: abnormalities suspicious of lung cancer are identified at the screening examination. The participant receives a recommendation to consult a pulmonologist for diagnostic work-up.

An overview of the NELSON nodule management protocol is presented in figure 7. At baseline screening, only the size category of detected nodules can be determined, as only one CT examination is available. All nodules in size category NODCAT I and NODCAT II are classified as a negative screening test result (Table 5). Nodules with size category NODCAT III are classified as an indeterminate screening test result, and nodules with size category NODCAT IV are classified as a positive screening test result (Table 5). At the follow-up CT examination in the participants with indeterminate baseline screening test results, the growth category determines the final screening test result. Hence, nodules with growth category GROWCAT A or GROWCAT B are classified as a negative screening result, and nodules with growth category GROWCAT C are classified as a positive screening result.

From the second screening round onwards, a different classification is used. Nodules with size category NODCAT I or growth category GROWCAT A are classified as a negative screening test result (Table 5). All nodules with size category NODCAT II or NODCAT III or growth category GROWCAT B are classified as an indeterminate screening test result, and nodules with size category NODCAT IV or growth category GROWCAT C as a positive screening test result (Table 5).

Figure 7. Nodule management protocol of the NELSON trial
Diagnostic work-up after positive screening tests

All participants who receive a positive screening result are referred to a pulmonologist via their general practitioner. Most often, participants are referred to one of the pulmonologists involved in the NELSON trial at one of the four screening hospitals (University Medical Center Groningen, University Medical Center Utrecht, and the Kennemer Gasthuis Haarlem in the Netherlands, and University Hospital Gasthuisberg Leuven in Belgium). The nodule detected by screening, which was classified as positive, is considered suspicious for lung cancer, and a diagnostic work-up needs to be performed to diagnose or exclude lung cancer. The NELSON trial provides directives for the diagnostic work-up after a positive screening test result, but did not orchestrate its effectuation. As a result, the work-up was usually performed according to the national guideline.60

The diagnostic work-up usually consisted of: personal history, physical examination, regular dose contrast-enhanced CT scan from the supra-clavicular region down to the adrenals, whole-body fluorodesoxyglucose (FDG) -positron emission tomography (PET) examination, and conventional white light bronchoscopy (with endobronchial washing and brushing, and biopsy of the nodule or lymph nodes if possible). CT-guided trans-thoracic biopsy of the suspicious nodule was performed only in a small minority of the diagnostic work-ups. Next, the results of this series of initial diagnostic procedures are discussed in the local multidisciplinary lung oncology team, which usually has members from the following departments: pulmonary medicine, thoracic surgery, radiation oncology, radiology, nuclear medicine and pathology.

In case the initial series of diagnostic procedures did not yield any result that supported the suspicion of lung cancer, or a benign cause of the nodule was identified, the multidisciplinary team would usually decide to end the clinical evaluation and to refer the participant back to the screening programme of the NELSON trial.

In case the initial series of diagnostic procedures did not yield conclusive results, the multidisciplinary team would usually recommend to perform another diagnostic CT examination after three to six months, in accordance with international guidelines.118,119

In case the initial series of diagnostic procedures confirmed the suspicion of lung cancer, or yielded a cytological diagnosis of lung cancer, the decision of the multidisciplinary team will depend on the clinical TNM disease stage and the participant's operability.36,120

Lung cancer staging

The participants of the NELSON trial who were diagnosed with lung cancer were staged according to the IASLC (International Association for the Study of Lung Cancer) TNM lung cancer staging system. This system uses criteria for the extensiveness of the primary tumour, metastasis in regional lymph nodes and metastasis at distant sites, to classify patients in subgroups with comparable prognoses. As the NELSON trial was initiated in 2003, the sixth edition of the TNM staging system121 was used. However from 2009
onwards, the seventh edition of the staging system was used.\textsuperscript{122} For all studies in this thesis, the lung cancers that have initially been staged according to the sixth edition, were re-staged according to the seventh edition.

To determine the clinical tumour stage (cT), the contrast enhanced CT scan and bronchoscopy are the most important diagnostic procedures. Hence, they are used to measure the size of the primary tumour, to determine the distance of the primary tumour to the lobar bronchus and carina, and to assess the presence of tumour invasion of the pleura or extra-pulmonary structures, separate tumour nodules in the ipsilateral lung, obstructive pneumonitis or atelectasis. Using this information, the T stage can be determined with the criteria presented in table 6a.

To determine the clinical node stage (cN), the contrast enhanced CT scan and the FDG-PET scan are used initially. They are used to determine whether the tumour is adjacent to the mediastinum, whether there are any hilar, mediastinal, infra-clavicular, supra-clavicular or scalene lymph nodes with a short axis diameter of 10 mm or more, or with relevant FDG uptake. If any of the previous is observed, the Dutch guideline recommends to obtain a mediastinal tissue diagnosis using endosonography or surgical mediastinoscopy.\textsuperscript{123} Using this information, the N stage can be determined with the criteria presented in table 6b.

To determine the clinical distant metastasis stage (cM), the contrast enhanced CT scan and the FDG-PET scan are used. They are used to determine whether there are any tumour nodules in the contralateral lung, pleural nodules, pleural or pericardial effusions or distant metastasis. Additionally, the Dutch guideline recommends obtaining magnetic resonance imaging (MRI) of the skull to rule out brain metastases in patients with clinical stage III.\textsuperscript{123,124} Using this information, the M stage can be determined with the criteria presented in table 6c.

Once the clinical T, N and M stage of the (suspected) lung cancer are known, the disease stage can be determined using the classification presented in table 7. The TNM disease stage is closely correlated with prognosis, and determines which treatment options are feasible.\textsuperscript{60,122-125}

\textbf{Treatment of screen-detected lung cancer}

Participants who are diagnosed with lung cancer through the screening program are treated in accordance with the national guidelines for the treatment of non-small cell and small cell lung carcinoma.\textsuperscript{60,123,124} The NELSON trial did not provide any directives for the treatment of screen-detected lung cancer.

\textit{Small cell lung cancer}

The treatment of small cell lung cancer according the national Dutch guideline\textsuperscript{124} is divided in two different paths; one for small cell lung cancer diagnosed at limited disease stage,
Table 6a. Criteria for tumour stage 7th edition IASLC staging protocol

<table>
<thead>
<tr>
<th>T stage (primary tumour)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour less ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour &gt; 2 cm but ≤ 3 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt; 3 cm but ≤ 7 cm or tumour with any of the following features (T2 tumours with these features are classified T2a if ≤ 5 cm): involves main bronchus, ≥ 2 cm distal to the carina, invades visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour &gt; 3 cm but ≤ 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour &gt; 5 cm but ≤ 7 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour &gt; 7 cm or directly invading any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus (&lt; 2 cm distal to the carina), but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, separate tumour nodule(s) in a different ipsilateral lobe</td>
</tr>
</tbody>
</table>

*The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.*

Table 6b. Criteria for node stage 7th edition IASLC staging protocol

<table>
<thead>
<tr>
<th>N stage (regional lymph nodes)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
</tbody>
</table>

Table 6c. Criteria for node stage 7th edition IASLC staging protocol

<table>
<thead>
<tr>
<th>M stage (distant metastasis)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial) effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

*Most pleural (and pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.*
and another for small cell lung cancer diagnosed at extensive disease stage. Whether lung cancer is diagnosed at limited or advanced disease stage is determined by the possibility to capture all tumour in a single radiation field. In case this is possible, the disease stage is limited, which are usually unilateral tumours with no, hilar or ipsilateral mediastinal lymph node involvement, otherwise the disease stage is extensive.

Patients with small cell lung carcinomas diagnosed at limited disease stage, are recommended to be treated with multimodality therapy. This is usually concomitant chemotherapy, consisting of four cycles of Cisplatin - Etoposide, and radiotherapy, consisting of chest irradiation of 30 fractions of 1.5 Gy. For very early stage small cell lung carcinomas (T1-2N0-1M0) surgical resection may be added to the multimodality treatment. After the initial treatment, prophylactic cranial irradiation (10 fractions of 2.5 Gy) is recommended in patients without disease progression.

Patients with small cell lung carcinomas diagnosed at extensive disease stage, who have a WHO performance score of 0 to 3, are recommended to be treated with chemotherapy, for example 4 to 6 cycles of Cisplatin or Carboplatin - Etoposide. Radiotherapy is only recommended for palliative purposes, such as haemoptysis, superior vena cava syndrome or painful bone metastases. After the initial treatment, prophylactic cranial irradiation (10 fractions of 2.5 Gy) is recommended in patients without disease progression.

As the majority of the patients with limited disease and about all patients with extensive disease will be confronted with recurrence of the cancer after the initial therapy, the recommended treatment for recurrent small cell lung cancer is described as well. Hence, chemotherapy is the only therapeutic option and should be offered to all patients that are not compromised as a result of advanced age, marginal performance status, co-morbidity and complications from the first series of chemotherapy. In case the cancer was sensitive

<table>
<thead>
<tr>
<th>Stage groups</th>
<th>T stage</th>
<th>N stage</th>
<th>M stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>T1a,b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Ib</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Ia</td>
<td>T1a,b</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>T2a</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>T2b</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>T1-3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>N0,1</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>T4</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>T1-4</td>
<td>N3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T1-4</td>
<td>N0-3</td>
<td>M1a,b</td>
</tr>
</tbody>
</table>

Table 7. Stage groupings 7th edition of the staging protocol
for the first chemotherapeutic, re-induction therapy or Topotecan may be given. In case the cancer was not sensitive for the first chemotherapeutic, other chemotherapeutics should be chosen as monotherapy or combination therapy.

**Non-small cell lung cancer**

The treatment of non-small cell lung cancer according the national Dutch guideline depends on the TNM disease stage at diagnosis. Patients diagnosed with resectable or locally advanced non-small cell lung cancer are recommended to undergo surgical resection of the tumour and dissection of the mediastinal lymph nodes. In case it was not possible to establish an histological or cytological diagnosis of lung cancer pre-operatively, an initial limited resection of the tumour should be performed to confirm the diagnosis by frozen section examination.

For confirmed non-small cell lung cancers limited to one lobe, lobectomy with systematic mediastinal lymph node resection is the treatment of choice. If this is not possible due to poor pulmonary function, a more limited resection, such as a segmentectomy or wedge resection can be performed. In such patients without lymph node involvement stereotactic radiotherapy should also be considered. For lung cancers that are not limited to one lobe and a limited resection of the other lobe, or by performing a bilobectomy or a pneumonectomy. For lung tumours that cannot be resected completely with a lobectomy due to tumour extension up to the ostium of the main bronchus of a lobe or the carina, a sleeve-lobectomy or sleeve-pneumonectomy can be performed. For lung tumours that extended up to or in the parietal pleura or thorax, an ‘en bloc’ resection of the affected section of the thorax should be performed. For tumours that per-operatively appear to have invaded the intra-pericardial part of the pulmonary artery, a pneumonectomy should be considered. Surgical resection of lung tumours that per-operatively appear to have invaded the superior vena cava, the adventitia of the aortic wall, the pericardium or diaphragm is not excluded. However, lung tumours that have substantially invaded the left atrium or the vertebral column are rarely resectable. Lung tumours that invade the pulmonary trunk, the oesophagus, or through the aortic wall or tumours that have caused pleuritis carcinomatosis are irresectable.

The aforementioned procedures are usually performed via thoracotomy, however video-assisted thoracoscopic procedures are also acceptable in selected patients by experienced surgeons.

Adjuvant radiotherapy is recommended in case of irradical resection and unexpected N2-3 disease. Adjuvant chemotherapy, such as four cycles of Cisplatin combination therapy, is recommended in case of stage II-IIIA disease in patients with a good performance status (WHO 0-1).
Patients with unresectable, locally advanced non-small cell lung cancer (stage III), and a good performance status are recommended to be treated with concomitant chemoradiation therapy. After this initial treatment, the tumour should be re-staged to determine whether complete resection has become an option.

Patients with advanced stage non-small cell lung cancer (stage IV) and performance stage 0-3 are recommended to be treated with combination chemotherapy. For non-squamous cell cancers, a combination therapy of Cisplatin and a third-generation cytostatic (except Gemcitabin) is recommended. However treatment with Carboplatin, Paclitaxel or Bevacizumab can also be considered. For squamous cell carcinomas, Carboplatin combination therapy is recommended (not with Pemetrexed). Only in patients a known activating EGFR-mutation, EGFR-TKIs should be used as initial treatment. EGFR-TKIs can be used second and later treatment lines in patients with known and unknown EGFR status. Pemetrexed can be used as maintenance therapy in progression-free patients after first line chemotherapy, as well as EGFR-Tyrosine-kinase-inhibitors in in patients with an activating EGFR mutation.

**Follow-up**

After the initial treatment of lung cancer, the Dutch guidelines recommend to perform regular follow-up consisting of anamnesis, physical examination and possibly a chest radiograph. Follow-up using imaging, which enables the assessment of disease progression, is only recommended in case an active second or third treatment line can be offered, and in case screening for late side-effects is useful. Follow-up is recommended every three months during the first year, every six months during the second year, and every year for at least five years. The NELSON trial is not actively involved in the follow-up process of the participants who have been treated for lung cancer.

**Data collection**

To determine the main outcome of the NELSON trial and to be able to perform side-studies, data needs to be collected on the diagnosis, treatment and follow-up of lung cancer. This information is required for both the participants diagnosed with lung cancer through screening and the participants who were diagnosed with lung cancer outside the screening program; e.g. before screening has started, between screenings, after screening has stopped and in the participants randomised to the control group.

The first step of data collection is to identify all participants who were diagnosed with lung cancer. The information on all lung cancer diagnoses is obtained via linkages with the national cancer registries of the Netherlands and Belgium, which have national coverage. The second step is to collect copies of the medical files of all participants diagnosed with lung cancer from the date of the first consultation for (suspected) lung cancer, until the date death or the end of the study. Finally, to obtain medical information on the
General introduction

last phase of the participants’ life, the general practitioner was approached and requested to answer a number of questions concerning the cause of death.

End point verification

Lung cancer-specific mortality is the main outcome measure of the NELSON trial. Therefore, verification of the cause of death of the study participants who were ever diagnosed with lung cancer is crucial. The cause of death could be obtained by using the direct and underlying causes of death reported on the official death certificates of the deceased participants. However, the use of the official certificates for this purpose is debated for several reasons. Firstly, two forms of bias especially affect death certification in screening trials:

I) Sticky-diagnosis bias: CT screening leads to an increased incidence of lung cancer through advanced diagnoses and overdiagnosis. As a result, the prevalence of lung cancer is higher in the screening group than in the control group. Since lung cancer is commonly recognised as a lethal disease, the deaths in the screening group are more likely to be attributed to lung cancer than deaths in the control group.128

II) Slippery-linkage bias: deaths as a result of interventions of treatments for lung cancer may be difficult to trace back to screening and could easily be certified as death due to other causes.128

Secondly, the merit of death certificates depends on the accuracy of the certifying clinician and nosologist, and the establishment of a correct ante mortem diagnosis.129,130 Common reasons for misclassification are coinciding malignancies, considerable comorbidity and death after a surgical procedure.131,132 Finally, the sensitivity and specificity of the death certificate has been reported to range from 84.5 to 99.7% and 91.3 to 99.7%; causing an error that tends to reduce the effect of screening.132-135

To overcome these problems, clinical expert committees that review the medical files of the deceased participants to determine the cause of death, are frequently employed in cancer screening trials.132-137 Assessing the cause of death by such a committee should yield an uniform, objective ad unbiased determination of the trials’ main end point. The development of a cause of death review process protocol for the NELSON trial was part of this thesis (Chapter 9).
RESEARCH QUESTIONS

The purpose of this thesis was to evaluate lung cancer screening using low-dose computed tomography in the Dutch-Belgian NELSON trial. Implications for future lung cancer screening programs were identified by assessing the screening strategy’s performance and outcomes. The research questions and hypotheses of the studies described in the subsequent chapters of this thesis are described next.

Research question I

Chapter 2. Predictive value of screening test results

Volumetric computer tomography screening for lung cancer: three rounds of the NELSON trial.

*European Respiratory Journal*

Main research question

What was the screening performance of the nodule management protocol of the NELSON trial?

Sub research questions

a) What were the detection rates, test characteristics and numbers needed to screen of the nodule management protocol of the NELSON trial?

b) What was the incidence of invasive diagnostic procedures for false-positive screening test results?

c) What were participant’s probabilities of false-positive screening results and lung cancer after baseline and subsequent screening test results?

Research question II

Chapter 3. Characteristics of screen-detected lung cancer

Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial.
**American Journal of Respiratory and Critical Care Medicine**

**Main research question**
What was the effect of screening using low-dose computed tomography on the characteristics of screen-detected lung cancer?

**Sub research questions**

a) What were the tumour characteristics of lung cancers detected by low-dose CT screening?
b) What was the effect of screening round and gender on the characteristics of screen-detected lung cancer?
c) To what extent was screening able to detect lung cancer before the onset of symptoms?

**Research question III**

**Chapter 4. Epidemiological evaluation**


**Lancet Oncology**

**Main research question**
How can knowledge on the lung cancers not detected by low-dose computed tomography screening be used to improve the performance of the screening strategy?

**Sub research questions**

a) What were the detection rates and test characteristics of the nodule management protocol of the NELSON trial?
b) Were there any differences in the characteristics between the participants diagnosed with screen-detected lung cancer and the participants diagnosed with an interval cancer?
c) What were the tumour characteristics of the lung cancers not detected by low-dose computed tomography screening?
d) What were the causes of the failure to detect the interval cancers?
Research question IV

Chapter 5. Radiological evaluation

Computed tomographic characteristics of interval and post-screen carcinomas in lung cancer screening.

*European Radiology*

**Main research question**
How can knowledge on the radiological characteristics of lung cancers not detected by low-dose CT screening be used to improve the performance of the screening strategy?

**Sub research questions**

a) What proportion of the lung cancers not diagnosed through screening were, in retrospect, present at the last LDCT screening examination?

b) What were the causes of the failure to detect the missed lung cancers?

c) What were the characteristics of the carcinomas missed on the LDCT screening examination due to radiological detection or interpretation errors?

Research question V

Chapter 6. Optimisation of screening protocols

Lung cancer probability in subjects with CT-detected pulmonary nodules: an analysis of data from the NELSON trial of low-dose CT screening.

*Lancet Oncology*

**Main research question**
How should a participant's predicted lung cancer probability, based on size and growth of CT-detected nodules, be used to optimise the nodule management protocol of the NELSON trial?

**Sub research questions**

a) Was it valid to predict the two-year lung cancer probability of an individual who underwent screening using low-dose computed tomography, using a model based on nodule size and growth rate?
b) What was the probability of lung cancer in an individual who underwent screening using low-dose computed tomography, based on nodule size and growth rate?

c) How should the current thresholds for nodule size and growth rate be adjusted to improve risk stratification, test characteristics and reduce harms?

**Research question VI**

**Chapter 7. Evaluation of bronchoscopy**

The role of conventional bronchoscopy in the work-up of suspicious CT screen-detected pulmonary nodules.

*Chest*

**Main research question**

What was the value of bronchoscopy for diagnosing lung cancer in screen-detected nodules?

**Sub research questions**

a) What were the test characteristics of bronchoscopy and its ancillary procedures?

b) What were predictors for a true-positive bronchoscopic procedure?

c) Which diagnoses were made in false-negative bronchoscopic procedures?

**Research question VII**

**Chapter 8. Evaluation of surgical procedures**

Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial.

*European Journal of Cardio-Thoracic Surgery*

**Main research question**

To what extent did adverse events related to thoracic surgery, occur in participants after a positive screening test results?

**Sub research questions**

a) How often occurred re-thoracotomy, complications, and post-operative mortality in participants who underwent thoracic surgery for a positive screening test result?
b) What was the length of hospital stay for lung resection performed by thoracotomy and video-assisted thoracoscopic surgery?

c) To what extent were surgical procedures performed for benign nodules?

Research question VIII

Chapter 9. Endpoint determination

Uniform and blinded cause of death verification in a lung cancer CT screening trial.

Lung Cancer

Main research question

How should the endpoint verification process of the NELSON trial be designed to ensure uniform, objective and unbiased endpoint determination?

Sub research questions

a) How to develop a cause of death review protocol that ensures uniform, objective and unbiased endpoint determination?

b) How was the performance of the developed cause of death protocol compared to the official death certificates?

c) What were sources of disagreement between users of the developed cause of death protocol?

d) What were the best sources of information for a review of the cause of death of a participant?
OUTLINE OF THIS THESIS

Part I of this thesis “Introduction” consists of the General introduction (Chapter 1). Part II of this thesis “Evaluation of findings” consists of four chapters, covering several aspects of the performance screening algorithms. In the first study (Chapter 2), data on screening test results and screen-detected lung cancer were used to determine positive predictive value and 5.5-year lung cancer probability. In the second study (Chapter 3) the tumour characteristics of the lung cancers detected by screening are presented. In the third study (Chapter 4), the performance of the screening algorithm of the NELSON trial was estimated, and opportunities to improve the performance were identified. In the fourth study of part II of this thesis (Chapter 5), radiological causes of the failure to detect the lung cancers not diagnosed through screening were assessed, and opportunities to improve the performance of the screening algorithm were identified. Part III of this thesis “Optimisation of screening” presents three studies. In the first study, (Chapter 6), lung cancer probability of participants was estimated and used to design improved nodule management protocols. In the second study (Chapter 7), the value of bronchoscopy in the diagnostic work-up of suspicious CT-detected nodules was determined. In the third study (Chapter 8), adverse events related to thoracic surgery, performed in the diagnostic work-up of suspicious CT-detected nodules were assessed. Part IV of this thesis “Evaluation of effectiveness” consists of one study (Chapter 9), which presents the design and evaluation of the endpoint verification process of the NELSON trial. Part V of this thesis “Implications for implementation”, presents an overview of lung cancer screening and the studies presented in the parts II to IV of this thesis. Firstly, a review of the currently published literature (Chapter 10) is performed to determine the state of the art in lung cancer screening. Secondly, a review of the studies of this thesis (Chapter 11) is performed to interpret important results, answer the research questions of this thesis, and formulate general conclusions and recommendations. Furthermore, a summary of this thesis in English (Chapter 12) and in Dutch (Chapter 13) is provided. Finally, part VI of this thesis “Miscellaneous” consists of acknowledgements (Chapter 14), curriculum vitae (Chapter 15), PhD portfolio of the Erasmus University (Chapter 16), and the list of publications (Chapter 17).
REFERENCE LIST


Part II

Evaluation of findings
Chapter 2

Predictive value of screening test results

Volumetric computer tomography screening for lung cancer: three rounds of the NELSON trial


European Respiratory Journal
December 2013
**Volumetric computed tomography screening for lung cancer: three rounds of the NELSON trial**


**ABSTRACT**

Several medical associations recommended lung cancer screening by low-dose computed tomography scanning for high-risk groups. Counselling of the candidates on the potential harms and benefits and their lung cancer risk is a prerequisite for screening.

In the NELSON trial, screenings are considered positive for (part) solid lung nodules with a volume \(>500 \text{ mm}^3\) and for (part) solid or nonsolid nodules with a volume-doubling time \(<400\) days. For this study, the performance of the NELSON strategy in three screening rounds was evaluated and risk calculations were made for a follow-up period of 5.5 years.

458 (6%) of the 7582 participants screened had a positive screen result and 200 (2.6%) were diagnosed with lung cancer. The positive screenings had a predictive value of 40.6% and only 1.2% of all scan results were false-positive. In a period of 5.5 years, the risk of screen-detected lung cancer strongly depends on the result of the first scan: 1.0% after a negative baseline result, 5.7% after an indeterminate baseline and 48.3% after a positive baseline.

The screening strategy yielded few positive and false-positive scans with a reasonable positive predictive value. The 5.5-year lung cancer risk calculations aid clinicians in counselling candidates for lung cancer screening with low-dose computed tomography.
INTRODUCTION

A number of prominent medical associations recently recommended screening for lung cancer in high-risk groups by low-dose computed tomography (LDCT) scanning. The recommendation resulted from the efforts that have been made by many researchers over the past decade, especially by the National Lung Screening Trial (NLST) research team. The latest systematic review on computed tomography (CT) screening for lung cancer concluded that there are still substantial uncertainties regarding how to translate the positive recommendation into clinical practice.

Most individuals eligible for screening will not develop lung cancer but are exposed to several potential harms: radiation exposure, psychological distress while awaiting results, and distress, morbidity and mortality in case of false-positive results. However, for individuals who actually will develop lung cancer, LDCT screening is often able to detect lung cancer at an early stage. The NLST has demonstrated that LDCT screening reduces the risk of dying from lung cancer significantly. Nevertheless, the early detection of lung cancer also leads to a prolonged disease course and will not be beneficial in persons who would otherwise never be diagnosed with lung cancer.

Therefore, to be able to counsel individuals adequately on the benefits and harms of LDCT-screening, clinicians should inform the candidates of their risk of true-positive and false-positive screen results. In the NLST, for example, 24.2% of the subjects had a positive screening, but only 3.6% was diagnosed with lung cancer. Furthermore, to be able to make an informed choice on future screenings, high-risk subjects should know how their probability of screen-detected lung cancer changes after their first screening.

In our trial, the Dutch–Belgian lung cancer screening trial (NELSON) solid lung nodules are assessed with three-dimensional measurements (volume). Screening results are considered positive for volumes >500 mm³ (diameter ~9.8 mm) or volume-doubling times (VDT) <400 days. This is considerably more stringent than the NLST policy to refer any nodule with a maximum diameter ≥4 mm. The volumetry-based screening strategy of the Danish lung cancer screening trial (DLCST) was adopted from our trial and led to a positive screen result in 2.0% of the participants with 34.8% of these results being true-positive.

In this study, we will evaluate the performance of the NELSON screening strategy in the first three screening rounds. We will calculate lung cancer detection rates and positive predictive values and compare our results with other LDCT screening trials. Furthermore, we will calculate the 5.5-year risk of false-positive screen results and screen-detected lung cancer stratified by the result of the first screening scan. This will provide valuable information for clinicians who are confronted with individuals who consider or have already undergone LDCT screening for lung cancer.
METHODS

Details of the design and conduct of the NELSON trial have been reported elsewhere.\textsuperscript{11,14} Briefly, subjects aged 50–75 years, who had smoked either 15 cigarettes or more per day for 25 years or 10 cigarettes or more for 30 years and were still smoking or had quit less than 10 years ago met the inclusion criteria. Before inviting the eligible subjects, persons with a moderate or bad self-reported health, the inability to climb two flights of stairs, a body weight of 140 kg or more, current or past renal cancer, melanoma or breast cancer and lung cancer diagnosed less than 5 years ago or still under treatment were excluded.\textsuperscript{14}

Ultimately, 15,822 individuals were randomised (1:1) to screening (n=7915) with low-dose CT at baseline (first round), 1 year later (second round) and 3 years later (third round) or no screening (n=7909). The main purpose of the trial is to determine whether CT screening will have reduced mortality from lung cancer by at least 25% at 10 years of follow-up.\textsuperscript{14,15}

For this study, all 7915 participants randomised to the screening arm were included. Complete data on interval cancers were not yet available and, consequently, no analyses of screening sensitivity were performed.

Equipment and execution of screening examinations

A detailed description of the equipment and the execution of the screening examinations have previously been published.\textsuperscript{11} In short, in each of the four screening sites, 16-detector CT scanners were used in a low-dose setting, without the administration of intravenous contrast media.\textsuperscript{11} Datasets were derived from images of the thorax with a slice thickness of 1 mm and a slice interval of 0.7-mm.\textsuperscript{11} CT images were analysed using software for semi-automated volume measurements (LungCARE; Siemens AG, Erlangen, Germany).\textsuperscript{16–18} In cases where the software was not able to measure nodule volume (e.g. in pleural based or nonsolid nodules), the diameter of the nodule was measured manually by the radiologist.

Nodule management protocol

The management protocol of the NELSON trial has been published previously.\textsuperscript{9,11,19} Briefly, screening could lead to three different outcomes: I) a negative screen result (no other action than an invitation for the next screening round); II) an indeterminate result (invitation for a follow-up scan); III) a positive result (referral to a pulmonologist for diagnostic work-up).

For newly detected solid nodules and the solid component of part-solid nodules, the volume determined the screening result as follows: <50 mm\textsuperscript{3} was negative, 50–500 mm\textsuperscript{3} was indeterminate and >500 mm\textsuperscript{3} was positive.

For previously detected and nonsolid nodules, the percentage volume change was calculated: <25% was a negative result and ≥25% led to the assessment of the VDT. The VDT in days was calculated using the following formula:
Predictive value of screening test results

VDT=\left(\ln 2 \times \Delta t\right)/\left(\ln\left(V_2/V_1\right)\right)

where V_1 represents nodule volume on the first examination and V_2 the volume the second examination and \Delta t the time between the examinations in days. In case the software was not able to measure nodule volume, manually measured diameters were used to calculate VDT in days using the following formula:

VDT=\left(\ln 2 \times \Delta t\right)/\left(\ln\left(\text{MaxDiam}_{XY}^2 \times \text{PerpDiam}_{XY} \times \text{MaxDiam}_{Z}^2\right)/\text{MaxDiam}_{XY}^1 \times \text{PerpDiam}_{XY}^1 \times \text{MaxDiam}_{Z}^1\right)

where MaxDiam_{XY} is the maximum diameter in the x/y-axis, PerpDiam_{XY} the maximum diameter perpendicular to MaxDiam_{XY} and MaxDiam_{Z} is the maximum diameter in z-axis.

For nodules with VDTs of 400–600 days, the result was indeterminate; for VDTs of <400 days the result was positive. From the second round onwards, participants with a nodule with a VDT of 400–600 days were invited for a 12-month repeat scan. Furthermore, the screening was also positive if a new solid component had emerged in a previously nonsolid nodule. The screening result was negative for all nodules with fat, benign calcification patterns or other benign abnormalities.

Referral, diagnostic work-up and diagnoses

After a positive screening, participants were referred for diagnostic work-up via their general practitioner and received usual care according to national and international guidelines. All data were prospectively collected and histological specimens were reassessed by our chief pathologist (ET).

Definitions and statistics

Screen-detected lung cancers are the lung cancers that are diagnosed by the diagnostic work-up initiated for a positive screening. The lung cancer detection rate is the number of screen-detected lung cancers divided by the number of screened participants. A true-positive test result is a positive scan in a participant who actually has lung cancer. A false-positive test result is a positive scan, when lung cancer is not diagnosed.

The normality of the distribution of the continuous variables (age and pack-years) was evaluated by studying the Q-Q plots. As the variables were not normally distributed, the variables were described by the median and interquartile range. For analysing the difference between the continuous variables across the three screening rounds, the Kruskal–Wallis H test was used. For analysing the difference between the nominal variables (sex and smoking status) across the three screening rounds, the likelihood ratio-based
Chi-squared test was used. To calculate 95% confidence intervals of proportions, bootstrapping was performed based on 1000 samples. For all analysis, α<0.05 was considered significant and PASW Statistics, SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used.

Ethics and legal approval
The NELSON trial was approved by the Dutch Minister of Health and the ethics board at each participating centre. The NELSON trial is registered at www.trialregister.nl (number ISRCTN63545820). All participants gave written informed consent for participation and the evaluation of personal data from hospital charts and national registries.

RESULTS

7,582 (95.8%) of the 7,915 participants randomised to the screen-arm of the trial were actually screened. The participation rates remained high across the three screening rounds: 7,557 (95.5%) in round one, 7,295 (92.2%) in round two and 6,922 (87.5%) in round three.

In three screening rounds, 24,354 CT scans were made. 21,773 (89.4%) of the scans were a regular “round scans” and 2,581 (10.6%) were follow-up scans, performed to assess the VDT of indeterminately sized nodules. The scans detected a total of 31,683 nodules: 266 (0.8%) were part-solid and 298 (0.9%) nonsolid.

The screening result was negative in 87.2% of all scans (21,232 out of 24,354). The result was indeterminate in 10.8% (2,629 out of 24,354) and positive in 2.0% (493/24,354) of the scans. In the first round, the proportion of indeterminate and positive scan results was relatively higher than in later rounds. A detailed overview of the scan results per screening round is presented in figures 1-3.

The 493 positive screen results led to the diagnosis of lung cancer in 200 participants. 14 (7.0%) of these 200 participants were referred for a part-solid nodule and eight participants (4.0%) for a nonsolid nodule. 40.6% (200 out of 493) of all positive screenings were “true-positive” (95% CI 36.1-45.2%). The positive predictive value slightly increased across the three rounds, from 35.5% (95% CI 28.4-42.1%) in round one to 42.0% in round two (95% CI 34.4-49.6%) to 45.5% (95% CI 37.6-53.3%) in round three.

The cumulative lung cancer detection rate of the three rounds was 200 (2.6%) out of 7582 (95% CI 2.3-3.0%). This detection rate was relatively stable across the three screening rounds: 0.9% (75 of 6,922, 95% CI 0.7-1.2%) in round one, 0.8% (55 of 7,295, 95% CI 0.6-1.0%) in round two and 1.1% (75 of 6,922, 95% CI 0.8-1.3%) in round three.

The 493 positive screen results did not lead to a lung cancer diagnosis in the remaining 293 cases. Hence, 59.4% (293 of 493, 95% CI 54.8-63.9%) of the positive screen results
Predictive value of screening test results

Figure 1. Results of the first round of screening

<table>
<thead>
<tr>
<th>First Round of Screening</th>
<th>7557 participants* - January 2004 to December 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Scans</td>
<td>Negative 5986 (79.2%)</td>
</tr>
<tr>
<td>Follow-up Scans*</td>
<td>Negative 1341 (92.4%)</td>
</tr>
<tr>
<td>Result Round 1</td>
<td>Negative 7360 (97.4%)</td>
</tr>
<tr>
<td>Referral and Work-up</td>
<td>Not referred 16 (8.1%)</td>
</tr>
<tr>
<td>Outcome Round 1</td>
<td>No malignancy 103 (52.3%)</td>
</tr>
</tbody>
</table>

* 7,915 participants were randomised to the screen-arm of the trial and invited for screening; 25 (0.3%) participants missed screening in the first round, but were screened in the second round and 333 (4.2%) participants did not respond to the invitation.

# Follow-up scans were performed after 99.6 days (mean; SD 18.3). In 8.3% of the subjects with an indeterminate result the nodule(s) had disappeared.

^ Reasons: administrative error (n=15), no show (n=13), refusal (n=3), already receiving treatment from other specialist (n=2).

~ Reasons: decision by tumour board (n=10), administrative error (n=3), already receiving treatment from other specialist (n=3).

$ 67 of 70 (95.7%) lung cancer diagnoses were confirmed by cytology or histology. Details concerning the basis of the diagnosed the three other cases can be found in the Appendix.

were actually “false-positive”. Overall, 1.2% (293 of 24,354) of the scans performed in three rounds of the NELSON trial had a false-positive result.

The ratio of the overall true-positive and false-positive results (the true-positive/false-positive ratio) was 0.69. The true-positive/false-positive ratio tended to improve over time, from 0.69 in round one to 0.72 in round two, and to 0.83 in round three.

To detect lung cancer in 200 participants, 7,582 individuals underwent three rounds of screening. In the first screening round, 108 (7,557/70) participants were screened to detect one lung cancer. In the second round, 133 (7,295/55) and in the third round 92
(6,922/75) subjects were screened for the detection of one lung cancer. Cumulatively, to detect one lung cancer 38 participants underwent three screening rounds.

Figure 2. Results of the second round of screening

<table>
<thead>
<tr>
<th>Second Round of Screening</th>
<th>7295 participants* - January 2005 to September 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-round Scans</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>6724 (92.2%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>480 (6.6%)</td>
</tr>
<tr>
<td>Positive</td>
<td>90 (1.2%)</td>
</tr>
<tr>
<td>Follow-up Scans</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>416 (86.7%)</td>
</tr>
<tr>
<td>No follow-up scan^</td>
<td>24 (5.0%)</td>
</tr>
<tr>
<td>Positive</td>
<td>40 (8.3%) + 1*</td>
</tr>
<tr>
<td>Result Round 2</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>7164 (98.2%)</td>
</tr>
<tr>
<td>Positive</td>
<td>131 (1.8%)</td>
</tr>
<tr>
<td>Referral and Work-up</td>
<td></td>
</tr>
<tr>
<td>Not referred ~</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td>Referred to pulmonologist</td>
<td>124</td>
</tr>
<tr>
<td>Outcome Round 2</td>
<td></td>
</tr>
<tr>
<td>No malignancy</td>
<td>64 (48.9%)</td>
</tr>
<tr>
<td>Other cancer</td>
<td>5 (3.8%)</td>
</tr>
<tr>
<td>Lung cancer $</td>
<td>55 (42.0%)</td>
</tr>
</tbody>
</table>

* 287 participants did not undergo a second-round scan (7,557 participants of the first round plus 25 participants who missed screening in round 1, minus 7,295) because of: lung cancer (n=68: two subjects diagnosed with lung cancer did receive a second round scan because of an administrative error), death (n=27), participant declined (n=115), participant unattainable or repeatedly no show (n=47), still in diagnostic work-up round one (n=1), administrative error (n=1), no screening in second round, but screened in third round (n=28).

+ Cave: 1 participant missed the second round scan (therefore only 7,294 second-round scans were performed and only 480 scans were indeterminate), but he received a follow-up scan instead later on, which had a positive result.

# Follow-up scans were performed after 76.5 days (mean; SD=35.4). In 15.5% of the subjects with an indeterminate result the nodule(s) had disappeared.

^ Reasons: administrative error (n=12), no show (n=6), already receiving treatment from other specialist (n=5), death (n=1).

~ Reasons: administrative error (n=2), already receiving treatment from other specialist (n=5).

$ 52 of 55 (94.5%) lung cancer diagnoses were confirmed by cytology or histology. Details concerning the basis of the diagnosed the three other cases can be found in the Appendix.

Cave: mortality data were available only for the Dutch participants until August 14th 2011.
**False-positive screenings**

6% (458 out of 7,582) of the participants had at least one positive screening result. 31 subjects had two positive screening results and two subjects had three positive screens. As 200 individuals were diagnosed with lung cancer, this implies that the remaining 258 participants had one or more false-positive screening result (244 subjects had one, 12 subjects had two and two subjects had three false-positive results). However, even 15 participants who were diagnosed with lung cancer had a false-positive screening in an...
earlier round. Thus, 3.6% of all participants (273 out of 7,582) had a false-positive screening result.

67 (24.5%) out of the 273 participants with one or more false-positive screen result underwent an invasive procedure in the diagnostic work-up. 61 (91.0%) of these invasive procedures were surgeries (three mediastinoscopies, one sternotomy, nine video-assisted thoracoscopies and 48 thoracotomies) and the remaining six procedures were trans-thoracic biopsies (more details are supplied in the Appendix). Hence, 0.9% (67 out of 7,582) of all screened participants underwent an, in retrospect, “unnecessary” invasive diagnostic procedure.

5.5-year risk calculations

In this part of the study, we present an overview of subsequent screening results and lung cancer diagnoses to visualise the longitudinal character of the 5.5-year risk calculations (Figures 1a-d in Appendix). 70.4% of the screened participants (5,340 out of 7,582) had exclusively negative screening results.

The individuals with a negative first screening had a probability of 86.5% to receive exclusively negative screening results in 5.5 years (Figure 1a in Appendix). Furthermore, their risk of a false-positive screen result in the following 5.5 years was 1.3% (80 out of 5,986 participants) and their 5.5-year risk of lung cancer was only 1.0% (60 out of 5,986 participants).

The participants with an indeterminate result from their first screening had a probability of 72.1% to have exclusively negative screening results in the 5.5 years after the first screening (Figure 1b in Appendix). Their risk of a false-positive follow-up scan in the first screen round was 4.3% (62 out of 1,451). The risk of one or more false-positive scans in round two or three in this subgroup was 4.8% (70 out of 1,451). To summarise, after an indeterminate baseline scan result, the risk of one or more false-positive scan results in 5.5 years was 8.8% (128 out of 1,451). The risk of screen-detected lung cancer after an indeterminate baseline scan was 1.0% (15 out of 1,451) in round one and 4.6% (67 out of 1,451) in rounds two and three. Hence, the 5.5-year lung cancer risk after an indeterminate baseline scan result was 5.7% (82 out of 1,451).

The participants with a positive first screen result had a probability of 30.0% (36 out of 120) to have only negative screening results in the following 5.5 years (Figure 1c in Appendix). Their risk of a false-positive screening was 54.2% (65 out of 120) in the first round and 4.2% (five out of 120) in the second or third round. Furthermore, their risk to be diagnosed with screen-detected lung cancer within 5.5 years was 48.3% (58 out of 120). This was 45.8% (55 out of 120) directly in round one and 2.5% (three out of 120) in rounds two and three. The three individuals with a lung cancer diagnosis in rounds two or three were, in retrospect, referred twice for the same suspicious nodule.
The risk calculations show that the result of the baseline scan divides the screened population in three subgroups with distinct risks of lung cancer. The characteristics of the screened participants and the three subgroups are presented in Table 1. When comparing participants with a negative, indeterminate and a positive baseline scan result, a statistically significant increase in age and number of pack-years was observed. However, there was no significant difference in the proportion of females and current smokers (Table 1).

### Table 1. Participants’ characteristics and comparison stratified by baseline scan result

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All screened participants</th>
<th>Baseline scan result</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Females</td>
<td>1,254 (16.5)</td>
<td>1,016 (17.0)</td>
<td>210 (14.5)</td>
</tr>
<tr>
<td>Age - median (IQR)</td>
<td>58.0 (8)</td>
<td>57.0 (8)</td>
<td>59.0 (8)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4,215 (55.6)</td>
<td>3315 (55.4)</td>
<td>809 (55.8)</td>
</tr>
<tr>
<td>Pack-years - median (IQR)</td>
<td>37.8 (19.8)</td>
<td>38.0 (19.8)</td>
<td>38.7 (19.8)</td>
</tr>
<tr>
<td>Total</td>
<td>7,582 (100.0)</td>
<td>5,986 (100.0)</td>
<td>1,451 (100.0)</td>
</tr>
</tbody>
</table>

Data are presented as n or n (%), unless otherwise stated.
Definition of abbreviations: IQR = interquartile range; NA = not applicable.

### DISCUSSION

In this study, we evaluated the performance of the NELSON screening strategy in the first three screening rounds and we assessed the 5.5-year risk of false-positive screenings and screen-detected lung cancer.

If we compare the performance of the NELSON screening strategy with other LDCT screening trials we find notable differences. The percentage of positive scans in our trial (2.0%) was the same as in a Danish trial, but substantially lower than in the NLST (24.2%). Also, the percentage of participants with one or more positive scan was 6.0% in our trial, which is low compared with the 39.1% in the NLST (the percentage in DLCST was not published).

Despite the lower percentage positive screenings, our strategy detected 200 lung cancers in the three screening rounds. As a result, the cumulative lung cancer detection rate (2.6%) was a little higher than in the NLST (2.4%: 649 out of 26,309), but lower than in the DLCST (3.4%: 69 out of 2,047). The latter is probably due to the two additional screening rounds that have been completed in the DLCST.

The predictive value of a positive screen result was higher in the NELSON trial (40.6%) than in both the DLCST (34.8%) and the NLST (3.6%). Hence, the percentage of false-positive results was 59.4% in the NELSON trial, 65.2% in the DLCST and 96.4% in...
the NLST. The proportion of false-positive scans out of all scans is 1.2% in the NELSON trial, 1.3% in the DLCST and 23.3% in the NLST.\textsuperscript{5,10,13}

In the NELSON trial, we observed that the ratio between the true-positive and false-positive results improved over the rounds (0.69, 0.72 and 0.83 respectively in rounds one, two and three). This is probably the result of the possibility in later rounds to compare current with previous images and to calculate VDTs. In the NLST, the true-positive/false-positive ratios were respectively 0.039 in round one, 0.025 in round two and 0.055 in round three (figures in the DLCST were not published).\textsuperscript{5} The improvement in the third round probably results from the fact that only in the third round were stable nodules $\geq 4$ mm in diameter not classified as positive.

Finally, the number needed to screen for the detection of one lung cancer was 92-133 per round in the NELSON trial, which is a little less than in the other trials (97-147 in the NLST and 116-180 in the DLCST).\textsuperscript{5,10}

In the three screening rounds, 3.6% of all participants had a false-positive screening result and this led to invasive diagnostic procedures in 0.9% of all participants. Although we are convinced of the need to reduce these numbers, we realise that these “unnecessary” invasive procedures cannot be eliminated because it is sometimes the only way to distinguish lung cancer from other malignancies or benign conditions.

In the second part of this study, we found that participants with a negative, indeterminate or positive baseline scan had very distinct risks of positive screening results and lung cancer. Hence, the risk of a false-positive screening result in the next 5.5 years was respectively 1.3%, 8.8% and 54.2% for the individuals with a negative, indeterminate or positive baseline scan. Moreover, the 5.5-year risk of screen-detected lung cancer was only 1.0% for the individuals with a negative baseline scan result, 5.7% for subjects with an indeterminate baseline result and 48.3% for those with a positive baseline. In other words, after the first screening, the individual’s lung cancer risk has either decreased by 62% or increased by 219% or 1858%.

Analyses showed a significant increase in age and number of pack-years when comparing participants with a negative, indeterminate and positive baseline scan, which are all well known risk factors for developing lung cancer.\textsuperscript{24}

The presented results could aid clinicians when counselling high-risk subjects who are considering or have already undergone LDCT screening for lung cancer. This study has created the opportunity to personalise counselling and enables the individual at risk to make an informed choice. Moreover, this is the first study that quantifies both the potential benefit of screening (early detection) and a potential harm of screening (false-positive screening results).

The main strengths of this trial are its design (a large, randomised controlled trial), the population-based recruitment and prospective data collection.\textsuperscript{14,25} Limitations of the current study are the lack of data on false-negative screenings, the control arm of the trial
and lung cancer mortality. These analyses were not performed because the required data was not yet available.\textsuperscript{14}

Future research should focus on confirming the efficacy of LDCT screening for reducing lung cancer mortality. The planned lung cancer mortality analyses of the NELSON trial will be crucial in this part, as our trial is the only other trial (besides the NLST) that is sufficiently powered. Furthermore, efforts should be made to reduce false-positive screen results by optimising the cut-off criteria for nodule volume and VDT.

CONCLUSION

In this study, we evaluated the performance of the NELSON screening strategy in the first three screening rounds. We demonstrated that our strategy yields a low percentage of positive and false-positive scans with a reasonable positive predictive value. Furthermore, we used our experience with lung cancer screening to provide an overview of the 5.5-year risks of lung cancer and false-positive screenings, which aids clinicians in counselling individuals who are considering or have already undergone LDCT screening for lung cancer.
TWITTER

@ERSpublications
5.5-year lung cancer risk calculations aid clinicians in counselling for lung cancer screening with low-dose CT http://ow.ly/p9J3q

SUPPORT STATEMENT

The NELSON trial is supported by: “Zorg Onderzoek Nederland-Medische Wetenschappen” (ZonMw) (grant number 120610015), “KWF Kankerbestrijding” (grant number EMCR 2007-3857) and “Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen” (RvvZ).

Roche Diagnostics provided a grant for the performance of proteomics-research. Siemens Germany provided four digital workstations and LungCARE for the performance of the volumetric measurements of lung nodules.

CONFLICTS OF INTEREST

None declared

ACKNOWLEDGEMENTS

We thank our secretary M. Quak, our data manager R.M. Vernhout and our system controllers R. Faber and F.J.P. Santegoets (all at the Erasmus Medical Center, Rotterdam, the Netherlands) for their contributions and maintenance of the database.
REFERENCES


APPENDIX

Lung cancer diagnoses not proven by histology
Lung cancer diagnoses in the first three rounds of the NELSON trial were based on histology or cytology in 187 of 200 (93.5%). The basis for the diagnosis in the 13 participants without histology or cytology is:

Round one:
1) Tumour in the right upper lobe, volume 1502mm³, PET-positive, cT1aN0M0, patient did not undergo thoracic surgery due to cardiac impairment.
2) Tumour in left lower lobe, volume 2687mm³, and PET positive, and cT1aN0M0, patient did not undergo thoracic surgery due to COPD stage IV.
3) Tumour in left lower lobe, volume 2792mm³, PET-positive, cT1aN0M0, patient did not undergo thoracic surgery due to COPD and renal failure.

Round two:
1) Tumour in right upper lobe, volume 580mm³, PET-positive, cT1aN0M0, the patient did not undergo thoracic surgery due to metastasized prostate carcinoma.
2) Tumour in right lower lobe, volume 2793mm³, PET-positive, cT1bN0M0, the patient did not undergo thoracic surgery due to poor pulmonary function.
3) Tumour in right upper lobe, volume 891mm³, PET indeterminate, cT1aN0M0, the patient died just before intended thoracic surgery due to bowel ischemia.

Round three:
1) Tumour in right lower lobe, volume 731mm³, PET-positive, cT1aN0M0, the patient did not undergo thoracic surgery due to poor pulmonary function.
2) Tumour in left lower lobe, volume 108mm³, VDT 125 days, PET-positive, cT1aN0M0, the patient did not undergo thoracic surgery because he also participated in another study and was randomised to the radiotherapy treatment arm.
3) Tumour in right upper lobe, volume 383mm³, VDT 289 days, PET indeterminate, cT1aN0M0, the patient did not undergo thoracic surgery because he refused, he was treated with stereotactic radiotherapy instead.
4) Tumour in left lower lobe, volume 1108mm³, PET positive, cT1aN1M0, the patient did not undergo thoracic surgery due to poor pulmonary function.
5) Tumour in left lower lobe, diameter 10mm, PET positive, cT1aN0M0, and the patient did not undergo thoracic surgery due to poor pulmonary function.
6) Tumour in right upper lobe, diameter 13.2x11.6mm, PET positive, cT1aN0M0, the patient did not undergo thoracic surgery due to poor pulmonary function and general condition.
7) Tumour in right upper lobe, diameter 19.2x12.7mm, PET positive, cT1bN0M0, the patient did not undergo thoracic surgery due to poor general condition.

Figure 1a. Overview of subsequent screening test results and lung cancer diagnoses: participants with a negative baseline scan.

Figure 1b. Overview of subsequent screening test results and lung cancer diagnoses: participants with an indeterminate baseline scan.
Figure 1c. Overview of subsequent screening test results and lung cancer diagnoses: participants with a positive baseline scan

<table>
<thead>
<tr>
<th>Result screening scan round 1 N (%)</th>
<th>Participants with lung cancer round 1 N (%)</th>
<th>Participants with lung cancer round 2 N (%)</th>
<th>Participants with lung cancer round 3 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive: 2 (5.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Indeterminate: 2 (42.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Negative: 38 (66.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Total first round scans: N=120
Total participants with lung cancer round 1: N=55
Total second round screening scans: N=54
Total participants with lung cancer round 2: N=3
Total third round screening scans: N=47
Total participants with lung cancer round 3: N=0

* 25 participants had no screening scan in the first round, because there was a delay in the returning of the informed consent.
# 15 participants had no screening scan in the second round because: participant declined (n=1), participant unattainable or repeatedly no show (n=14).
¶ 12 participants had no screening scan in the second round because: still in diagnostic work-up round one (n=2), participant declined (n=2), participant unattainable or repeatedly no show (n=4), administrative error (n=4).
+ 1 participant had no screening scan in the second round because: still in diagnostic work-up round one (n=1)
a 142 participants (5,986 minus 5,829) were not screened in the second and third round. Reasons: death (n=19), participant declined (n=81), participant unattainable or repeatedly no show (n=41), administrative error (n=1).
b 52 participants (1,451 minus 1,399) were not screened in the second and third round. Reasons: lung cancer (n=13), death (n=7) still in diagnostic work-up round one (n=1), participant declined (n=25), participant unattainable or repeatedly no show (n=6). Cave: the other two subjects with screen-detected lung cancer did receive a second round scan because of an administrative error.
c 66 participants (120 minus 54) were not screened in the second and third round. Reasons: screen-detected lung cancer (n=55), death (n=1), participant declined (n=10).

Figure 1d. Overview of subsequent screening test results and lung cancer diagnoses: participants with no baseline scan

<table>
<thead>
<tr>
<th>Result screening scan round 1 N (%)</th>
<th>Participants with lung cancer round 1 N (%)</th>
<th>Participants with lung cancer round 2 N (%)</th>
<th>Participants with lung cancer round 3 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive: 20 (80.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Indeterminate: 988 (87.0)</td>
<td>2 (22.2)</td>
<td>2 (22.2)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Negative: 100 (75.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Total first round scans: N=0
Total participants with lung cancer round 1: N=0
Total second round screening scans: N=25
Total participants with lung cancer round 2: N=20
Total third round screening scans: N=1,088
Total participants with lung cancer round 3: N=0
d  255 participants (5,479 minus 5,224) were not screened in the third round. Reasons: death (n=56), participant declined (n=112), participant unattainable or repeatedly no show (n=82), administrative error (n=2), unknown (n=3).
e  21 participants (311 minus 290) were not screened in the third round. Reasons: lung cancer (n=7), death (n=3), participant declined (n=9), participant unattainable or repeatedly no show (n=2).
f  19 participants (39 minus 20) were not screened in the third round. Reasons: lung cancer (n=13), death (n=2), participant declined (n=4).
g  49 participants (1,184 minus 1,135) were not screened in the third round. Reasons: death (n=16), participant declined (n=22), participant unattainable or repeatedly no show (n=10), administrative error (n=1).
h  23 participants (155 minus 132) were not screened in the third round. Reasons: lung cancer (n=10), death (n=6), participant unattainable or repeatedly no show (n=2), participant declined (n=5). Cave, one participant was already diagnosed with lung cancer in first round, but received a second round scan because of an administrative error.
i  25 participants (48 minus 23) were not screened in the third round. Reasons: lung cancer (n=24), participant declined (n=1). Cave, one participant was already diagnosed with lung cancer in first round, but received a second round scan because of an administrative error.
j  4 participants (41 minus 37) were not screened in third round. Reasons: death (n=1), participant declined (n=2), participant unattainable or repeatedly no show (n=1).
k  2 participants (9 minus 7) were not screened in the third round. Reasons: lung cancer (n=2).
l  1 participant (3 minus 2) were not screened in the third round. Reasons: lung cancer (n=1).
m  1 participant (5 minus 4) were not screened in the third round. Reasons: participant unattainable or repeatedly no show (n=1).
Chapter 3

Characteristics of screen-detected lung cancer

Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial

Horeweg N,
van der Aalst CM,
Thunnissen E,
Nackaerts K,
Weenink C,
Groen HJM,
Lammers JWJ,
Aerts JG, Scholten ET,
von Rosmalen J,
Mali W, Oudkerk M,
de Koning HJ

American Journal of Respiratory and Critical Care Medicine
April 15th, 2013
Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial


ABSTRACT

The NELSON trial is, with 15,822 participants, the largest European lung cancer computer tomography screening trial. A volumetry-based screening strategy, stringent criteria for a positive screening, and an increasing length of screening interval are particular features of the NELSON trial.

To determine the effect of stringent referral criteria and increasing screening interval on the characteristics of screen-detected lung cancers, and to compare this across screening rounds, between sexes, and with other screening trials.

All NELSON participants with screen-detected lung cancer in the first three rounds were included. Lung cancer stage at diagnosis, histological subtype, and tumour localisation were compared between the screening rounds, the sexes, and with other screening trials.

In the first three screening rounds, 200 participants were diagnosed with 209 lung cancers. Of these lung cancers, 70.8% were diagnosed at stage I and 8.1% at stage IIIB–IV, and 51.2% were adenocarcinomas. There was no significant difference in cancer stage, histology, or tumour localisation across the screening rounds. Women were diagnosed at a significantly more favourable cancer stage than men. Compared with other trials, the screen-detected lung cancers of the NELSON trial were relatively more often diagnosed at stage I and less often at stage IIIB–IV.

Despite stringent criteria for a positive screening, an increasing length of screening interval, and few female participants, the screening strategy of the NELSON trial resulted in a favourable cancer stage distribution at diagnosis, which is essential for the effectiveness of our screening strategy.
INTRODUCTION

Lung cancer is the leading cause of cancer-related death in males and the second in females globally, accounting for 1.4 million lung cancer deaths per year.\(^1\) Despite treatment advances, survival has not improved substantially, mainly because the majority of the patients have distant metastases at the time of diagnosis.\(^2\) Several randomised lung cancer screening trials were conducted with low-dose computer tomography (LDCT) scanning of high-risk groups, aiming to detect lung cancer at an earlier and curable stage.\(^3\)–\(^7\)

The world’s largest randomised CT screening trial, the National Lung Screening Trial (NLST), demonstrated in 2011 that early detection by LDCT scanning has yielded a 20% lung cancer mortality reduction compared with screening by chest radiograph.\(^8\) Sixty-one percent of the LDCT-detected lung cancers were diagnosed at stage I. To accomplish this impressive result, considerable efforts were made. Namely, 26,722 high-risk subjects underwent annual LDCT screening for 3 years. Positive screening results were defined as any non-calcified pulmonary nodule measuring at least 4 mm in any diameter. In the three screening rounds, 39.1% of the individuals had at least one positive result.\(^8\)

Our trial, the Dutch–Belgian Lung Cancer Screening Trial (Nederlands-Leuven longkanker screeningsonderzoek; the NELSON trial), is the world’s second-largest randomised CT screening trial and differs from the NLST by screening interval, referral policy, and a control arm wherein individuals receive no screening.\(^2\) The 7,915 participants randomised to the screening arm of the NELSON trial underwent LDCT screening at baseline, 1 year later, 2 years later, and finally 2.5 years later. Positive screening results were defined as non-calcified nodules with a volume greater than 500 mm\(^3\) (about 9.8 mm in diameter) or volume-doubling time (VDT) less than 400 days.\(^3\)\(^,\)\(^9\)\(^,\)\(^10\) In the first three screening rounds, 6.0% of the participants had at least one positive screening. Clearly, the differences between the two largest randomised CT screening trials are substantial. Whether the NELSON trial will be able to demonstrate a significant lung cancer mortality reduction must be awaited, because the mortality analyses are planned 10 years after randomisation.\(^11\) However, the characteristics of the screen-detected lung cancers, especially the stage distribution, might give an indication of the effectiveness of our screening strategy.

For this study, all participants with screen-detected lung cancer in the first three rounds of the NELSON trial were included. Lung cancer stage at diagnosis, histological subtype, and tumour localisation were compared between the screening rounds, the sexes, and several randomised CT screening trials.
METHODS

NELSON trial
The 15,822 individuals in the NELSON trial were randomised (1:1) to screening (n = 7,915) with LDCT at baseline (first round), 1 year later (second round), 3 years later (third round), and 5.5 years later (fourth round) or no screening (n = 7,907) (Figure 1). The main purpose of the trial is to determine whether LDCT screening will have reduced lung cancer mortality by at least 25% at 10 years of follow-up.11,12 A more detailed report of the design and conduct was published previously.9,11

Figure 1. Participant flowchart in the first three rounds of the NELSON trial

* 219 participants were not screened in the second round because of death (n = 27), participant declined (n = 115), participant unattainable or repeatedly no show (n = 47), administrative error (n = 1), still in diagnostic work-up round 1 (n = 1), no screening in second round, but screened in third round (n = 27).

# 345 participants were not screened in the third round because of lung cancer in round 1 (n = 2), death (n = 84), participant declined (n = 155), participant unattainable or repeatedly no show (n = 98), administrative error (n = 3), unknown (n = 3).

Note: mortality data were available only for the Dutch participants until August 14, 2011.
Characteristics of screen-detected lung cancer

Participants

Individuals aged 50 to 75 years, who had smoked 15 or more cigarettes per day for 25 years or 10 or more cigarettes for 30 years and were still smoking or had quit less than 10 years ago, met the inclusion criteria. The exclusion criteria and calculation of expected lung cancer mortality were published in 2006. For this study, all participants diagnosed with screen-detected lung cancer in the first three screening rounds were included (Figure 1). Hence, the interval cancers were not included in the analyses.

Equipment and Nodule Management Protocol

In short, 16-detector CT modality was used in a low-dose setting, without intravenous contrast medium. CT images were analysed with software for semi-automated volume measurements (LungCARE, Siemens Healthcare, Erlangen, Germany). Briefly, the screening test result could be negative (invitation for the next screen round), indeterminate (invitation for a repeat scan to determine the VDT), or positive (referral for diagnostic work-up). The nodule volume determined the screen result for newly detected nodules: less than 50 mm$^3$ was negative, 50 to 500 mm$^3$ was indeterminate, and more than 500 mm$^3$ was positive. The percentage volume change was calculated for previously detected nodules: at least 25% led to the assessment of the VDT. The VDT was calculated according to the formula: VDT(days) = [ln 2 x (time between current scan and baseline screening)]/[ln(nodule volume on current scan/volume on baseline scan)]. The screen result was positive for a VDT less than 400 days. A full description of the protocol was published previously.

Referral and Diagnostic Work-Up

After a positive screening, the participants were referred for diagnostic work-up via their general practitioner and received usual care according to national and international guidelines. All data were prospectively collected and histological specimens were reassessed by our chief pathologist (E.T.).

Statistical Analyses

Continuous variables were tested for normality using the Kolmogorov-Smirnov test for 50 or more samples, and using the Shapiro-Wilk test for fewer than 50 samples. Continuous, normally distributed variables were described by means and standard deviations. The difference between the means of continuous variables was calculated by one-way analysis of variance. Non-normally distributed variables were described by medians and interquartile ranges. The difference between nominal variables was calculated using the chi$^2$-test and differences between categorical variables were calculated using the Mann-Whitney U test. The difference between more than two samples of a categorical variable was calculated using the Kruskal-Wallis H test. Predictors of cancer stage were tested.
using ordinal logistic regression; variables entered multivariate models when the P-value did not exceed 0.05 univariately. P-values less than 0.05 were treated as significant. SPSS Statistics version 20 (IBM, Armonk, NY) was used for all analyses.

Ethics and Legal Approval
The NELSON trial was approved by the Dutch Ministry of Health and the ethics board at each participating centre. All participants gave written informed consent for participation and the evaluation of personal data from hospital charts.

RESULTS

Participants
Of the 7,915 (95.8%) participants randomised to the screening arm of the trial, 7,582 received at least one screening (Figure 1). Their baseline characteristics are presented in Table 1. The three screening rounds yielded 493 positive screen results and 200 (40.6%) participants were diagnosed with lung cancer. Synchronous double tumours were detected in four participants in round 1, in three participants in round 2, and in two participants in round 3. Thus, 200 participants were diagnosed with a total of 209 lung cancers. The patients with lung cancer were significantly older and had smoked significantly more pack-years than had the subjects not diagnosed with lung cancer (Table 1).

Table 1. Characteristics of the NELSON participants

| Characteristics | All participants n (%) | Participants diagnosed with lung cancer n (%) | Participants not diagnosed with lung cancer n (%) | p-value *
|-----------------|------------------------|-----------------------------------------------|-------------------------------------------------|---------
| Female gender, n(%) | 1,254 (16.5) | 34 (17.0) | 1,220 (16.5) | 0.86
| Current smoker, n(%) | 4,215 (55.6) | 112 (56.0) | 4,103 (55.6) | 0.91
| Pack-years, median (IQR) | 38.0 (29.7 - 49.5) | 43.7 (32.2 - 75.8) | 38.0 (29.7 - 49.5) | < 0.001
| BMI, median (IQR) | 25.8 (23.9 - 28.1) | 25.4 (23.3 - 28.0) | 25.8 (23.9 - 28.1) | 0.09
| Total | 7,582 (100.0) | 200 (100.0) | 7,382 (100.0) | NA

Definition of abbreviations: IQR= interquartile range; BMI= body mass index; NA = not applicable.
* At randomisation.
† In the first three screening rounds of the NELSON trial.
‡ Comparison participants with versus without lung cancer.

Lung Cancer Symptoms
Eleven of the 200 participants (5.5%) had symptoms suspicious of lung cancer before they were diagnosed. Five of them had symptoms before the screening scan was made;
however, none of them had symptoms at randomisation. Three subjects had symptoms in the period between the positive scan and the first consultation, and three subjects had symptoms in the period between the first consultation and the diagnosis date. Box plots of the time to screening result, referral, and diagnosis of the 200 participants and a detailed description of the symptoms can be found in the Appendix (Figure 1).

**Lung Cancer Characteristics**

More than half of the 209 screen-detected lung cancers were adenocarcinomas (51.2%) and a large majority was diagnosed at an early stage (stage I, 70.8%) (Table 2). Adenocarcinomas appeared to be diagnosed at a significantly lower cancer stage (univariate analysis p = 0.045), but in multivariate analysis this was no longer significant (p = 0.56) (Table 1 in Appendix). However, all bronchoalveolar carcinomas (n = 11) and carcinoids (n = 6) were diagnosed at stage Ia (Table 2). Four other histological subtypes were prone

<table>
<thead>
<tr>
<th>Cancer stage</th>
<th>Ia</th>
<th>Ib</th>
<th>IIa</th>
<th>IIb</th>
<th>IIIa</th>
<th>IIIb</th>
<th>IV</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology†</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
<td>n(%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>75 (70.1)</td>
<td>9 (8.4)</td>
<td>8 (7.5)</td>
<td>.</td>
<td>9 (8.4)</td>
<td>4 (3.7)</td>
<td>2 (1.9)</td>
<td>107 (51.2)</td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>11 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
<td>11 (5.3)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>21 (61.8)</td>
<td>.</td>
<td>3 (8.8)</td>
<td>.</td>
<td>8 (23.5)</td>
<td>.</td>
<td>2 (5.9)</td>
<td>34 (16.3)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>7 (41.2)</td>
<td>1 (5.9)</td>
<td>.</td>
<td>.</td>
<td>6 (35.3)</td>
<td>2 (11.8)</td>
<td>1 (5.9)</td>
<td>17 (8.1)</td>
</tr>
<tr>
<td>Large cell neuro-endocrine carcinoma</td>
<td>2 (50.0)</td>
<td>1 (25.0)</td>
<td>.</td>
<td>.</td>
<td>1 (25.0)</td>
<td>.</td>
<td>.</td>
<td>4 (1.9)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>5 (62.5)</td>
<td>.</td>
<td>3 (37.5)</td>
<td>8 (3.8)</td>
</tr>
<tr>
<td>Small/large cell carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (50.0)</td>
<td>.</td>
<td>1 (50.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Pleiomorph carcinoma</td>
<td>.</td>
<td>.</td>
<td>1 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>NSCLC-NOS</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td></td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>6 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>No histological diagnosis‡</td>
<td>12 (92.3)</td>
<td>.</td>
<td>1 (7.7)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
<td>13 (6.2)</td>
</tr>
<tr>
<td>Total</td>
<td>137 (65.6)</td>
<td>11 (5.3)</td>
<td>14 (6.7)</td>
<td>.</td>
<td>30 (14.4)</td>
<td>7 (3.3)</td>
<td>10 (4.8)</td>
<td>209 (100)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: NSCLC = non-small cell lung carcinoma; NOS = not otherwise specified.

* 7th edition of the IASLC TNM staging system (2009).
‡ In 13 participants no histological diagnosis was established because biopsies were unsuccessful or not performed and the patient did not undergo thoracic surgery because of poor pulmonary function (n = 7), poor heart function (n = 1), poor general condition (n = 1), metastasised prostate carcinoma (n = 1), death due to mesenteric ischemia before intended surgery (n = 1), radiotherapy because of participation in other clinical trial (n = 1) and refusal (n = 1). In 10 lung resection specimens the pathologist found, besides the lung cancer, a focus of atypical adenomatous hyperplasia.
to be diagnosed at a higher cancer stage; for example, small cell carcinomas (multivariate analysis P < 0.001) (Table 1 in Appendix).

Most lung cancers were localised in the right lung (65.6%) and a large proportion (45.0% of all lung cancers) was localised in the right upper lobe (Figure 2). We also observed that the lung cancers were localised predominantly in the periphery of lungs (Figure 3). Of the nodules, 62.2% were found in the outer one-third of the costal-hilar diameter (Figure 3). In particular, adenocarcinomas were more often detected in the periphery and attached to the pleura than in the middle or central one-third of the lungs (82.2% vs. 17.8%; p = 0.001). But the reverse was not true for squamous cell carcinomas (62.9% peripheral or pleural-attached vs. 37.1% central or middle one-third; p = 0.16).

**Figure 2. Localisation across the lobes of the 209 screen-detected lung cancers.**

![Diagram of lung cancers localisation](image)

A schematic depiction of the lungs and large airways. The right lung is displayed on the left side and vice versa, as on a chest radiograph. The left upper lobe is divided in the pars superior and the lingula by the dotted line. The lung cancers are depicted as dark grey dots; their localisation corresponds with the lobe where the nodule was detected, not with the exact localisation.

**Effect of screen round**

The lung cancers detected in round 1 had a slightly higher disease stage (stage Ia 59.5%, stage IV 6.8%) than in later rounds (round 2: stage Ia 74.1%, stage IV 3.4%, and round 3:
Characteristics of screen-detected lung cancer stage Ia 64.9%, stage IV 3.9%) (Tables 2a-2c in Appendix). But this was not statistically significant between rounds 1 and 2 (p = 0.09) or across the three rounds (p = 0.23).

Also, the proportion adenocarcinomas was not significantly different between rounds 1 and 2 (47.3% vs. 60.3%; p = 0.14) or across the three rounds (round 3: 48.1% adenocarcinomas; p = 0.26) (Tables 2a-2c in Appendix).

Likewise, tumour localisation was not significantly different across the screen rounds: neither for the division over the lobes (p = 0.88) nor for the division over the peripheral versus central lung fields (p = 0.09).

Effect of sex
The women diagnosed with lung cancer were significantly younger (58.0 vs. 62.0 years; p = 0.03), had smoked less (pack-years: 36.0 vs. 43.0; p = 0.03) and had a lower BMI (23.8...
vs. 25.9; p = 0.03) than the men diagnosed with lung cancer. The percentage current smokers however, was not lower in females (56.7 vs. 55.9%; p = 0.93).

None of the histological subtypes were unevenly distributed between the sexes (Tables 3a and 3b in Appendix). Also, the localisation of the lung cancers was not significantly different between the sexes: neither for the left lung versus right lung localisation (p = 0.92), nor for peripheral versus central localisation (p = 0.89). However, the cancer stage at diagnosis was significantly lower in women than in men (p = 0.005) (Tables 3a and 3b in Appendix). When correcting for the sex differences in age, number of pack-years and BMI, women still had a statistically significant lower cancer stage than men (p = 0.028) (Table 4 in Appendix).

Coincidentally, we found that a higher body mass index (BMI) (before randomisation) was a significant multivariate predictor (p = 0.004) of a more unfavourable cancer stage at diagnosis in both sexes (Table 4 in Appendix).

Comparison of trials
A total of 1,078 lung cancers were detected by CT screening in 43,983 participants of randomised screening trials (Table 3). On average, 64.7% of the lung cancers were diagnosed at stage I and 10.9% at stage IIIb–IV (Table 3). The stage distribution in the NELSON trial appears to be relatively favourable compared with the other trials. When we compare the

Table 3. Overview of cancer stage at diagnosis of screen-detected lung cancers in randomised CT screening trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants screen arm</th>
<th>Screening rounds</th>
<th>Length screening interval (yrs)</th>
<th>Males – females (%)</th>
<th>No. of published CT-detected lung cancers</th>
<th>Stage Ia + Ib lung cancers n (%)</th>
<th>Stage IIIb + IV lung cancers n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST8</td>
<td>26,722</td>
<td>3</td>
<td>1</td>
<td>59.0 – 41.0</td>
<td>649</td>
<td>400 (61.6)</td>
<td>130 (20.0)</td>
</tr>
<tr>
<td>NELSON</td>
<td>7,915</td>
<td>4</td>
<td>1, 2 and 2.5</td>
<td>83.5 – 16.5</td>
<td>209</td>
<td>148 (70.8)</td>
<td>17 (8.1)</td>
</tr>
<tr>
<td>DLST36</td>
<td>2,052</td>
<td>5</td>
<td>1</td>
<td>54.6 – 45.4</td>
<td>69</td>
<td>47 (68.1)*</td>
<td>11 (15.9)†</td>
</tr>
<tr>
<td>ITALUNG7</td>
<td>1,613</td>
<td>4</td>
<td>1</td>
<td>64.2 – 35.8</td>
<td>22</td>
<td>11 (50.0)‡</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>DANTE37</td>
<td>1,276</td>
<td>4</td>
<td>1</td>
<td>100.0 – 0.0</td>
<td>58</td>
<td>41 (70.7)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>MILD38</td>
<td>1,190</td>
<td>10</td>
<td>1</td>
<td>68.4 – 31.6</td>
<td>29</td>
<td>18 (62.1)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>LUSI39</td>
<td>2,029</td>
<td>4</td>
<td>1</td>
<td>64.8 – 35.2</td>
<td>22</td>
<td>18 (81.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>43,983</strong></td>
<td><strong>3 to 10</strong></td>
<td><strong>1 to 2.5</strong></td>
<td><strong>65.4 – 34.6</strong></td>
<td><strong>1078</strong></td>
<td><strong>697 (64.7)§</strong></td>
<td><strong>118 (10.9)</strong>*</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CT = computed tomography; DLST = Danish Lung Cancer Screening Trial; MILD = Multicentric Italian Lung Detection; NELSON = Nederlands-Leuvens Longkanker screeningsOnderzoek (Dutch–Belgian Lung Cancer Screening Trial); NSLT = National Lung Screening Trial.

* This not include two participants diagnosed with limited stage small cell lung carcinoma.
† This includes the participant diagnosed with extensive stage small cell lung carcinoma.
‡ This not include the three participants diagnosed with limited stage small cell lung carcinoma.
§ This does not include the four participants with limited stage small cell lung carcinoma.
whole range of cancers stages between the two largest trials (NLST and NELSON) we observe that the cancer stage was significantly lower (p = 0.001) in the NELSON trial.

DISCUSSION

In this study, we have presented the characteristics of the lung cancers detected in the first three rounds of the NELSON trial. We investigated whether the screening strategy of the NELSON trial led to detection of lung cancer at a more favourable stage and how this relates to other randomised lung cancer CT screening trials.

In the three screening rounds, 493 participants had a positive screening result and were referred for diagnostic work-up. Ultimately, 200 (40.6%) participants were diagnosed with a total of 209 lung cancers. Eleven (5.5%) of these participants had symptomatic lung cancer before diagnosis; in five subjects the symptoms emerged before the screening scan was made.

More than half of the 209 screen-detected lung cancers were adenocarcinomas (51.2%) and a large majority was diagnosed at stage I (70.8%). Moreover, only 10 lung cancers were diagnosed at stage IV. This favourable stage distribution has created the opportunity for most patients to undergo curative surgery, which hopefully will reduce lung cancer mortality. However, screening detected only a few small cell lung cancers and all were diagnosed at stage III-IV. This finding could imply that LDCT screening is not, or is less, capable of early detection in some fast-growing histological subtypes of lung cancer. Further research should be conducted to investigate whether the lung cancers not detected by screening are predominantly of the same histological subtypes that are detected only in small amounts or high stages by screening.

Most screen-detected lung cancers were localised in the periphery of the lungs, which is probably a result of the large amount of adenocarcinomas that are significantly more often localised peripherally (p = 0.001). We also observed that 45.0% of all lung cancers were localised in the right upper lobe. This is a known phenomenon in patients with non-small cell lung cancer and could be explained by the fact that the airflow at the beginning of the breath is the largest toward the right upper lobe bronchus. As a result, the deposition of particles in tobacco smoke and their carcinogenic effects are the largest in the right upper lobe.

Further, our analyses showed no significant effect of screening round on cancer stage, histology, or tumour localisation. However, a decrease in advanced-stage lung cancers was observed at the second screening round (stage IV dropped from 6.8 to 3.4%). This was probably not statistically significant because of the low absolute number of advanced-stage lung cancers. In the third screening round, no evidential increase in stage IV lung cancers was observed (3.9%), despite the screening interval of 2 years.
The differences in lung cancer characteristics between men and women have been studied extensively. In general, studies demonstrated that women are diagnosed at an earlier age,24,25 at a more favourable cancer stage,25-27 and are more often diagnosed with adenocarcinomas than are men.24,28,29 NELSON is the first trial to report on these differences in a screening setting. We also found that women were diagnosed at a significantly more favourable cancer stage than men (p = 0.028, after correction for confounding). However, the histological subtype and localisation of the lung cancers were not significantly different between the sexes.

In the NELSON trial, the body mass index (BMI) was not significantly higher in the participants diagnosed with lung cancer than in participants who were not diagnosed (p = 0.09). However, a higher BMI was a significant multivariate predictor of a more unfavourable cancer stage at diagnosis (p = 0.004). This finding is in line with one other study.30 However, most studies demonstrated a negative association between BMI and lung cancer risk and prognosis.31-33 This discrepancy could be explained in the first place by reversed causation: BMI is usually measured at diagnosis, at that time weight loss has often occurred, especially patients with a higher cancer stage. In the NELSON trial, BMI was measured just before randomisation and because none of the participants had symptomatic lung cancer at that time, the BMI was not influenced by lung cancer itself. In the second place, the discrepancy could be explained by the strong confounding effect of smoking in many trials: smokers have a lower mean BMI than non-smokers34 and smoking is major risk factor for lung cancer mortality.32 This bias is probably limited in the NELSON trial because we included only (ex-)smokers.11

In this article, we have presented an overview of the disease stage of the LDCT-detected lung cancers of the randomised screening trials. The cancer stage distribution in the NELSON trial appeared favourable relative to the other trials and was significantly lower (p < 0.001) than in the NLST. This last finding should be interpreted with caution because the NELSON trial used the 7th edition and the NLST the 6th edition of the TNM staging system.16,35 Classification according to the 7th edition results more often in a lower cancer stage than in a higher stage compared with classification according to the 6th edition.16,35 Consequently, this might have contributed to the lower cancer stage in the NELSON trial. Nonetheless, the NELSON trial has a number of features that could cause a higher cancer stage: firstly, relatively few female participants (16.5% vs. 41% in NLST), who are diagnosed at a lower stage; secondly, larger nodules at referral, due to relatively stringent referral criteria (nodule volume > 500 mm³ or nodule VDT < 400 days vs. nodule diameter > 4 mm in NLST); and thirdly, a longer screening interval (1, 2, and 2.5 years vs. annual screening in NLST). All things considered, it seems that the NELSON strategy is at least as capable as the NLST strategy to diagnose lung cancer at a more favourable stage.
Naturally, this result rises a question concerning what the difference in cancer stage between the two trials would be if all lung cancers in screened participants were compared. Analysis showed no significant difference (p = 0.21), despite the shorter interval between screen rounds in the NLST.8

Strengths of this study are the robust design (a large, randomised controlled trial) and prospective data collection. Limitations of this study are the lack of data for the control arm of the trial and lung cancer mortality. We have planned to perform analyses with those data 10 years after randomisation, in accordance with the main purpose of our trial.11

CONCLUSION

Despite stringent referral criteria, an increasing length of screening interval, and a small proportion of female participants, the screening strategy of the NELSON trial resulted in a favourable cancer stage distribution at diagnosis, which is a pre-requisite for the effectiveness of our screening strategy.
Chapter 3

SUPPORT STATEMENT

Supported by Zorg Onderzoek Nederland-Medische Wetenschappen (ZonMw), KWF Kankerbestrijding, and Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen (RvvZ). Roche Diagnostics provided a grant for the performance of proteomics research. Siemens Germany provided four digital workstations and LungCARE for the performance of 3D measurements.

CONFLICTS OF INTEREST

None declared

ACKNOWLEDGEMENTS

The authors thank their secretary M. Quak, data manager R. M. Vernhout, and system controllers R. Faber and F. Santegoets for contributions and for maintenance of the database. Also, the authors thank Dr. H. Stam (lung physiologist, Erasmus Medical Center) for useful comments.
REFERENCES


APPENDIX

Figure 1. Time from positive screen to first consultation and to lung cancer diagnosis

Time to screening result, referral and diagnosis

The dotted line represents the deadline according to the NELSON protocol in the first box plot and the deadline according to the national Dutch guideline in the other three box plots.

Panel A: The median time to the final screening result for the 200 participants with screen-detected lung cancer was twelve days (interquartile range (IQR): 8 - 16) and 87.5% (175/200) waited ≤3 weeks.

Panel B: Thereafter, the median time to the first consultation by a pulmonologist was 13 days (IQR: 7 - 20.75) and 27.5% (55/200) had their first consultation in ≤5 work-days.

Panel C: In subjects who did not undergo a mediastinoscopy as part of the diagnostic work-up (n = 162), was the median time from the first consultation to the lung cancer diagnosis 42 days (IQR: 26.75 - 69), 17.9% was diagnosed in 3 weeks.

Panel D: When mediastinoscopy was performed (n = 38) the median time to diagnosis was 49 days (IQR: 31.5 - 66) and 28.9% was diagnosed in 5 weeks.

Analyses showed that neither a delayed final scan result (p = 0.39) nor a delayed first consultation (p = 0.19) was related to a more unfavourable cancer stage at diagnosis. Moreover, the participants with a delayed lung cancer diagnosis had a significantly lower disease stage than the persons without a delay (p < 0.001).
Outliers

Three participants had an extremely long lead-time between the positive scan and the first consultation (marked with a * in panel A). One participant (134 days) refused to go to the pulmonologist before a planned stay abroad. The two other participants (106 and 100 days) were delayed because of an administrative error.

Fifteen subjects had an extremely long lead-time between the first consultation and the diagnosis (marked with a * in panel B). Reasons were: watchful waiting approach by the pulmonologist (n = 9), delay caused by the participant (n = 2), comorbidity that required immediate treatment (n = 2), malignant nodule missed by wedge-resection; requiring a second procedure to perform a lobectomy (n = 1) and treatment of another benign nodule first (n = 1).

In total, eleven of the 200 (5.5%) participants had symptoms suspicious of lung cancer before they were diagnosed.

Symptomatic participants

Five participants had already symptoms suspicious of lung cancer before the screening scan was made:

1) 74 days before the third round scan: dyspnoea and cough
2) 287 days after the pre-randomisation questionnaire and 15 days before the baseline scan: dyspnoea, cough and thoracic pain.
3) 172 days before the second round scan: start weight loss >10%
4) 88 days before the baseline scan: start weight loss >10% and thoracic pain
5) 224 days after the pre-randomisation questionnaire and 124 days before the baseline scan: fatigue

Three participants got their first symptoms suspicious of lung cancer in the interval between the positive scan and the first consultation:

1) weight loss >10% and fatigue (interval was 15 days)
2) haemoptysis and thoracic pain (interval was 4 days)
3) cough (interval was 10 days)

Three other participants developed symptoms suspicious of lung cancer in the interval between the first consultation and the diagnosis date:

1) cough (interval was 278 days, delay due to cardiac valve replacement that had to be performed before lung surgery)
2) weight loss >10% (interval was 131 days, delay due to a false-positive N3 on the PET-scan, which required CT-guided puncture and mediastinoscopy, that were both negative) haemoptysis (interval was 30 days, no delay)
3) cough (interval was 10 days)
# Characteristics of screen-detected lung cancer

## Table 1. Predictive value of histological subtype for cancer stage at diagnosis

<table>
<thead>
<tr>
<th>Thresholds for significant histological subtypes</th>
<th>Adenocarcinoma</th>
<th>Large cell carcinoma</th>
<th>Small cell carcinoma</th>
<th>Mixed LCSC carcinoma</th>
<th>NSCLC-NOS</th>
<th>All significant histological subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage Ia to Ib</td>
<td>0.35</td>
<td>0.74</td>
<td>0.75</td>
<td>0.67</td>
<td>0.67</td>
<td>1.08</td>
</tr>
<tr>
<td>Stage Ib to Ila</td>
<td>0.59</td>
<td>0.99</td>
<td>1.02</td>
<td>0.92</td>
<td>0.92</td>
<td>1.37</td>
</tr>
<tr>
<td>Stage Ila to IIIa</td>
<td>0.95</td>
<td>1.36</td>
<td>1.41</td>
<td>1.28</td>
<td>1.28</td>
<td>1.82</td>
</tr>
<tr>
<td>Stage IIIa to IIIb</td>
<td>2.16</td>
<td>2.58</td>
<td>2.75</td>
<td>2.51</td>
<td>2.55</td>
<td>3.40</td>
</tr>
<tr>
<td>Stage IIIb to IV</td>
<td>2.73</td>
<td>3.15</td>
<td>3.36</td>
<td>3.09</td>
<td>3.17</td>
<td>4.11</td>
</tr>
</tbody>
</table>

### Histological subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Univariate log regression analyses</th>
<th>Multivariate log regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>-0.57</td>
<td>-1.13—0.01</td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0.19</td>
<td>-0.54—0.92</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>-0.60</td>
<td>-2.94—1.74</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>1.16</td>
<td>0.25—2.08</td>
</tr>
<tr>
<td>Large cell NE carcinoma</td>
<td>0.32</td>
<td>-1.61—2.24</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>2.93</td>
<td>1.57—4.28</td>
</tr>
<tr>
<td>Mixed LCSC carcinoma</td>
<td>3.08</td>
<td>0.45—5.72</td>
</tr>
<tr>
<td>Pleiomorph carcinoma</td>
<td>1.07</td>
<td>-2.48—4.63</td>
</tr>
<tr>
<td>NSCLC-NOS</td>
<td>3.67</td>
<td>0.84—6.50</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>No histological diagnosis</td>
<td>-1.95</td>
<td>-4.04—0.13</td>
</tr>
</tbody>
</table>

The thresholds in the columns “adenocarcinomas”, “large cell carcinoma”, “small cell carcinoma”, “mixed LCSC” and “NSCLC-NOS” are parameters for the effect of the variable on the cancer stage (like; the distance between the stages) in four separate univariate logistic categorical regression analysis. There is no threshold for stage IIA to stage IIB because none of the participants were diagnosed with stage IIB lung carcinoma.

The threshold column “all significant histological subtypes” represents the threshold for the multivariate (adenocarcinoma, large cell, small cell, mixed and NSCLC-NOS) logistic categorical regression model.

Definition of abbreviations: Mixed LCSC carcinoma = mixed large cell and small cell lung carcinoma; NSCLC-NOS = non-small cell lung carcinoma; not otherwise specified; 95% CI = 95% confidence interval of the estimate; Large cell NE carcinoma = large cell neuro-endocrine carcinoma.

* Both the bronchoalveolar carcinomas and the carcinoids were all diagnosed in stage IA, which caused separation, therefore no estimate or p-value could be calculated.
### Table 2a. Histology and disease stage of the 74 screen-detected lung cancers in round one

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Ia</th>
<th>Ib</th>
<th>IIA</th>
<th>IIB</th>
<th>IIIA</th>
<th>IIIIB</th>
<th>IV</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology†</strong></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>21 (60.0)</td>
<td>2 (5.7)</td>
<td>4 (11.4)</td>
<td>4 (11.4)</td>
<td>3 (8.6)</td>
<td>1 (2.9)</td>
<td>35 (47.3)</td>
<td></td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>2 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>9 (60.0)</td>
<td>.</td>
<td>2 (13.3)</td>
<td>3 (20.0)</td>
<td>.</td>
<td>1 (6.7)</td>
<td>15 (20.3)</td>
<td></td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>2 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>2 (40.0)</td>
<td>1 (20.0)</td>
<td>.</td>
<td>2 (40.0)</td>
<td>.</td>
<td>.</td>
<td>5 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Large cell NE carcinoma</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>.</td>
<td>1 (33.3)</td>
<td>.</td>
<td>.</td>
<td>3 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (100.0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Mixed LCSC carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (100.0)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Pleiomorph carcinoma</td>
<td>.</td>
<td>1 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>NSCLC-NOS</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>.</td>
<td>2 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Carcinoid</td>
<td>4 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>4 (5.4)</td>
</tr>
<tr>
<td>No histological diagnosis§</td>
<td>3 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>44 (59.5)</td>
<td>4 (5.4)</td>
<td>7 (9.5)</td>
<td>.</td>
<td>10 (13.5)</td>
<td>4 (5.4)</td>
<td>5 (6.8)</td>
<td>74 (100.0)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: large cell NE carcinoma = large cell neuro-endocrine carcinoma; mixed LCSC carcinoma = mixed large cell/small cell carcinoma; NSCLC-NOS = non-small cell lung carcinoma, not otherwise specified; . = 0.0.

† According to IARC Tumours of the Lung, Pleura and Heart (2004).
§ In three participants no histological diagnosis was established because biopsies were unsuccessful or not performed and the patient did not undergo thoracic surgery because of poor pulmonary function (N = 2) and poor heart function (N = 1).

### Table 2b. Histology and disease stage of the 58 screen-detected lung cancers in round two

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Ia</th>
<th>Ib</th>
<th>IIA</th>
<th>IIB</th>
<th>IIIA</th>
<th>IIIIB</th>
<th>IV</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology†</strong></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>29 (82.9)</td>
<td>1 (2.9)</td>
<td>3 (8.6)</td>
<td>.</td>
<td>2 (5.7)</td>
<td>.</td>
<td>.</td>
<td>35 (60.3)</td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>3 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>2 (66.7)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (33.3)</td>
<td>.</td>
<td>.</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>1 (50.0)</td>
<td>.</td>
<td>1 (50.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>5 (50.0)</td>
<td>.</td>
<td>.</td>
<td>2 (20.0)</td>
<td>2 (20.0)</td>
<td>1 (10.0)</td>
<td>10 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Large cell NE carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>.</td>
<td>.</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Mixed LCSC carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Pleiomorph carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>NSCLC-NOS</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>No histological diagnosis§</td>
<td>3 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43 (74.1)</td>
<td>1 (1.7)</td>
<td>4 (6.9)</td>
<td>.</td>
<td>6 (10.3)</td>
<td>2 (3.4)</td>
<td>2 (3.4)</td>
<td>58 (100.0)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: . = 0 (0.0); large cell NE carcinoma = large cell neuro-endocrine carcinoma; mixed LCSC carcinoma = mixed large cell/small cell carcinoma; NSCLC-NOS = non-small cell lung carcinoma, not otherwise specified.

† According to IARC Tumours of the Lung, Pleura and Heart (2004).
§ In 3 participants no histological diagnosis was established because biopsies were unsuccessful or not performed and the patient did not undergo thoracic surgery because of poor pulmonary function (n = 1), metastasised prostate carcinoma (n = 1) and death due to mesenteric ischemia before intended surgery (n = 1).
### Table 2c. Histology and disease stage of the 77 screen-detected lung cancers in round three

<table>
<thead>
<tr>
<th>Disease stage*</th>
<th>Ia</th>
<th>Ib</th>
<th>IIa</th>
<th>IIb</th>
<th>IIIa</th>
<th>IIIb</th>
<th>IV</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology†</strong></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>25 (67.6)</td>
<td>6 (16.2)</td>
<td>1 (2.7)</td>
<td>.</td>
<td>3 (8.1)</td>
<td>1 (2.7)</td>
<td>1 (2.7)</td>
<td>37 (48.1)</td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>6 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>10 (62.5)</td>
<td>.</td>
<td>1 (6.3)</td>
<td>.</td>
<td>4 (25.0)</td>
<td>.</td>
<td>1 (6.3)</td>
<td>16 (20.8)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>2 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Large cell NE carcinoma</td>
<td>1 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>4 (80.0)</td>
<td>.</td>
<td>1 (20.0)</td>
<td>.</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Mixed LCSC carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Pleiomorph carcinoma</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>NSCLC-NOS</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>2 (100.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>No histological diagnosis§</td>
<td>6 (85.7)</td>
<td>.</td>
<td>1 (14.3)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>7 (9.1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50 (64.9)</td>
<td>6 (7.8)</td>
<td>3 (3.9)</td>
<td>.</td>
<td>14 (18.2)</td>
<td>1 (1.3)</td>
<td>3 (3.9)</td>
<td>77 (100.0)</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** . = 0 (0.0); large cell NE carcinoma = large cell neuro-endocrine carcinoma; mixed LCSC carcinoma = mixed large cell/small cell carcinoma; NSCLC-NOS = non-small cell lung carcinoma, not otherwise specified.

† According to IARC Tumours of the Lung, Pleura and Heart (2004).
§ In 7 participants no histological diagnosis was established because biopsies were unsuccessful or not performed and the patient did not undergo thoracic surgery because of poor pulmonary function (n= 4), poor general condition (n = 1), radiotherapy because of participation in other clinical trial (n = 1) and refusal (n = 1).
### Table 3a. Histology and disease stage of the 175 screen-detected lung cancers in 166 men

<table>
<thead>
<tr>
<th>Disease stage*</th>
<th>Ia (%)</th>
<th>Ib (%)</th>
<th>IIA (%)</th>
<th>IIB (%)</th>
<th>IIIA (%)</th>
<th>IIIB (%)</th>
<th>IV (%)</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>58 (66.7)</td>
<td>8 (9.2)</td>
<td>8 (9.2)</td>
<td>7 (8.0)</td>
<td>4 (4.6)</td>
<td>2 (2.3)</td>
<td></td>
<td>87 (49.7)</td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>8 (100.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8 (4.6)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>17 (56.7)</td>
<td>3 (10.0)</td>
<td></td>
<td>8 (26.7)</td>
<td></td>
<td>2 (6.7)</td>
<td>30 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>1 (50.0)</td>
<td></td>
<td>1 (50.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>6 (40.0)</td>
<td>1 (6.7)</td>
<td></td>
<td>5 (33.3)</td>
<td>2 (13.3)</td>
<td>1 (6.7)</td>
<td>15 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Large cell NE carcinoma</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td></td>
<td></td>
<td>5 (62.5)</td>
<td></td>
<td>3 (37.5)</td>
<td>8 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed LCSC carcinoma</td>
<td></td>
<td></td>
<td>1 (50.0)</td>
<td></td>
<td>1 (50.0)</td>
<td>2 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleiomorph carcinoma</td>
<td></td>
<td></td>
<td>1 (100.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>NSCLC-NOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td></td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>No histological diagnosis§</td>
<td>12 (92.3)</td>
<td>1 (7.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13 (7.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>108 (61.7)</td>
<td>10 (5.7)</td>
<td>14 (8.0)</td>
<td>26 (14.9)</td>
<td>7 (4.0)</td>
<td>10 (5.7)</td>
<td>175 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Definition of abbreviations.** = 0 (0.0); large cell NE carcinoma = large cell neuro-endocrine carcinoma; mixed LCSC carcinoma = mixed large cell/small cell carcinoma; NSCLC-NOS = non-small cell lung carcinoma, not otherwise specified.

† According to IARC Tumours of the Lung, Pleura and Heart (2004).
§ In 13 participants no histological diagnosis was established because biopsies were unsuccessful or not performed and the patient did not undergo thoracic surgery because of poor pulmonary function (n = 7), poor heart function (n = 1), poor general condition (n = 1), metastasized prostate carcinoma (n = 1), death due to mesenteric ischemia before intended surgery (n = 1), radiotherapy because of participation in other clinical trial (n = 1) and refusal (n = 1).

### Table 3b. Histology and disease stage of the 34 screen-detected lung cancers in 34 women

<table>
<thead>
<tr>
<th>Disease stage*</th>
<th>Ia (%)</th>
<th>Ib (%)</th>
<th>IIA (%)</th>
<th>IIB (%)</th>
<th>IIIA (%)</th>
<th>IIIB (%)</th>
<th>IV (%)</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>17 (85.0)</td>
<td>1 (5.0)</td>
<td></td>
<td>2 (10.0)</td>
<td></td>
<td></td>
<td></td>
<td>20 (58.8)</td>
</tr>
<tr>
<td>Bronchoalveolar carcinoma</td>
<td>3 (100.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 (8.8)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4 (100.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 (11.8)</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>2 (100.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>1 (50.0)</td>
<td></td>
<td>1 (50.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Large cell NE carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 (100.0)</td>
<td></td>
<td></td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Mixed LCSC carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Pleiomorph carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>NSCLC-NOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (5.9)</td>
</tr>
<tr>
<td>No histological diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 (5.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>29 (85.3)</td>
<td>1 (2.9)</td>
<td></td>
<td>4 (11.8)</td>
<td></td>
<td></td>
<td></td>
<td>34 (100.0)</td>
</tr>
</tbody>
</table>

**Definition of abbreviations.** = 0 (0.0); large cell NE carcinoma = large cell neuro-endocrine carcinoma; mixed LCSC carcinoma = mixed large cell/small cell carcinoma; NSCLC-NOS = non-small cell lung carcinoma, not otherwise specified.

† According to IARC Tumours of the Lung, Pleura and Heart (2004).
Table 4. Predictive value of histological subtype for cancer stage at diagnosis

<table>
<thead>
<tr>
<th>Thresholds</th>
<th>Gender</th>
<th>Age</th>
<th>BMI</th>
<th>Pack-years</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage Ia to Ib</td>
<td>0.39</td>
<td>-0.28</td>
<td>4.11</td>
<td>1.20</td>
<td>3.90</td>
</tr>
<tr>
<td>Stage Ib to IIa</td>
<td>0.65</td>
<td>-0.03</td>
<td>4.38</td>
<td>1.45</td>
<td>4.18</td>
</tr>
<tr>
<td>Stage IIa to IIIa</td>
<td>1.01</td>
<td>0.33</td>
<td>4.77</td>
<td>1.82</td>
<td>4.58</td>
</tr>
<tr>
<td>Stage IIIa to IIIb</td>
<td>2.23</td>
<td>1.53</td>
<td>6.01</td>
<td>3.04</td>
<td>5.85</td>
</tr>
<tr>
<td>Stage IIIb to IV</td>
<td>2.80</td>
<td>2.09</td>
<td>6.64</td>
<td>3.61</td>
<td>6.48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter estimates</th>
<th>Univariate log regression analyses</th>
<th>Multivariate log regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Estimate 95% CI p-value</td>
<td>Estimate 95% CI p-value</td>
</tr>
<tr>
<td>Gender</td>
<td>-1.36 -2.35--0.37 0.007</td>
<td>-1.13 -2.13--0.12 0.028</td>
</tr>
<tr>
<td>Age</td>
<td>-0.01 -0.06-0.03 0.54</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.14 0.06-0.21 0.001</td>
<td>0.12 0.038-0.20 0.004</td>
</tr>
<tr>
<td>Pack-years</td>
<td>0.01 -0.000-0.03 0.047</td>
<td>0.008 -0.005-0.021 0.22</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: BMI = body-mass index; 95% CI = 95% confidence interval of the estimate.

The thresholds in the columns “gender” (male as reference), “age”, “BMI” and “pack-years” are parameters for the effect of the variable on the cancer stage (like; the distance between the stages) in four separate univariate logistic categorical regression analysis. There is no threshold for stage IIa to stage IIb because none of the participants were diagnosed with stage IIb lung carcinoma. The threshold column “all” represents the threshold for the multivariate (gender and BMI) logistic categorical regression model.
Chapter 4

Epidemiological evaluation

Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers


*Lancet Oncology*

*November 2014*
Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers

*Lancet Oncol. 2014 Nov;15(11).*

**ABSTRACT**

Low-dose CT screening is recommended for individuals at high risk of developing lung cancer. However, CT screening does not detect all lung cancers: some might be missed at screening, and others can develop in the interval between screens. The NELSON trial is a randomised trial to assess the effect of screening with increasing screening intervals on lung cancer mortality. In this study, we aimed to assess screening test performance, and the epidemiological, radiological, and clinical characteristics of interval cancers in NELSON trial participants assigned to the screening group.

Eligible participants in the NELSON trial were those aged 50–75 years, who had smoked 15 or more cigarettes per day for more than 25 years or ten or more cigarettes for more than 30 years, and were still smoking or had quit less than 10 years ago. We included all participants assigned to the screening group who had attended at least one round of screening. Screening test results were based on volumetry using a two-step approach. Initially, screening test results were classified as negative, indeterminate, or positive based on nodule presence and volume. Subsequently, participants with an initial indeterminate result underwent follow-up screening at short notice to classify their final screening test result as negative or positive, based on nodule volume doubling time. We obtained information about all lung cancer diagnoses made during the first three rounds of screening, plus an additional 2 years of follow-up from the national cancer registry. We determined epidemiological, radiological, participant, and tumour characteristics by reassessing medical files, screening CTs, and clinical CTs. The NELSON trial is registered at www.trialregister.nl, number ISRCTN63545820.

15,822 participants were enrolled in the NELSON trial, of whom 7,915 were assigned to low-dose CT screening with increasing interval between screens, and 7,909 to no screening. We included 7,155 participants in our study, with median follow-up of 8.16 years (IQR 7.56-8.56). 187 (3%) of 7,155 screened participants were diagnosed with 196 screen-detected lung cancers, and another 34 (<1%, 19 [56%] in the first year of the interval, and 15 [44%] in the second year) were diagnosed with 35 interval cancers. The overall (three rounds of screening, and 2 years' follow-up) sensitivity was 84.6% (95% CI 79.6-89.2), specificity was 98.6% (98.5-98.8), positive predictive value was 40.4% (35.9-44.7), and negative predictive value was 99.8% (99.8-99.9). Retrospective assessment of
Epidemiological evaluation

CT examinations showed that 12 (35%) of the 35 interval cancers were not visible at the last screening CT. The remaining cancers were visible when retrospectively assessed, but were not diagnosed because of radiological detection and interpretation errors (17 [50%]), misclassification by the protocol (two [6%]), participant noncompliance (two [6%]), and non-adherence to protocol (one [3%]). Compared with screen-detected cancers, interval cancers were diagnosed at more advanced stages (29 [83%] of 35 interval cancers vs 44 [22%] of 196 screen-detected cancers diagnosed in stage III or IV; p < 0.001, were more often small cell carcinomas (seven [20%] vs. eight [4%], p = 0.003) and less often adenocarcinomas (nine [26%] vs. 102 [52%], p = 0.005).

Lung cancer screening in the NELSON trial yielded high specificity and sensitivity, with only a small number of interval cancers. The results of this study could be used to improve screening algorithms, and reduce the number of missed cancers.

INTRODUCTION

Until the 1990s, no effective screening test for lung cancer was available. Screening studies using sputum cytology or chest radiography did not show a significant reduction in lung cancer mortality. In the 1990s, cohort studies using low-dose CT as a lung cancer screening test were initiated.\(^1\) Low-dose CT seemed to be able to detect more and smaller lung cancers than chest radiography, with most being diagnosed at stage I.\(^2\)\(^-\)\(^6\) Moreover, survival in patients with screen-detected lung cancer was impressive. In 2011, the National Lung Screening Trial (NLST) showed a 20% reduction in lung cancer mortality using low-dose CT compared with screening using chest radiography.\(^7\)

The CISNET lung cancer working group modelled and assessed hundreds of screening scenarios using data from NLST; 26 selected efficient screening scenarios led to reductions in lung cancer mortality of between 4.6% to 21.2%.\(^8\) As a result, the US Preventative Services Task Force and several medical societies recommended annual low-dose CT screening in the USA for subjects at high risk of developing lung cancer.\(^8\)\(^-\)\(^10\) However, no reduction in lung cancer mortality with an annual low-dose CT screening strategy has been reported in three smaller European trials,\(^11\)\(^-\)\(^13\) and results of several other European trials are still awaited. In many European countries, the outcome of the NELSON trial or pooled analyses is awaited before a decision about implementation of a national service lung cancer screening programme is made.

Efficacy and acceptance of low-dose CT screening for lung cancer depends on the sensitivity of the screening test (i.e., the risk of not detecting a lung cancer through screening). Lung cancers not detected by screening but diagnosed during the screening interval, known as interval cancers, might have been missed at screening or might have developed between screening and detection. Few studies about the incidence and characteristics of
interval cancers in lung cancer screening have been reported.\textsuperscript{14-16} None of these studies assessed causes of interval cancers, or whether improvements to the screening algorithm were possible.

The NELSON trial is a randomised trial to assess whether low-dose CT screening with an increasing length of screening interval (1, 2, and 2.5 years) compared with no screening reduces lung cancer mortality.\textsuperscript{20} In this retrospective analysis, we aimed to assess the performance of the screening test to detect interval cancers, and provide insights into the incidence, histopathology, and causes for failed detection of these cancers.

METHODS

Study design and participants

Individuals from four centres in the Netherlands and Belgium were enrolled and randomly assigned to receive low-dose CT screening or no screening. Eligible participants were adults aged 50–75 years, who had smoked 15 or more cigarettes per day for more than 25 years or ten or more cigarettes per day for more than 30 years, and were still smoking or had stopped smoking less than 10 years previously. People with self-reported moderate or bad health, inability to climb two flights of stairs, bodyweight of 140 kg or more, current or past renal cancer, melanoma, or breast cancer, lung cancer diagnosed less than five years ago, or a chest CT examination less than one year ago, were excluded. Design of the NELSON trial is presented in Figure 1.

In this study to assess the performance of the screening and the causes of the failure to detect the interval cancers, we included all Dutch participants who were randomly assigned to the screening group and received at least one screening in the first three

Figure 1. Design NELSON trial

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>Baseline</th>
<th>1 year</th>
<th>3 years</th>
<th>5.5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen group</td>
<td>Round 1 CT scan</td>
<td>interval 1 year</td>
<td>Round 2 CT scan</td>
<td>Round 3 CT scan</td>
<td>Round 4 CT scan</td>
</tr>
<tr>
<td>Control group</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analyses of this study include data from the first screening round up to two years of follow-up after the third round scan. Median length of follow-up, from randomisation to end of follow-up at 31-12-2011 was 8.16 years (interquartile range: 7.56 to 8.56 years). Note, 32 of 7155 (0.4%) participants had their third round scan after 2009; as a result, their two-year follow-up period is not completely covered by the data of the national cancer registry.
screening rounds at baseline, one year later, and three years later. We did not include Belgian participants from the NELSON trial in this study because no data were available from the Belgian Cancer Registry.

The NELSON trial was approved by the Dutch Minister of Health and ethics boards at each participating centre. All participants gave written informed consent for participation and evaluation of personal data from hospital charts.

**Procedures**

Screening was done using 16-detector CT scanners in a low-dose setting (effective radiation dose <0.4 mSv to <1.6 mSv depending on bodyweight). Datasets were derived from images of the thorax (slice thickness 1 mm, interval 0.7 mm) and volumes of nodules were measured using semi-automatic volumetric software (LungCARE, Siemens, Somaris/5 VB 10A-W). Volume doubling time was calculated for all nodules (no selection was made based on any characteristics suspicious for malignancy) with at least two measurement of its size using the formula:

\[
VDT = \frac{\ln(2) \Delta t}{\ln(V_2) - \ln(V_1)}
\]

in which \(\Delta t\) represents time in days between scans, \(V_1\) the volume of the nodule at baseline, and \(V_2\) the volume of the nodule at the current CT examination.

The screening test results were determined by the presence, size and growth rate of pulmonary nodules. Screening test results were defined to be negative: in the absence of nodules, for all nodules with fat, benign calcification patterns or other benign abnormalities, and for non-calcified nodules with a volume <50 mm³, a percentage volume-change (PVC) <25%, or a percentage volume change ≥25% combined with a volume doubling-time ≥600 days. Screening test results were defined to be positive for non-calcified nodules with a volume >500 mm³, or with a PVC of ≥25% combined with a VDT <400 days. Moreover, screening test results were also positive if a new solid component had emerged in a previously non-solid nodule. Screening test results were defined to be indeterminate for nodules with a volume 50-500 mm³, or a PVC ≥25% combined with a VDT of 400-600 days. Subjects with an indeterminate screening test result were invited for one additional LDCT examination at the screening center at short notice to determine whether their final screening test result was positive or negative using the aforementioned criteria.

After a negative final screening test result, participants did not undergo any additional diagnostic procedures, but only received an invitation for the next screening round. After a positive final screening result, participants were referred to a pulmonologist via their general practitioner for diagnostic work-up to exclude or diagnose lung cancer.
To assess interval cancers, we obtained data for all lung cancers diagnosed since the first screening in round one to the last screening in round three, plus an additional two years of follow-up from the Dutch Cancer Registry. For every patient diagnosed with lung cancer outside of screening (i.e., diagnosed with interval cancer), we collected medical and radiological files. Two radiologists (with 10 [PAJ] and >30 years [ETHS] of experience with chest CT) reviewed the last screening CT from the study and the clinical CT used for diagnosis of lung cancer, and reached a consensus on whether or not the lung cancer could retrospectively be identified on the screening CT. We determined epidemiological, radiological, participant, and tumour characteristics by reassessing medical files, screening CTs, and clinical CTs.

Outcomes
The primary endpoint of the NELSON trial is reduction of lung cancer mortality by 25% or more at ten years after randomisation. The primary aim of this analysis was to assess the frequency of interval lung cancers, and to determine the sensitivity, specificity, positive predictive value, and negative predictive value of the screening protocol. The secondary aim was to assess, and compare, the histopathological type and stage of screen-detected and interval lung cancers, and to assess the causes of the failure to detect the interval cancers.

Screen-detected cancers were defined as lung cancers diagnosed by diagnostic work-up initiated for a positive screening test result. We defined interval cancers as: lung cancers diagnosed after a negative screening test; lung cancers diagnosed after an indeterminate screening test, but without any follow-up low-dose CT examination or diagnostic work-up being done in the screening programme; or lung cancers diagnosed after a positive screening result if the diagnostic work-up initiated for the positive screening result did not yield a diagnosis of lung cancer, and the diagnosis was made later because symptoms had triggered diagnostic assessment that eventually yielded diagnosis of lung cancer. Diagnostic work-up was defined not to have yielded diagnosis of lung cancer if a pulmonologist had concluded that the suspicious nodule was not lung cancer and dismissed the participant from any further diagnostic procedures or follow-up, or if diagnostic workup did not yield diagnosis of lung cancer and was still ongoing after two years of follow-up.

A true-positive test result was a positive result in a participant who actually was diagnosed with lung cancer by diagnostic work-up. A false-positive test result was a positive result in the absence of lung cancer. A true-negative test result was a negative scan in the absence of lung cancer, and a false-negative test result was a negative scan followed by diagnosis of interval cancer.

Statistical analysis
All screening test characteristics were estimated with the detection method, as done in the NLST. We estimated sensitivity by dividing the number of true-positive screens by the
numbers of true-positive and false-positive screens. We estimated specificity by dividing the number of true-negative screens by the numbers of true-negative and false-negative screens. We estimated positive predictive value by dividing all participants with a true-positive screening by all participants with positive screening. We estimated negative predictive value by dividing all participants with a true-negative screening by all participants with negative screening. To calculate 95% CIs, we did bootstrapping based on 5,000 samples. Continuous variables were tested for normality; the significance of the differences was assessed using one-way analysis of variance. For nominal variables we used Fisher’s exact test or likelihood-based χ² test. For categorical variables we used the Mann-Whitney U test. All analyses were done with PASW Statistics, IBM SPSS (version 20).

RESULTS

Epidemiological characteristics
Between Dec 23, 2003, and July 6, 2006, 15,822 individuals from four centres in the Netherlands and Belgium were enrolled and randomly assigned to receive low-dose CT screening (n = 7,915) or no screening (n = 7,907). For this analysis, we excluded the 7,909 participants randomly assigned to the no screening group, the 477 participants from Belgium (because no data were yet available from the Belgian Cancer Registry), and 283 participants who did not attend their screening examinations (because no screening test characteristics could be calculated in the absence of screening). Thus, we included 7,155 participants in our analysis (Figure 2). Median length of follow-up was 8.16 years (IQR 7.56–8.56).

There was no significant difference between included and excluded participants’ baseline characteristics (Table 1). 7,135 (96%) of 7,438 participants in the screening group attended the first round of screening, 6,890 (93%) attended the second round, and 6,538 (88%) attended the third round. The final positive screening test results led to the diagnosis of lung cancer in 187 participants (3%, Table 2). Additionally, 34 (<1%) participants were diagnosed with lung cancer between screening rounds (19 in the first year since screening and 15 in the second year, Table 2).

Test characteristics for each separate screening round are provided in table 2. For the three screening rounds combined, sensitivity was 84.6% (95% CI 79.6–89.2%), specificity was 98.6% (95% CI 98.5–98.8%), positive predictive value was 40.4% (95% CI 35.9–44.7%), and negative predictive value was 99.8% (95% CI 99.8–99.9%). When only the first year of the screening interval was considered, five (26%) of the 19 participants with interval cancers were identified during the interval. This finding implies that maximum sensitivity (assuming not a single lung cancer was missed) of an annual screening programme would be 97.4% (95% CI 94.8–99.5%), and of a two-yearly screening programme (with an initial annual screening round) would be 94.0% (95% CI 90.5–97.0%).
Figure 2. Flowchart of included participants

- **All NELSON participants**
  - Randomised to control group
    - n = 7,909
  - Randomised to screen group
    - n = 7,915
- **Dutch NELSON participants**
  - Screened
    - n = 7,155
  - Not screened
    - n = 283*
- **Belgian NELSON participants**
  - n = 477

*No response despite repeated invitations for first screening round.*

†Reasons: screen-detected lung cancer (n = 61), death (n = 25), participant declined (n = 110), participant unattainable or repeatedly no show (n = 42), and still in diagnostic work-up round one (n = 1).

‡Reasons: screen-detected lung cancer (n = 54), death (n = 79), participant declined (n = 145), participant unattainable or repeatedly no show (n = 94), administrative error (n = 3), and unknown (n = 3).
Epidemiological evaluation

Table 1. Characteristics of included and excluded participants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All participants</th>
<th>Included n (%)</th>
<th>Excluded n (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>2,597 (16.5)</td>
<td>1,156 (16.2)</td>
<td>1,441 (16.7)</td>
<td>0.34</td>
</tr>
<tr>
<td>Current smoker</td>
<td>8,768 (55.4)</td>
<td>3,959 (55.3)</td>
<td>4,809 (55.5)</td>
<td>0.82</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>58.0 (54.0 - 62.0)</td>
<td>58.0 (54.0 - 62.0)</td>
<td>58.0 (54.0 - 62.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Pack-years, median (IQR)</td>
<td>38.0 (29.7 - 49.5)</td>
<td>38.0 (29.7 - 49.5)</td>
<td>38.0 (29.7 - 49.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>Total</td>
<td>15,822 (100.0)</td>
<td>7,155 (45.2)</td>
<td>8,667 (54.8)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Definition of abbreviations: IQR= interquartile range; NA = not applicable.
* Difference between included and excluded participants.

Table 2. Epidemiological characteristics round one to three

<table>
<thead>
<tr>
<th>Epidemiological characteristics</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3</th>
<th>1-year follow-up</th>
<th>2-year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening participants</td>
<td>7,135</td>
<td>6,890</td>
<td>6,538</td>
<td>7,155</td>
<td>7,155</td>
</tr>
<tr>
<td>Negative test result</td>
<td>6,951</td>
<td>6,769</td>
<td>6,380</td>
<td>20,100</td>
<td>20,100</td>
</tr>
<tr>
<td>- true negative</td>
<td>6,946</td>
<td>6,762</td>
<td>6,750</td>
<td>20,081</td>
<td>20,066</td>
</tr>
<tr>
<td>- false negative</td>
<td>5</td>
<td>7</td>
<td>7 + 12</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Positive test result</td>
<td>184</td>
<td>121</td>
<td>158</td>
<td>463</td>
<td>463</td>
</tr>
<tr>
<td>- true positive</td>
<td>62</td>
<td>53</td>
<td>53</td>
<td>187</td>
<td>187</td>
</tr>
<tr>
<td>- false positive</td>
<td>122</td>
<td>68</td>
<td>68</td>
<td>276</td>
<td>276</td>
</tr>
<tr>
<td>Total no. of detected cancers</td>
<td>62</td>
<td>53</td>
<td>72</td>
<td>187</td>
<td>187</td>
</tr>
<tr>
<td>- per 1000 screened</td>
<td>8.69</td>
<td>7.69</td>
<td>11.0</td>
<td>26.1</td>
<td>26.1</td>
</tr>
<tr>
<td>Total no. of interval cancers</td>
<td>5</td>
<td>7</td>
<td>19</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>- per 1000 screened</td>
<td>0.70</td>
<td>1.02</td>
<td>2.76</td>
<td>1.07</td>
<td>1.53</td>
</tr>
<tr>
<td>Ratio detected : interval</td>
<td>12.4:1</td>
<td>7.6:1</td>
<td>2.8:1</td>
<td>10.3:1</td>
<td>7.2:1</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>92.5</td>
<td>88.3</td>
<td>73.6</td>
<td>91.1</td>
<td>87.8</td>
</tr>
<tr>
<td>Specificity</td>
<td>98.3</td>
<td>99.0</td>
<td>99.0</td>
<td>98.7</td>
<td>98.7</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>33.7</td>
<td>43.8</td>
<td>43.8</td>
<td>45.6</td>
<td>45.6</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>99.9</td>
<td>99.9</td>
<td>99.7</td>
<td>99.9</td>
<td>99.9</td>
</tr>
</tbody>
</table>

Radiological characteristics

Reassessment of CT examinations of the 34 participants with an interval cancer suggested that no lung cancer was present at the last screening examination in 12 cases (35%, Table 3). In the remaining 22 (65%) cases, we retrospectively identified a suspicious abnormality on the screening CT examination. In most cases, the suspicious abnormality was missed. Causes of the failure to detect these lung cancers were human error (two [6%]), interpretation error (two [6%]), and detection error due to various causes (13 [38%]). The 13 lung
Table 3. Radiological characteristics interval lung cancers

<table>
<thead>
<tr>
<th>Radiological characteristics</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3</th>
<th>Total round 1-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal screening CT</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Non-compliance participant</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>Non-adherence to protocol</td>
<td>.</td>
<td>.</td>
<td>1 (14.3)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Inadequacy protocol</td>
<td>1 (20.0)</td>
<td>.</td>
<td>1 (14.3)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Detection error*</td>
<td>3 (60.0)</td>
<td>2 (28.6)</td>
<td>3 (42.9)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Interpretation error</td>
<td>.</td>
<td>1 (14.3)</td>
<td>1 (8.3)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Human error</td>
<td>.</td>
<td>1 (14.3)</td>
<td>.</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Total no. of interval cancers</td>
<td>5</td>
<td>7</td>
<td>12</td>
<td>3</td>
</tr>
</tbody>
</table>

Definition of abbreviation: . = 0 (0.0)

Cancers missed because of these detection errors were: intra-bronchial localised lesions (five [15%]); pleural-attached lesions (two [6%]); lesion adjoining bullous structure (one [3%]); lesion surrounded by extensive honeycombing (one [3%]); and four cases where an intrapulmonary lesion was not visible but signs of lung cancer metastasis were missed (three [9%] cases of mediastinal lymphadenopathy, and one [3%] case of pleural effusion). In the remaining five cases, the abnormality was detected, but lung cancer was not diagnosed because of participant non-compliance (two [6%]), or the abnormality was not classified as suspicious by the protocol (one [3%]), or the abnormality was manually classified as not suspicious by the radiologist because of a negative diagnostic work-up in a previous screening round (two [6%]).

We calculated test sensitivity using the results of this retrospective radiological assessment, using only those interval cancers that were due to test failures. Assuming a 1-year screening interval, test sensitivity would have been 93.9% (95% CI 87.9-98.5%) in round one, 93.0% (95% CI 86.0-98.2%) in round two, and 92.3% (95% CI 85.9-97.4%) in round three.

Clinical characteristics

Participants diagnosed with lung cancer (both detected and interval cancers) were significantly older than were participants without lung cancer (Table 4). Only participants with an interval cancer (but not those with detected cancer) were significantly more likely to be current smokers than were participants with no cancer (Table 4).

The 187 participants with screen-detected lung cancer had a total of 196 tumours, and the 34 participants with interval cancer had a total of 35 tumours; nine participants with screen-detected cancers and one participant with interval cancer were diagnosed with synchronous double tumours. Interval cancers were diagnosed at a significantly higher disease stage (p <0.001) than were screen-detected lung cancers (Table 5a).
Epidemiological evaluation

Diagnosis at stage T1N0M0 occurred only in three (9%) of 35 interval cancers, whereas 130 (66%) of 196 screen-detected lung cancers were diagnosed at that stage. The disease stage of interval cancers diagnosed in the first year since screening was significantly higher than the stage of those diagnosed in the second year (p = 0.02). Interval cancers

Table 4. Characteristics of 7,155 included participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No lung cancer</th>
<th>Detected cancer</th>
<th>Interval cancer</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,817 (83.9)</td>
<td>154 (82.4)</td>
<td>28 (82.4)</td>
<td>0.81</td>
</tr>
<tr>
<td>Age - median (IQR)</td>
<td>58.0 (54.0 - 62.0)</td>
<td>61.0 (57.0 - 66.0)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>3,827 (55.3)</td>
<td>104 (55.6)</td>
<td>28 (82.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pack-years - median (IQR)</td>
<td>38.0 (30.0 - 49.0)</td>
<td>44.0 (32.0 - 55.0)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6,934</td>
<td>187 NA</td>
<td>34 NA</td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: IQR = interquartile range; NA = not applicable.
* Compared to included participants without lung cancer.

Table 5a. Clinical characteristics detected and interval cancers - disease stage

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Ia n (%)</th>
<th>Ib n (%)</th>
<th>Ila n (%)</th>
<th>IIb n (%)</th>
<th>IIIa n (%)</th>
<th>IIIb n (%)</th>
<th>IV n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected cancer</td>
<td>41 (62.1)</td>
<td>3 (4.5)</td>
<td>5 (7.6)</td>
<td>.</td>
<td>10 (15.2)</td>
<td>3 (4.5)</td>
<td>4 (6.1)</td>
<td>66 (100.0)</td>
</tr>
<tr>
<td>Interval cancer</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (20.0)</td>
<td>4 (80.0)</td>
<td>5 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Round 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected cancer</td>
<td>41 (73.2)</td>
<td>1 (1.8)</td>
<td>4 (7.1)</td>
<td>.</td>
<td>6 (10.7)</td>
<td>2 (3.6)</td>
<td>2 (3.6)</td>
<td>56 (100.0)</td>
</tr>
<tr>
<td>Interval cancer first year</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>7 (100.0)</td>
<td>7 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Interval cancer second year</td>
<td>1 (8.3)</td>
<td>.</td>
<td>1 (8.3)</td>
<td>3 (25.0)</td>
<td>.</td>
<td>7 (58.3)</td>
<td>12 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Round 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected cancer</td>
<td>48 (64.9)</td>
<td>6 (8.1)</td>
<td>3 (4.1)</td>
<td>.</td>
<td>13 (17.6)</td>
<td>1 (1.4)</td>
<td>3 (4.1)</td>
<td>74 (100.0)</td>
</tr>
<tr>
<td>Interval cancer first year</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (14.3)</td>
<td>.</td>
<td>1 (14.3)</td>
<td>5 (71.4)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Interval cancer second year</td>
<td>2 (50.0)</td>
<td>.</td>
<td>1 (25.0)</td>
<td>.</td>
<td>.</td>
<td>1 (25.0)</td>
<td>4 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All detected cancers</td>
<td>130 (66.3)</td>
<td>10 (5.1)</td>
<td>12 (6.1)</td>
<td>.</td>
<td>29 (14.8)</td>
<td>6 (3.1)</td>
<td>9 (4.6)</td>
<td>196 (100.0)</td>
</tr>
<tr>
<td>Interval cancers first year</td>
<td>.</td>
<td>.</td>
<td>1 (5.3)</td>
<td>.</td>
<td>2 (10.5)</td>
<td>16 (84.2)</td>
<td>19 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Interval cancers second year</td>
<td>3 (18.8)</td>
<td>.</td>
<td>2 (12.5)</td>
<td>3 (18.8)</td>
<td>.</td>
<td>8 (50.0)</td>
<td>16 (100.0)</td>
<td></td>
</tr>
<tr>
<td>All interval cancers</td>
<td>3 (8.6)</td>
<td>.</td>
<td>3 (8.6)</td>
<td>3 (8.6)</td>
<td>2 (5.7)</td>
<td>24 (68.6)</td>
<td>35 (100.0)</td>
<td></td>
</tr>
<tr>
<td>All lung cancers</td>
<td>133 (57.6)</td>
<td>10 (4.3)</td>
<td>12 (5.2)</td>
<td>3 (1.3)</td>
<td>32 (13.9)</td>
<td>8 (3.5)</td>
<td>33 (14.3)</td>
<td>231 (100.0)</td>
</tr>
</tbody>
</table>

Definition of abbreviation: . = 0 (0.0)
* According to the 7th edition of the TNM staging system for lung cancer.
The numbers of lung cancers presented are not equal to the number of participants as nine participants with screen-detected lung cancer (round 1 n = 4; round 2 n = 3; round 3 n = 2), and 1 participant with an interval cancer (second year round 3) were diagnosed with synchronous double tumours.

Diagnosis at stage T1N0M0 occurred only in three (9%) of 35 interval cancers, whereas 130 (66%) of 196 screen-detected lung cancers were diagnosed at that stage. The disease stage of interval cancers diagnosed in the first year since screening was significantly higher than the stage of those diagnosed in the second year (p = 0.02). Interval cancers
were significantly more often small-cell carcinomas \((p = 0.003)\) and less often adenocarcinomas \((p = 0.005)\) than were screen-detected cancers (Table 5b). There was no significant difference between other histological subtypes between screen-detected and interval cancers. The localisation of tumours across the lungs did not significantly differ between interval and screen-detected lung cancers (data not shown).

**Table 5b. Clinical characteristics detected and interval cancers - histological subtype**

<table>
<thead>
<tr>
<th>Lung cancer</th>
<th>Adeno n (%)</th>
<th>BAC n (%)</th>
<th>Squamous n (%)</th>
<th>Large cell n (%)</th>
<th>Small cell n (%)</th>
<th>Other† n (%)</th>
<th>Unknown‡ n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected cancer</td>
<td>32 (48.5)</td>
<td>2 (3.0)</td>
<td>11 (16.7)</td>
<td>5 (7.6)</td>
<td>1 (1.5)</td>
<td>12 (18.2)</td>
<td>3 (4.5)</td>
<td>66 (100.0)</td>
</tr>
<tr>
<td>Interval cancer</td>
<td>1 (20.0)</td>
<td>.</td>
<td>3 (60.0)</td>
<td>.</td>
<td>1 (20.0)</td>
<td>.</td>
<td>.</td>
<td>5 (100.0)</td>
</tr>
<tr>
<td>Round 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected cancer</td>
<td>34 (60.7)</td>
<td>3 (5.4)</td>
<td>3 (5.4)</td>
<td>10 (17.9)</td>
<td>2 (3.6)</td>
<td>1 (1.8)</td>
<td>3 (5.4)</td>
<td>56 (100.0)</td>
</tr>
<tr>
<td>Interval cancer first year</td>
<td>2 (28.6)</td>
<td>.</td>
<td>.</td>
<td>1 (14.3)</td>
<td>4 (57.1)</td>
<td>.</td>
<td>.</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Interval cancer second year</td>
<td>2 (16.7)</td>
<td>.</td>
<td>5 (41.7)</td>
<td>.</td>
<td>3 (25.0)</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>12 (100.0)</td>
</tr>
<tr>
<td>Round 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected cancer</td>
<td>36 (48.6)</td>
<td>5 (6.8)</td>
<td>15 (20.3)</td>
<td>2 (2.7)</td>
<td>5 (6.8)</td>
<td>4 (5.4)</td>
<td>7 (9.5)</td>
<td>74 (100.0)</td>
</tr>
<tr>
<td>Interval cancer first year</td>
<td>1 (14.3)</td>
<td>.</td>
<td>1 (14.3)</td>
<td>2 (28.6)</td>
<td>.</td>
<td>2 (28.6)</td>
<td>1 (14.3)</td>
<td>7 (100.0)</td>
</tr>
<tr>
<td>Interval cancer second year</td>
<td>3 (75.0)</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>1 (25.0)</td>
<td>.</td>
<td>4 (100.0)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All detected cancers</td>
<td>102 (52.0)</td>
<td>10 (5.1)</td>
<td>29 (14.8)</td>
<td>17 (8.7)</td>
<td>8 (4.1)</td>
<td>17 (8.7)</td>
<td>13 (6.6)</td>
<td>196 (100.0)</td>
</tr>
<tr>
<td>Interval cancers first year</td>
<td>4 (21.1)</td>
<td>.</td>
<td>1 (5.3)</td>
<td>6 (31.6)</td>
<td>4 (21.1)</td>
<td>3 (15.8)</td>
<td>1 (5.3)</td>
<td>19 (100.0)</td>
</tr>
<tr>
<td>Interval cancers second year</td>
<td>5 (31.3)</td>
<td>.</td>
<td>5 (31.3)</td>
<td>.</td>
<td>3 (18.8)</td>
<td>2 (12.5)</td>
<td>1 (6.3)</td>
<td>16 (100.0)</td>
</tr>
<tr>
<td>All interval cancers</td>
<td>9 (25.7)</td>
<td>.</td>
<td>6 (17.1)</td>
<td>6 (17.1)</td>
<td>7 (20.0)</td>
<td>5 (14.3)</td>
<td>2 (5.7)</td>
<td>35 (100.0)</td>
</tr>
<tr>
<td>All lung cancers</td>
<td>107 (46.3)</td>
<td>10 (4.3)</td>
<td>35 (15.2)</td>
<td>23 (10.0)</td>
<td>15 (6.5)</td>
<td>22 (9.5)</td>
<td>15 (6.5)</td>
<td>231 (100.0)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: . = 0 (0.0); Adeno = adenocarcinoma; BAC = bronchoalveolar carcinoma.

* According to the 7th edition of the TNM staging system for lung cancer.

† Other histological subtypes of lung cancer were: adenosquamous carcinoma; mixed large cell small cell carcinoma; large cell neuroendocrine carcinoma; carcinoid; mucinous carcinoma; pleiomorph carcinoma; non-small cell lung carcinoma, not otherwise specified.

‡ In 15 participants no histological diagnosis was established because biopsies were unsuccessful or not performed and the patient did not undergo thoracic surgery because of poor pulmonary function \((n=7)\), poor heart function \((n=1)\), poor general condition \((n=3)\), metastasized prostate carcinoma \((n=1)\), death due to mesenteric ischemia before intended surgery \((n=1)\), radiotherapy because of participation in other clinical trial \((n=1)\), and refusal \((n=1)\).

The numbers of lung cancers presented are not equal to the number of participants as nine participants with screen-detected lung cancer \((\text{round 1 } n = 4; \text{round 2 } n = 3; \text{round 3 } n = 2)\), and 1 participants with an interval cancer \((\text{second year round 3})\) were diagnosed with synchronous double tumours.
DISCUSSION

In this study, we assessed the epidemiological, radiological, and clinical characteristics of screen-detected and interval lung cancers in the NELSON trial. 187 (3%) of the 7,155 participants studied were diagnosed with lung cancer detected by screening, and another 34 (<1%) participants were diagnosed with interval lung cancer. Overall, sensitivity was about 85%, specificity about 99%, positive predictive value about 40%, and negative predictive value greater than 99%. Retrospectively, about a third of the interval cancers were not visible on the last screening CT; the remaining cancers were retrospectively visible, but were not diagnosed. Interval cancers were diagnosed at more advanced stages, and were more often small cell carcinomas and less often adenocarcinomas than were screen-detected cancers.

Screening test results were based on nodule volume and growth rate, measured by volumetry. Because indeterminate screening test results were not communicated to study participants as being suspicious for lung cancer, and follow-up low-dose CT examinations were done in the context of the screening trial, indeterminate screening results should not be regarded as positive screening test results for the purposes of comparison with other screening trials.

Because all participants received a final screening result that was either positive or negative, calculated test characteristics can be compared with those from other screening trials.

Almost all participants received negative final results from the screening test; only 2.6% had positive final results, and needed diagnostic procedures to exclude or diagnose lung cancer. In other trials of low-dose CT lung cancer screening, the proportion of positive screening tests was higher: 15% (annual screening group) and 14% (biennial screening group) in the Italian MILD trial,13 24% in the US NLST,7 26% in the ITALUNG trial,28 27% in the German LUSI trial,16 and 27% in the Italian DANTE trial.12 These differences were probably caused by differences in the criteria for screening test results and the applied screening technique. In the NELSON trial, relatively stringent criteria for a positive screening result (nodule volume >500 mm³ or volume doubling time <400 days)18 and volumetry were used, which might have increased measurement accuracy, and reduced false-positive screening results.17,29

The predictive value of the positive screening test results was 40.4% (95% CI 35.9-44.7) in the NELSON trial. Although this figure implies that more than half of the participants were referred for false-positive results, this positive predictive value was high compared with positive predictive values of other trials: 3.8% (95% CI 3.4-4.3%) in the NLST,7 4.1% in the LUSI trial,16 and 12.7% (biennial screening group) and 16.4% (annual screening group) in the MILD trial.13
Sensitivity in the first (annual) screening round was 92.5% (95% CI 85.5-98.4%), which is similar to that in other screening trials using annual screening: 93.8% (90.6-96.3%) in the NLST,14,30 and 85.3% in the annual screening group of the MILD trial.13 However, specificity was higher in the NELSON trial (98.3% [95% CI 98.8-99.2%]) than in either the NLST (73.4% [95% CI 72.8-73.9%]) or the MILD trial (86.8%). Sensitivity in the second screening round (biennial screening) was 73.6% (95% CI 62.5-83.6%) and in the third screening round (the first 2 years of the screening interval) was 87.8% (79.5-92.8%), which is probably similar to the overall sensitivity of 80.0% in the biennial screening group of the MILD trial.13

No appropriate comparison of screening test characteristics between annual and biennial screening trials can be made, because differences in performance between screening trials are not only caused by differences in the length of screening interval, but also by differences in the length of follow-up, criteria for a positive screening result, and lung cancer risk of the study population. Some comparisons of annual versus biennial screening were made in two modelling studies.8,31 These findings suggested that biennial screening is less effective in absolute terms,8,31 but induces substantially fewer harms (i.e. radiation-related lung cancer deaths, false-positive screening test results, number of screening examinations required per subject, overdiagnosis) than does annual screening8, and might be similarly cost effective.31 However, because only data from annual screening trials was used for these two modelling studies,8,31 estimates of effectiveness and harms of biennial screening were based on extrapolations and thus these data may not be accurate.8,31

Whether the NELSON trial will show effectiveness with its increasing length of screening intervals can only be established by mortality analyses, which are planned at 10 years after randomisation. Nonetheless, both sensitivity and specificity noted in the current study are promising for cost-effectiveness. However, ratios between detected and missed lung cancers might be affected by overdiagnosis. The amount of overdiagnosis in the NELSON trial is still unknown because required data are not yet available, although overdiagnosis in lung cancer screening was estimated to be small in a modelling study using data from the NLST.8

Reassessment of clinical CT and last screening CT examination showed the causes of the failure to detect interval cancers. Two-thirds of the interval cancers were, retrospectively, visible at the last screening CT examination. Detection errors, interpretation errors, and human errors were identified as the main causes of failure in half of the interval cancers. Increased attention of screening radiologists for lung cancer presenting as endobronchial lesions, pleural-attached lesions, and bulla wall thickenings, and increased attention for extra-pulmonary signs of lung cancer, could help to reduce detection failures. Additionally, one of the interval cancers was not diagnosed through screening due to manual adjustment of the screening test result by the radiologist from positive to negative, because a diagnostic work-up done in an earlier round did not yield the diagnosis of lung cancer.
In view of the magnitude and importance of radiological causes, a second study on this topic was done.\textsuperscript{32} For this study, CT examinations of interval cancers and post-screening cancers (diagnosed ≥2 years since last attended screening) were reviewed to determine causes of these errors, and to provide recommendations specifically for radiologists.\textsuperscript{32}

Failure of the screening protocol to classify cancerous nodules as suspicious was rare. Only two of 34 participants with interval cancers were not diagnosed because the cancerous nodule shrunk or had a volume doubling time greater than 400 days, suggesting that the relatively stringent criteria for a positive result in the NELSON trial did not lead to notable numbers of missed cancers. This finding is encouraging for future screening programmes that aim to limit harms and costs.\textsuperscript{33} Moreover, two of 34 participants with interval cancers were actually identified, but diagnosis was not made through screening because participants did not comply with the screening protocol. Instead of undergoing receiving follow-up low-dose CT screening three months after their indeterminate screening test result, they directly underwent diagnostic resection of the nodule, which yielded the diagnosis of lung cancer. Arguably, these interval cancers might have been detected by screening if the participants had complied with the protocol. However, we decided not to classify these cancers as detected by screening because of uncertainty about whether the nodules would have shown malignant growth at follow-up CT screening, and whether diagnostic work-up would have yielded a diagnosis of lung cancer. Finally, a third of interval cancers were, also in retrospect, not visible at the last screening examination, and thus were not missed, but arose during the interval.

All participants of this study were at substantial risk of developing lung cancer because of the enrolment requirements. Even within this population, older age and being a current smoker were still significant risk factors for development of lung cancer. Notably, only interval cancers were significantly associated with being a current smoker, which might be because continued smoking promotes the development of lung cancer subtypes that grow faster and are less perceptible by low-dose CT screening (e.g., small-cell carcinomas).\textsuperscript{34} This finding reinforces urgency of smoking cessation in individuals receiving lung cancer screening.

Our findings showed that screening-detected lung cancers differed significantly to interval cancers with regards to stage of diagnosis, and histopathology. Differences in tumour characteristics are probably caused by both earlier diagnosis of screen-detected lung cancer as a result of screening asymptomatic individuals, and by the aggressive nature of interval lung cancers compared with detected cancers. In this study, all cancers that developed during the interval (i.e., were not missed at screening) were diagnosed at stage III or IV. Hence, these cancers grew from undetectable to incurable cancers in less than 1 year (five [36\%] of 19) or 2 years (seven [47\%] of 15), suggesting an enormous growth and metastatic potential. This observation is consistent with the finding that these
cancers were significantly more often small cell carcinomas than were interval cancers that did not arise during the screening interval.

In this study, 62% of all lung cancers were diagnosed at stage I, and only 18% were diagnosed at stage IIIB or IV. In the NLST, 59% of lung cancers were diagnosed at stage I, and 23% at stage IIIB or IV, which did not significantly differ from the NELSON trial (p = 0.20). Thus, despite longer screening intervals, slightly lower sensitivity, and fewer female participants (in whom CT screening appeared to detect lung cancer earlier than in males\textsuperscript{35}) in the NELSON trial, lung cancer was diagnosed as early as in the NLST\textsuperscript{7}. This finding is encouraging for effectiveness of lung cancer screening regimens using 2-yearly screening after an initial annual screening round.

CONCLUSION

In conclusion, our findings show that using low-dose CT screening with increasing intervals and stringent diagnostic criteria for a positive result to detect lung cancer gives high specificity and a high sensitivity. The results of this study could be used to improve screening algorithms and reduce the number of missed cancers.
RESEARCH IN CONTEXT

Systematic Review
As part of planning for this trial a systematic review was conducted in PubMed database. To identify all relevant articles on the performance of lung cancer screening test performance and interval cancers, the following search terms were used: “Lung Neoplasms”[Mesh], “Tomography, X-Ray Computed”[Mesh], “Mass screening”[Mesh], “Epidemiologic Study Characteristics as Topic”[Mesh]. In addition, Pubmed was searched for articles on all randomised controlled trials on lung cancer screening by searching for the trial's acronyms. Limits used for all searches: humans, adults; published in English, in core clinical journals or MEDLINE. Titles and abstracts of articles that were identified using these search terms were scanned to select articles relevant for this study. Reference lists of relevant articles were checked to identify more relevant articles.

Interpretation
Compared to the literature, the screening strategy of the NELSON trial performed well. Hence, screening test sensitivity was comparable other studies or slightly lower, the specificity was very high, negative predictive value was as high as in other studies and the positive predictive value was substantially higher. Moreover, lung cancer was as early diagnosed in the NELSON trial as in the NLST, which is a prerequisite for effectiveness.

Only a limited number of studies report on interval cancers in lung cancer CT screening, probably due to low incidence for interval cancers combined with limited sample size of most studies. Our study is the only that reports on radiological characteristics of interval cancers and the causes of the failure to detect interval cancers. In both our study and the literature, observations were made which suggests that interval cancers have different histopathology and are more aggressive than screening-detected lung cancers.
DECLARATION OF INTERESTS

NH, HJdK, CMvdA, KtH, and UAY-K report grants from ZonMw, grants from KWF, grants from Roche diagnostics, and non-financial support from Siemens Germany during the conduct of the study. Additionally, HJdK and KtH report grants from National Cancer Institute or National Institutes of Health and grants from The Agency for Healthcare Research and Quality during the conduct of the study, and grants from Sunnybrook Health Sciences and grants from Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen outside the submitted work. J-WJL reports grants from EU and grants from TiPharma outside the submitted work. KN reports grants from the Belgian Foundation against Cancer and grants from Flemish Cancer Ligue during the conduct of the study. All other authors declare no competing interests.

ACKNOWLEDGEMENTS

We thank M Quak, R Faber, F Santegoets, L van Dongen, and A de Bruijn (Erasmus University Medical Center Rotterdam, Netherlands), H Ziengs (University Medical Center Groningen, Netherlands), A Hamersma and S van Amelsvoort-van de Vorst (University Medical Center Utrecht, Netherlands), and L Peeters (University Hospital Gasthuisberg Leuven, Belgium). Finally, we would like to thank the Dutch Cancer Registry for the data linkages that identified the interval lung cancers. The NELSON trial is supported by Zorg Onderzoek Nederland-Medische Wetenschappen and KWF Kankerbestrijding. Roche diagnostics provided a grant for the performance of proteomics-research. Siemens Germany provided four digital workstations and LungCARE for the performance of 3D-measurements.
REFERENCES


35. Pinsky PF, Church TR, Izmirlian G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer*
Chapter 5

Radiological evaluation

Computed tomographic characteristics of interval and post screen carcinomas in lung cancer screening

Scholten ET*,
Horeweg N*,
de Koning HJ,
Vliegenthart R,
Oudkerk M,
Mali WPTM,
de Jong PA

European Radiology
September 14th 2014

* equal contribution
Computed tomographic characteristics of interval and post-screen cancers in lung cancer screening

_Eur Radiol. 2014 Sep 4 [Epub ahead of print]._

**ABSTRACT**

Objective of this study was to analyse computed tomography (CT) findings of interval and post-screen cancers in lung cancer screening.

Consecutive interval and post-screen cancers from the Dutch-Belgium lung cancer screening trial were included. The prior screening and the diagnostic chest CT were reviewed by two experienced radiologists in consensus with knowledge of the tumour location on the diagnostic CT.

Sixty-one participants (53 men) were diagnosed with an interval or post-screen cancer. Twenty-two (36%) were in retrospect visible on the prior screening CT. Detection error occurred in 20 and interpretation error in 2 cancers. Errors involved intrabronchial tumour (n=5), bulla with wall thickening (n=5), lymphadenopathy (n=3), pleural effusion (n=1), and intra parenchymal solid nodules (n=8). These were missed due to a broad pleural attachment (n=4), extensive reticulation surrounding a nodule (n=1) and extensive scarring (n=1). No definite explanation other than human error was found in two cases (n=2). None of the interval or post-screen cancers involved a sub-solid nodule.

Interval or post-screen cancers that were visible in retrospect were mostly due to detection errors of solid nodules, bulla wall thickening or endobronchial lesions. Interval or post-screen cancers without explanation other than human errors are rare.
INTRODUCTION

Early detection of lung cancer by low dose computed tomography (CT) scanning in asymptomatic smokers at high risk for developing lung cancer is a promising strategy to reduce lung cancer mortality. Several randomised lung cancer screening trials were conducted using low-dose CT scanning of high-risk groups, with the aim to detect lung cancer at an early and curable stage. The National Lung Screening Trial (NLST) reported in 2011 a 20.0% decrease in lung cancer mortality when comparing CT screening with chest radiography screening.

Fast growing tumours, protocol inadequacies and protocol violations and missed cancers on CT may result in an interval cancer. Interval cancers are cancers diagnosed between screening rounds after a negative or indeterminate screening result (defined as no recommendation for referral) or after a positive screen in which diagnostic work-up did not yield the diagnosis of cancer. Interval cancers may be missed or may arise during the screening interval. Missed cancers may be caused by detection and interpretation errors. In detection errors, the lesion is not mentioned in the report but can be seen in retrospect on the last CT. While in interpretation errors, the lesion was noted but considered a benign lesion. Post-screen cancers are lung cancers diagnosed after the last scheduled screening CT of the participant. In this study, interval cancers were distinguished from post-screen cancers; both are subdivided in radiological detection errors, interpretation errors and other causes (e.g. normal screening examination, or non-compliance participant).

Missed cancers in CT-based lung cancer screening trials have received limited attention in radiological literature. In 1999, Kakinuma et al concluded on a study of seven interval cancers, that minute nodules may be missed at spiral CT exams with a slice thickness of 10 mm. Further, Li et al reported in 2002 a study of 32 missed lung cancers in a CT screening setting (using 10-mm slice thickness) that the missed cancers were very subtle, appeared as small faint nodules, and 92% of their 20 detection errors involved sub-solid nodules. Henceforth, many studies were published on Computer Aided Diagnosis (CAD) systems for detection of pulmonary nodules and CT equipment improved substantially.

Purpose of the present study was to analyse CT findings in post-screen and interval cancers of the NELSON trial, focussing on CT findings in cases with radiological detection and interpretation errors. This is the first study reporting on missed lung cancers in a lung cancer screening program using multi-detector CT equipment and thin-slice reconstruction.
METHODS

This is an ancillary study of NELSON trial, which was approved by the Dutch Ministry of Health and ethical boards of participating hospitals. Written informed consent was obtained from each participant. Screening was initiated in 2004. Study population comprised of current and former smokers aged 50 to 75 years, with a smoking history of 15 or more cigarettes per day during more than 25 years, or 10 or more cigarettes per day during more than 30 years. Former smokers were included only if they quit smoking less than 10 years before start of the study. Exclusion criteria were: self-reported moderate or poor health status, inability to climb two flights of stairs, a chest CT within the last twelve months, body weight 140 kg or more, history of lung cancer in the last five years, history of melanoma, breast cancer or hypernephroma, and a previous pneumonectomy.

CT scanning and reading protocol

In participants randomised to the screening group, CT screening was performed at baseline, 1 year and 3 years and 5.5 years after baseline, plus additional follow-up CT exams in case indeterminate nodules were detected. Multi-detector scanners (Somatom Sensation 16, Siemens Medical Solutions, Mx8000 IDT or Brilliance-16, Philips Medical Systems, Cleveland, OH) were used with 16x0.75mm collimation and 1.3 pitch. Unenhanced full inspiration CTs were acquired using 30mAs at 120kVp for subjects weighing 80kg or less, and 30mAs at 140kVp for those weighing more than 80kg. Axial 1.0mm images were reconstructed at 0.7mm increment using a 512x512 matrix, with a moderately soft kernel and the smallest field of view that included both lungs.

All CTs were analysed for non-calcified nodules. Detected nodules were characterised as solid nodule or sub-solid nodule, the latter being either pure or part-solid. At each site, CT data were analysed by the local radiologist with 1 year to more than 20 years of experience with thoracic CT. Subsequently, CT data were independently analyses by a second central reader with more than 6 years of experience. One type of digital workstation (Leonardo, Siemens Medical Solutions) with software for nodule identification and semi-automated volume measurements (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions) was used; its use for nodule detection was not obligatory. After the radiologist marked a potential nodule with a mouse click, the program defines a volume of interest around the nodule which can further be analysed by volume rendering displays or multi-planar reformations. Once a potential nodule was approved, a second mouse-click initiated the automatic volume measurement program. In case of discrepancy, the radiologists tried to reach a consensus about the reading. If no consensus was reached, a third reading was performed by an expert radiologist with over twenty years of experience, who made the final decision.
Participants who were referred to a pulmonologist underwent diagnostic work-up which included a standard dose CT with intravenous contrast, bronchoscopy and/or biopsy. Based on results of these exams, the pulmonologist decided whether resection of the suspicious nodule was appropriate.

Study population
For the present study, all 7,155 participants (1254 females, 16.5%) randomised to the CT screening group of the participating Dutch screening centres (University Medical Center Groningen, University Medical Center Utrecht and Kennemer Gasthuis, Haarlem, The Netherlands) were included. Belgian participants (n=935) had to be excluded as no data on interval cancers were available yet. Median age at baseline of included subjects was 58.0 years (interquartile range (IQR) 54.0-62.0), median number of pack-years was 38.0 (IQR 29.7-49.5), and 4215 participants (55.6%) were current smokers.

Interval and post-screen cancers
Some participants developed lung cancer a considerable time, up to six years, after their last attended screening examination. Since conclusions may be drawn from these cases, they were included in this study. Interval and post-screen cancers were identified through linkages with the Dutch Cancer Registry, which has complete national coverage.

In the first three screening rounds, 187 of the 7,155 (2.6%) included subjects were diagnosed with screen-detected lung cancer. Between or after screening examinations in the NELSON trial, 61 of 7,155 participants (0.85%) were diagnosed with interval or post-screen cancer; 53 men and eight women. Hence, a total of 248 screen-detected-, interval, - and post-screen cancers were diagnosed. Median age of these participants at the time of the diagnosis was 64 years (IQR 6 years).

Of the 61 participants with interval or post-screen cancer, clinical and radiological files were retrieved from the various hospitals where diagnosis of lung cancer was established. Also, their last available screening CT examination was reviewed and compared to the clinical CT at the time of the diagnosis. Two radiologists, one chest radiologist with 10 years of experience, and one general radiologist with over 30 years of experience with chest CT decided in consensus whether or not lung cancer or CT evidence of metastatic disease (such as mediastinal or bone metastases) could in retrospect be identified on the screening CT, and whether it was not mentioned or misinterpreted in the original report in the trial database. Furthermore, significant other pathology that might has influenced the original reading was noted as well. Depending on the findings noted in the trial database, missed cancers were classified as either a detection error or an interpretation error. An error was considered a detection error if no mention of the lesion was found in the trial database and an interpretation error if the lesion was mentioned but the potentially
malignant character not recognized. An attempt was made to formulate reasons why the abnormality was not detected or misinterpreted by the screening radiologists.

Data analysis
Descriptive statistics were used to analyse and present the data.

RESULTS

Based on consensus reading, 26 of 61 cases (42.6%) had a normal last screening CT examination and the screening protocol was not violated. In 11 of these 26 cases (42.3%) the lung cancer was considered an interval cancer as it was diagnosed before the next scheduled screening CT examination, the remaining 15 cases (57.7%) were considered a post-screen cancer as they were diagnosed after the screening program was finished (Table 1).

<table>
<thead>
<tr>
<th>Findings</th>
<th>Interval cancer n (%)</th>
<th>Days since last CT at diagnosis median (range)</th>
<th>Post-screen cancer n (%)</th>
<th>Days since last CT at diagnosis median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening CT examination normal:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol followed</td>
<td>11 (18.0)</td>
<td>425 (169-676)</td>
<td>15 (24.6)</td>
<td>817 (202-2037)</td>
</tr>
<tr>
<td>Cancer not treated due to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol inadequate</td>
<td>1</td>
<td>257</td>
<td>1</td>
<td>349</td>
</tr>
<tr>
<td>False-negative work-up</td>
<td>0</td>
<td>NA</td>
<td>3</td>
<td>815 (68-1140)</td>
</tr>
<tr>
<td>Non-compliance participant</td>
<td>2</td>
<td>(373-461)</td>
<td>6</td>
<td>1805 (1339-2179)</td>
</tr>
<tr>
<td>Cancer not detected due to detection error:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrabronchial localisation</td>
<td>5</td>
<td>367 (232-646)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Adjoining bullous structure</td>
<td>1</td>
<td>358</td>
<td>3</td>
<td>890 (735-1290)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>3</td>
<td>310 (217-436)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1</td>
<td>177</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Extensive fibrotic changes</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>311</td>
</tr>
<tr>
<td>Small pleural attachment</td>
<td>1</td>
<td>581</td>
<td>1</td>
<td>1515</td>
</tr>
<tr>
<td>Large pleural attachment</td>
<td>1</td>
<td>234</td>
<td>1</td>
<td>1089</td>
</tr>
<tr>
<td>Probably human error</td>
<td>0</td>
<td>NA</td>
<td>1</td>
<td>323</td>
</tr>
<tr>
<td>Cancer not detected due to interpretation error:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large nodule classified as scarring</td>
<td>1</td>
<td>192</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Adjoining bullous structure</td>
<td>1</td>
<td>562</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>29 (47.5)</strong></td>
<td><strong>32 (52.5)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: CT = computed tomography; NA = not applicable.
Radiological evaluation

In 13 of 61 cases (21.3%), lung cancer was not diagnosed through screening due to a variety of reasons: participant drop-out (n=8, 61.5%); two (15.4%) were interval cancers and six (46.2%) post-screen cancers. Lung cancer was not diagnosed through screening after a previous false-negative work-up by the pulmonologist (n=3, 23.1%); both were post-screen cancers. In the remaining two of 13 cases (15.4%), the protocol was considered inadequate as it was adhered to but the malignant nodules were not classified as positive. Hence, one 13mm nodule failed to show growth on at follow-up scanning after 3 months (later diagnosed as interval cancer), and another 12 mm nodule was considered stable over a period of three years, but was later on diagnosed as a post-screen cancer.

The remaining 22 of 61 cases (36.1%) were 15 interval cancers and 7 post-screen cancers; the radiological abnormality was either not detected (in 20 cases) or misinterpreted (in 2 cases). These 22 cases were 0.31% of the total study population of 7,155 participants, and 8.9% of 248 lung cancers.

Table 2. Characteristics of participants with 22 missed lung cancers

<table>
<thead>
<tr>
<th>Participant characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis - median (range)</td>
<td>64.0 yrs (56-76 yrs)</td>
</tr>
<tr>
<td>Male gender</td>
<td>21 (95.5)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>15 (68.1)</td>
</tr>
<tr>
<td>Pack-years - median (range)</td>
<td>49.5 (28.0-123.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Computed tomography characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour size at diagnosis</td>
<td></td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>11 (50.0)</td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>10 (45.5)</td>
</tr>
<tr>
<td>Not measurable</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Tumour localisation</td>
<td></td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Right upper lobe</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>Middle lobe</td>
<td>1 (4.5)</td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Tumour type</td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td>17 (77.3)</td>
</tr>
<tr>
<td>Non-solid</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Bulla wall thickening</td>
<td>5 (22.7)</td>
</tr>
<tr>
<td>Underlying lung disease</td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>1 (4.5)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: yrs = years.*

In 13 of 61 cases (21.3%), lung cancer was not diagnosed through screening due to a variety of reasons: participant drop-out (n=8, 61.5%); two (15.4%) were interval cancers and six (46.2%) post-screen cancers. Lung cancer was not diagnosed through screening after a previous false-negative work-up by the pulmonologist (n=3, 23.1%); both were post-screen cancers. In the remaining two of 13 cases (15.4%), the protocol was considered inadequate as it was adhered to but the malignant nodules were not classified as positive. Hence, one 13mm nodule failed to show growth on at follow-up scanning after 3 months (later diagnosed as interval cancer), and another 12 mm nodule was considered stable over a period of three years, but was later on diagnosed as a post-screen cancer.

The remaining 22 of 61 cases (36.1%) were 15 interval cancers and 7 post-screen cancers; the radiological abnormality was either not detected (in 20 cases) or misinterpreted (in 2 cases). These 22 cases were 0.31% of the total study population of 7,155 participants, and 8.9% of 248 lung cancers.
Missed endobronchial abnormalities

In 5 of the 22 (22.7%) cases wherein the abnormality was not detected or misinterpreted, a central intra-bronchial tumour was overlooked on the screening examination. All were small, although difficult to measure, estimated to be about 5 mm (Figure 1). Four of the endobronchial tumours were right-sided: two localised in the pectoral segmental bronchus, one in the lateral segmental bronchus, and one in the right upper lobe bronchus. One endobronchial tumour was localised left at the lingular bronchus. In one of the cases, a note was made that lymphadenopathy was present, but no further action was taken. All five cancers were classified as interval cancers. Median number of days since the last screening CT at the time of diagnosis was 367 days (range 232-646).

Figure 1. Example of missed endobronchial lung cancer

Narrowing of right upper lobe segmental bronchus (arrows).

Missed focal bulla wall thickenings

In 5 of 22 cases (22.7%), a bulla with a thickening of the wall was noted during the consensus meeting that was not reported in the database. In four of these cases, the thickening of the wall was already visible at the first screening CT examination. In one case, the bulla with wall thickening developed in a previously normal lung. The five lesions were evenly distributed over the lungs: two in the right upper lobe, and one in the left upper lobe, right lower lobe and left lower lobe. In two cases the wall thickening was focal; in one of these cases a 7 mm nodule was noted in the trial database, so this was considered an
interpretation error as no mention was made about the adjoining bulla (Figure 2). Of the five lung cancers, two were classified as interval cancers and three as post-screen cancers; the latter were all detected more than two years after the last screening CT.

Figure 2. Example of missed lung cancer in bulla wall

Small (7 mm) elliptical nodule in bulla wall (arrow).

Missed lymphadenopathy
In 3 of 22 cases (13.6%), lymphadenopathy was missed: two were localised in a slightly enlarged right hilum, in which it was without intra venous contrast inseparable from the right pulmonary artery. One was mainly localised in the aortopulmonary window, maximal diameter was 22 mm. All three cases were classified as interval cancers. Time since the last screening CT at the time of diagnosis was 217, 310 and 436 days.

Missed pleural effusions
In one of 22 cases (4.5%), right-sided pleural fluid remained unnoticed on the screening CT examination. An interval cancer was diagnosed 177 days after the last CT, presenting as a large carcinoma with massive pleural effusions.
Missed cancers due to other reasons

The remaining 8 of 22 cases (36.4%) were not detected due to various causes. Small nodule size might have played a role in three cases, as small nodules of 7, 7 and 5 mm were not detected. However, two of these nodules were also attached to the pleura, which may also have played a role (delay of diagnosis were 581 days for the interval cancer, and 1515 days for the post-screen cancer). One nodule was surrounded by extensive reticulation (Figure 3), which probably caused the detection error (delays of diagnosis of this post-screen cancer was 311 days).

Further, five larger (>1 cm) nodules were also not detected: two in the left lower lobe, and one in the left upper lobe, right upper lobe and right lower lobe. Three of these large nodules were classified as an interval cancer, two as a post-screen cancer. One of these five nodules was a 22 mm-large pleural-attached nodule that was interpreted by the screening radiologists as scarring (Figure 4); consequently this lung cancer was considered missed due to interpretation error. Two of five lesions were broadly pleural-based (Figure 5). Two other of the five larger nodules were not attached to the pleura. As no obvious reason for not detecting these lesions was found, these detection failures were attributed to human error. Median number of days since the last CT at the time of diagnosis was 234 days (range 96-1089) for the five larger nodules.

Figure 3. Example of missed lung cancer due to distractive other pathology
Small nodule in left under lobe hidden in reticulation (arrow).
Figure 4. Example of missed lung cancer due to interpretation error

*Image suggestive of lung cancer, but interpreted as fibrotic scarring.*

Figure 5. Example of missed lung cancer attached to the pleura

*Prevertebral broad-based tumour on the right (arrows).*
DISCUSSION

In this study, the radiological characteristics and causes of the failure to detect interval cancers and post-screen cancers in the NELSON trial were investigated. The majority of the 61 (n=39, 64%) interval and post-screen cancers were not due to radiological detection or interpretation errors. A minority of 22 (36%) cancers was visible in retrospect at the last screening examination and missed. Most missed cancers were due to detection errors of a nodule either localised in a bronchus, attached to a bulla or sub-pleural in the lung parenchyma. According to the protocol, these nodules (with possibly exception of the bulla wall thickening) should have been followed up by either a repeat CT scan after three months or by referral to a pulmonologist for further evaluation. Interpretation errors seemed to have played a minor role in missed lung cancers. Findings of this study may aid improving lung cancer detection in lung cancer screening, although the predictive value of some findings, especially bulla wall thickenings, need to be determined yet.

Limited number of studies have been published on interval, - and post-screen cancers in a CT-based lung cancer screening setting. In contrast to the findings of Li et al.10, who reported in 2002 that 92% of their missed cancers were non-solid, none of the missed nodules were part or pure non-solid. This can at least partly be explained by the considerable difference in spatial resolution of the 1 mm slice thickness used in the NELSON study, compared to the 10 mm slice thickness in the study by Li et al.10 However, since sub-solid nodules may grow very slowly, it cannot be excluded that an interval cancer arising from a sub-solid nodule will manifest in a longer follow-up period.

In this study, the most common detection error was missing endobronchial lesions. This is probably because endobronchial nodules are far less common in a screening population than intraparenchymal nodules. As a result, attention of screening radiologists was probably primarily focused on the lungs and not the bronchi. This is not compensated by the CAD-system its search for nodules does not include the bronchi. In 1996, White et al.20 reported on 14 primary lung cancers overlooked on CT in a clinical setting; 67% were at a central endobronchial location.20 White et al. gave a similar explanation, not focusing on central airways, for detection error in their series. Another important factor at the time of their study was the use of 5 mm or even thicker sections. Computer Aided Diagnosis of lung cancer in the bronchi has had considerable attention in the literature21 and as a training tool.22 Extension of lung cancer detection CAD systems to the bronchi may prove helpful in reducing these detection errors. However, until this extension is realised extra focus on the bronchial tree is warranted.

Another common characteristic of missed lung cancers was a thickened bulla wall. This entity was not recognised as an important abnormality at the start of the NELSON screening trial in 2004. Therefore, bulla wall thickenings were not a pre-defined abnormality in the nodule management system. In 2010, Keneda et al.23 described clinical features of
primary lung cancer adjoining bullae. In their retrospective study of 545 clinical cases who underwent surgery for lung cancer, they identified an adjoining bulla in 19 cases (3.5%)\(^2\), which suggests that this finding is not uncommon. Keneda et al. also state that the association of bullae and lung cancer is not well recognised. This was confirmed in this study, as it was identified as one of the main causes for detection errors. Hence, in one of five cases with nodular thickening in the wall of a bulla the abnormality was noted and its nodule features were described in the database, but no mention was made of the adjoining bulla. In 2012, Farooqi et al. reported on lung cancers associated with cystic airspaces in the Early Lung Cancer Action Program.\(^2\) They found that in their baseline and annual screening series respectively 25% and 12% of lung cancers were associated with cystic airspaces. They concluded that the finding of an isolated cystic air space with increased wall thickness at annual repeat CT screening is suspicious for lung cancer. Since no data on the prevalence of bulla wall thickening in the NELSON population was collected, no positive predictive value of this finding can be estimated. However, findings of this study justify increased attention to focal and diffuse bulla wall thickenings in lung cancer screening.

Intraparenchymal nodules were, with 8 cases (36%), the most common cause for a missed cancer. Two smaller and two larger lesions were probably missed by the screening radiologist due to pleural-attachment or a broad shape. One case of these cases was interpreted as fibrotic scarring, which was classified as an interpretation error. White et al.\(^2\) reported in a clinical series of 14 primary lung cancers overlooked on CT that 6 of 14 cases (43%) were due to major distractive findings elsewhere in the chest, such as aortic aneurysm or large oesophageal tumour. In the current study, similar cases were not common. Only one lesion was missed due to extensive reticulation in its immediate surroundings. In two cases of a missed large intrapulmonary nodule no plausible reason other than human error could be found.

Lymphadenopathy is more difficult to detect on low-dose screening CTs without intravenous contrast than on clinical contrast enhanced CT’s. Moreover, the screening radiologist’s focus is primarily on the lungs, and significant lymphadenopathy uncommon compared to in a clinical setting. Concluding, missed lymphadenopathy, which was responsible for 13.6% of missed lung cancers, is probably difficult to prevent.

The most important limitation of this study was the lack of data on the prevalence of abnormalities such as bulla wall thickening. As a result, it is not possible to determine the positive predictive value of the characteristics of missed lung cancers. This problem may be resolved as screening programs check the CT for abnormalities such as bulla wall thickenings, and report them as a separate item. Another limitation was that the total number of cancers found in the NELSON study is not known at present, so this number cannot be related to the number of interval cancers. However, this study suggests that interval-, or post-screen cancers due to human errors were rare, as it only concerned 0.31%
of the total screen population. A third limitation is the inherent focus on cancers not detected by screening. Performing the same analysis of cancers found in during screening may learn whether and how screen-detected cancers can be detected in earlier screening rounds. Finally, limited experience of some screening radiologists with thoracic CT could have been a limitation of the study. However, this is not supported by a previous study on the benefit of consensus double reading in screening for lung cancer.25

In conclusion, interval-, and post-screen cancers in the NELSON trial that were visible in retrospect, were mostly due to detection errors of solid nodules. Thickening of a bulla wall should be looked at with suspicion, at least until more of the natural course of such lesions is known. Detection of endobronchial lesions might improve with extension of CAD systems to the bronchi.
SUPPORT STATEMENT


CONFLICTS OF INTEREST

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.
REFERENCES


Part III

Optimisation of screening
Chapter 6

Optimisation of screening protocols

Lung cancer probability in subjects with CT-detected pulmonary nodules: an analysis of data from the NELSON trial of low-dose CT screening


*Lancet Oncology
November 2014

*equal contribution
Lung cancer probability in subjects with CT-detected pulmonary nodules: an analysis of data from the NELSON trial of low-dose CT screening

*Lancet Oncol. 2014 Nov;15(11).*

**ABSTRACT**

The main challenge in CT screening for lung cancer is the high prevalence of pulmonary nodules and the relatively low incidence of lung cancer. Management protocols use thresholds for nodule size and growth rate to determine which nodules require additional diagnostic procedures, but these should be based on individuals’ probabilities of developing lung cancer. In this retrospective analysis, using data from the NELSON CT screening trial, we aimed to quantify how nodule diameter, volume, and volume doubling time affect the probability of developing lung cancer within two years of a CT scan, and to propose and evaluate thresholds for management protocols.

Eligible participants in the NELSON trial were those aged 50–75 years, who have smoked 15 cigarettes or more per day for more than 25 years, or 10 cigarettes or more for more than 30 years and were still smoking, or had stopped smoking less than 10 years ago. Participants were randomly assigned to low-dose CT screening at increasing intervals, or no screening. We included all participants assigned to the screening group who had attended at least one round of screening, and obtained data on lung cancer diagnoses from the national cancer registry database. We calculated lung cancer probabilities, stratified by nodule characteristics, by nodule diameter, volume and volume doubling time and did logistic regression analysis using diameter, volume, volume doubling time, and multinodularity as potential predictor variables. We assessed management strategies based on nodule threshold characteristics for specificity and sensitivity, and compared them to the American College of Chest Physicians (ACCP) guidelines.

Volume, volume doubling time and volumetry-based diameter of 9,681 non-calcified nodules detected by CT screening in 7,155 of 7,915 participants in the screening group of NELSON were used to quantify lung cancer probability. Lung cancer probability was low in participants with a nodule volume of 100 mm³ or smaller (0.6% [95% CI 0.4-0.8%] or maximum transverse diameter smaller than 5 mm (0.4% [CI 0.2-0.7%]), and not significantly different from participants without nodules (0.4% [0.3–0.6], p = 0.17 and p = 1.00, respectively. Lung cancer probability was intermediate if nodules had a volume of 100-300 mm³ (2.4% [1.7-3.5%]), or a diameter 5-10 mm (1.3% [1.0-1.8%]). Volume doubling time further stratified the probabilities: 0.8% (95% CI 0.4-1.7%) for volume doubling times of 600 days or more, 4.0 (1.8–8.3%) for volume doubling times 400-600 days, and...
9.9% (95% CI 6.9-14.1%) for volume doubling times of 400 days or fewer. Lung cancer probability was high for participants with nodule volumes 300 mm³ or bigger (16.9% [95% CI 14.1-20.0%]) or diameters 10 mm or bigger (15.2% [12.7-18.1%]), even if these nodules had long volume doubling times. The simulated ACCP management protocol yielded a sensitivity and specificity of 90.9% (95% CI 89.3-90.7), and 87.2% (86.4-87.9) respectively. A diameter-based protocol with slightly adjusted thresholds (based on lung cancer probability) yielded a higher sensitivity (92.4% [95% CI 83.1-97.1]), and a higher specificity (90.0% [81.2-96.1]). A volume-based protocol (with thresholds based on lung cancer probability) yielded the same sensitivity as the ACCP protocol (90.9% [95% CI 81.2-96.1]), and a very high specificity (94.9% [94.4-95.4]).

Small nodules (those with a volume <100 mm³ or diameter <5 mm) are not predictive for lung cancer. Immediate diagnostic evaluation is necessary for large nodules (≥300 mm³ or ≥10 mm). Volume doubling time assessment is advocated only for intermediate-sized nodules (with a volume ranging between 100–300 mm³ or diameter of 5–10 mm). Nodule management protocols based on these thresholds performed better than the simulated ACCP nodule protocol.

INTRODUCTION

Several prominent medical associations have recommended regular low-dose CT screening for subjects at high risk of developing lung cancer.1-2 The main challenge faced by clinicians doing CT screening for lung cancer is that about half of people screened have one or more pulmonary nodules, but only a small percent of these people either have lung cancer.3,4 Validated guidelines to determine optimum patient management strategies based on characteristics of detected nodules are urgently needed.

At first, the accepted standard of practice was to regard all non-calcified pulmonary nodules detected at CT as potentially malignant lesions requiring follow-up screening until proven stable for a period of 2 years.5,7 Later, the Fleischner Society recommended that nodules of 4 mm or smaller in diameter in high-risk people required no further follow-up if the nodule was unchanged at a 12-month follow-up examination, because the risk of the nodule being malignant was less than 1%.8 However, people with nodules 4-8 mm in size were still recommended to undergo two to three follow-up examinations over a period of 2 years. Individuals with nodules larger than 8 mm were recommended to undergo diagnostic work-up, which consisted of more invasive diagnostic procedures.8 Recently, the results of the Early Lung Cancer Action Project (ELCAP)9 - which suggested raising of the threshold for initiation of follow-up CT examinations to nodules of 8 mm or larger - were reproduced with data from the National Lung Screening Trial (NLST).10 However, the ELCAP analyses were limited to screen detected lung cancers, and only
false-positive values and time to diagnosis were taken into account when assessing new
thresholds for nodule diameter.

Increasing the protocol-screening thresholds for nodule diameter to determine which
patients should undergo diagnostic follow-up reduces the potential harms of diagnostic
procedures, exposure to ionising radiation, and costs.\textsuperscript{11,12} However, it might also decrease
the sensitivity for cancerous nodules, thus, in turn, increasing lung cancer mortality, and
so it is important to balance these potential benefits and harms.\textsuperscript{4} Therefore, thresholds
for negative, indeterminate, and positive screening results should be based on probability
of individual participants’ developing lung cancer, and should be assessed in terms of
sensitivity, specificity, number of required CT examinations, and number of required
invasive diagnostic procedures.

Recommendations of the latest American College of Chest Physicians (ACCP) guidelines for management of individuals with pulmonary nodules with a volume of 8 mm\textsuperscript{3} or larger were based on the consensus statement of the Fleischner Society.\textsuperscript{8} This statement has not been formally validated, and alternative management strategies might yield an improved performance in terms of sensitivity, specificity, and the number of required follow-up scans.

The NELSON trial is a randomised trial to assess whether low-dose CT screening with
an increasing length of screening interval (1, 2, and 2.5 years) compared with no screening
reduces lung cancer mortality.\textsuperscript{15} We used data from NELSON to quantify the probability
of developing lung cancer within two years of CT screening, based on measurements
of lung nodule diameters, volumes, and volume doubling times. We used lung cancer
probabilities to assess the nodule management protocol recommended by the ACCP, and
to propose improved management protocols.\textsuperscript{8,13}

METHODS

Study design and participants
Details about the design and conduct of the NELSON trial have been reported previously.\textsuperscript{15,16} Briefly, participants from four centres in the Netherlands and Belgium were enrolled and randomly assigned to receive low-dose CT screening or no screening. Eligible participants were adults aged 50–75 years, who had smoked 15 or more cigarettes per day for more than 25 years or ten or more cigarettes per day for more than 30 years, and were still smoking or had stopped smoking less than 10 years previously. People with self-reported moderate or bad health, inability to climb two flights of stairs, bodyweight of 140 kg or more, current or past renal cancer, melanoma, breast cancer, or lung cancer diagnosed less than 5 years ago, or a chest CT examination less than 1 year ago, were excluded.
All participants who were diagnosed with lung cancer were identified from the national cancer registries of the Netherlands. We included all Dutch participants who were randomly assigned to the screening group, who had attended at least one round of screening in the first two screening rounds at baseline and one year later. We excluded Belgian participants because data about interval cancers were not yet available from the Belgian cancer registry; interval cancers from Dutch participants were identified with use of the Dutch Cancer Registry.

Procedures

The protocol describing how CT screening was done in the NELSON trial has been previously published, and is summarised in the appendix. Briefly, CT screening was done with 16-detector CT scanners in a low-dose setting (effective radiation dose <0.4 mSv, <0.8 mSv and <1.6 mSv, dependent on bodyweight). Datasets were derived from images of the thorax (slice thickness 1 mm, interval 0.7 mm) and analysed with software for semi-automated volume measurements (LungCARE, Somaris/5 VB 10A-W, Siemens).

For any CT screen-detected non-calcified nodules, semi-automatic volumetric software independently then measured volume and maximum transverse diameter [A: please confirm edits correct?]. Hence, the diameters used in this study were not measured manually. In cases in which no volume (V) could be assessed (e.g., in non-solid nodules), volume was estimated with use of a manually measured diameter (D), assuming a spherical shape of the nodule with the formula:

$$V = \frac{1}{6} \pi D^3$$

When diameter was missing, it was estimated with the inverse of this formula. We calculated volume doubling time for the first and second round for all nodules detected on at least two scans. For the assessment of lung cancer probability by volume doubling time and the volume-based nodule protocol, we used the formula:

$$VDT = \frac{\ln(2) \Delta t}{\ln(V_2) - \ln(V_1)}$$

in which Δt represents time in days between scans. The volume doubling times of all nodules detected in round one and the newly detected nodules in round two were calculated with the volumes measured on the regular round scan (V₁) and the follow-up scan (V₂). The volume doubling times of nodules in round two that had also been detected at baseline were calculated with volumes measured on the baseline scan (V₁) and the second round scan (V₂). For the evaluation of the diameter-based nodule protocols, the following formula for volume doubling time was used:
in which Δt represents time in days between scans, and MaxDiamXY1 and MaxDiamXY2 are maximum diameters on the X-Y axis at first and second assessment. All analyses were done at the participant level; for participants with more than one nodule, we used the size of the largest nodule and volume doubling time of the fastest growing nodule (of 50–500 mm³).

Using these findings we calculated probabilities of developing lung cancer, stratified by nodule characteristics. Two-year probability was chosen because it is the recommended follow-up time for indeterminate nodules. We predicted lung cancer risk in the two years following each screening round using regression analysis with nodule characteristics as potentially predictive variables. Based on these outcomes, we designed nodule management protocols for both nodule volume and diameter. Participants without nodules or with a lung cancer probability not significantly different from those without nodules were classified as negative, and were not recommended undergoing intensified CT surveillance besides screening. Participants with a significantly increased lung cancer probability (but less than about 5%; adopted from ACCP guideline) were classified as indeterminate, and were recommended to undergo CT surveillance to assess nodule growth; if lung cancer probability based on volume doubling time was significantly higher than in participants without nodules, the final result was classified as positive, otherwise, it was classified as negative. Participants with a lung cancer probability of more than 5% were directly classified as positive, and recommended to undergo additional diagnostic procedures immediately (adopted from ACCP guideline for nodules with a 5% to 65% risk of malignancy). Furthermore, the ACCP management protocol (originally designed for manually measured nodules) was simulated as follows: follow-up CT at 12 months for nodules 4 mm or smaller (classified as negative); follow-up CT at 6-12 months and 18-24 months for nodules 4-8 mm in size (classified as indeterminate; final result positive for volume doubling times <400 days, otherwise negative); and additional diagnostic procedures for nodules larger than 8 mm (classified as positive).

Outcomes
The primary endpoint of the NELSON trial is reduction of lung cancer mortality by 25% or more at 10 years after randomisation. The primary aim of this study was to quantify the probability of developing lung cancer within two years after the screening round, stratified by measured nodule diameters, volumes, and volume doubling times. The secondary aims were to model lung cancer risk using predictive variables, and to propose and assess thresholds for nodule management protocols.

\[
VDT = \frac{\ln(2) \Delta t}{3 \ln(\frac{\text{MaxDiamXY}_2}{\text{MaxDiamXY}_1})}
\]
Statistical analysis

Probabilities of developing lung cancer stratified by different nodule variables were calculated by the number of cases with cancer by the total number of cases per stratum. Differences between lung cancer probabilities were tested using with Fisher’s exact test; 95% CIs were calculated using the Agresti-Coull method.

To predict lung cancer risk in the two years after each screening round, we did logistic regression analysis using diameter, volume, volume doubling time, and multinodularity as potential predictor variables. The model only included participants whose largest nodule measured 50–500 mm³ and who had one nodule or more growing in this volume range, because volume doubling time was available only for this subgroup. We accounted for non-linear effects of the predictor variables using fractional polynomials. For each predictor variable, we included two terms of the form $X^K$, with the value of $K$ chosen from the set $(-2, -1, -0.5, 0, 0.5, 1, 2, 3)$; $X^0$ denoted a logarithmic transformation. The predictor variables in the final model and the non-linear transformations were chosen with backward elimination with a significance level of 5%, on the basis of the multivariable fractional polynomials algorithm. We used a closed-test procedure to control the family-wise type I error rate in a situation with multiple testing. The calibration of the model was assessed with the Hosmer-Lemeshow test.

We estimated test characteristics of all three nodule management protocols using the detection method with a 1-year interval plus all lung cancers detected in the same screening round (details provided in the Appendix). Hence, we estimated sensitivity by dividing the number of true-positive screens by the numbers of true-positive and false-positive screens. We estimated specificity by dividing the number of true-negative screens by the numbers of true-negative and false-negative screens. We estimated positive predictive value by dividing all individuals with a true-positive screening by all individuals with positive screening. We estimated negative predictive value by dividing all participants with a true negative screening by all participants with negative screening (more details provided in the Appendix).

All statistical tests were two-sided, used a significance level of 5%, and were done with Stata (version 12), R (version 2.15), and Microsoft Excel (2010).

RESULTS

Participants

A total of 15,822 participants were enrolled in the NELSON trial between Dec 23, 2003, and July 6, 2006. Screening round one was conducted from Jan, 2004 to Dec, 2006, and screening round two from Jan, 2005 to Sept, 2008. For this study, we excluded 7,907 participants randomly assigned to the no screening group, 477 participants from Belgium
(no data were yet available from the Belgian Cancer Registry), and 283 participants who
did not attend their screening examinations (no screening test characteristics could be
calculated in the absence of screening). Thus, we included 7,155 participants in our
study; 7,135 of whom received screening at the first screening round, and 6,889 of whom
received screening at the second screening round (Figure 1).

Median length of available follow-up of the participants was 8.16 years (IQR 7.56-8.56).
Median age was 58 years (IQR 50-66). 1,206 (16%) of 7,438 participants were women,
6,232 (84%) were men, 4165 (56%) were current smokers, and their median number of
pack-years at randomisation was 38 (IQR 19-57).

**Figure 1. Participant flowchart**

Screening round one was conducted from January 2004 to December 2006 and screening round two from January

* 20 Dutch participants missed the baseline CT due to late returning of their informed consent.
† 283 Dutch participants were randomised but did not respond to the invitation for the baseline CT.
‡ 27 Dutch participants missed the second round CT, but were screened in the third round due to: participant
declined (n = 3), participant unattainable or repeated no show (n = 16), still in diagnostic work-up round one
(n = 3), administrative error (n = 5). The remaining 239 Dutch participants underwent no screening in the
second round due to lung cancer (n = 61), death (n = 25), participant declined (n = 110), participant unattain-
able or repeated no show (n = 42), still in diagnostic work-up round one (n = 1).
Quantifying lung cancer probability

Two-year lung cancer probability for all included participants was 1.3% (95% CI 1.2-1.5, Table 1). Participants without any pulmonary nodule (7,630 [54%] of 14,024 screenings in rounds one and two combined) had a lung cancer probability of 0.4% (95% CI 0.3-0.6). In all participants with CT-detected nodules, lung cancer probability was 2.5% (95% CI 2.1-2.9%), but individuals’ probabilities depended strongly on nodule volume, diameter and volume doubling time (Table 1).

We used volume, volume doubling time, and volumetry-based diameter of 9,681 non-calcified nodules detected by CT screening in 7,155 participants in the screening group of NELSON to quantify lung cancer probability (Table 1). Lung cancer probability did not significantly differ between participants who had nodules of less than 100 mm³ in volume and participants who had no detected nodules (0.6% [95% CI 0.4-0.8%] vs. 0.4% [95% CI 0.3-0.6], p=0.17. Participants who had nodules between 100-300 mm³ had a significantly greater probability of developing lung cancer compared to participants with no screening-detected nodules (2.4% [95% CI 1.7-3.5%], p <0.0001) and so these participants could be regarded as being at intermediate risk for developing lung cancer. Participants who had nodules of 300 mm³ or more also had a significantly greater probability of developing lung cancer compared to participants with no nodules (16.9% [95% CI 14.1-20.0%], p <0.0001 and so can be regarded at as a high risk of developing lung cancer.

We noted slightly different thresholds for volumetry-based nodule diameter (Table 1). Lung cancer probability was not significantly increased in participants whose nodules measured less than 5 mm compared with those with no nodules (0.4% [95% CI 0.2-0.7%] vs. 0.4% [0.3-0.6], p = 1.00, but was significantly increased for participants whose nodules measured 5-10 mm (1.3% [95% CI 1.0-1.8%], p <0.0001, and participants whose nodules measured 10 mm or more (15.2% [95% CI 12.7-18.1%], p <0.0001, who could be regarded at being at intermediate and high risk of developing lung cancer, respectively.

The probability of being diagnosed with lung cancer within two years after CT scan according to nodule volume doubling time for the participants whose largest nodule measured 50-500 mm³ is presented in Table 1. Participants with slowly-growing (volume doubling time ≥600 days), stable, shrunken, or resolved nodules had a low probability of lung cancer (0.0% to 1.0%). Lung cancer probability was not significantly increased for participants with nodule volume doubling times of 600 days or more (0.8% [95% CI 0.4-1.7], p = 0.06. Lung cancer probability was significantly increased for participants with nodule volume doubling times of times 400-600 days (4.0% [95% CI 1.8-8.3%], p <0.0001, who could be regarded at low risk of developing lung cancer, and for participants with a nodule volume doubling time of 400 days or, fewer (9.9% [95% CI 6.9-14.1%], p <0.0001, who could be regarded at high risk of developing lung cancer.

Probabilities of developing lung cancer according to other categories of nodule volume and volume doubling time (such as stable, shrinking, and resolving nodules) were done,
Table 1a. Probability of lung cancer diagnosis within two years after a screening test, by volume of largest nodule

<table>
<thead>
<tr>
<th>Volume of largest nodule in mm³†</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Rounds 1 and 2</th>
<th>Lung cancer probability†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases n</td>
<td>All n</td>
<td>Cases n</td>
<td>All n</td>
</tr>
<tr>
<td>≥1000</td>
<td>36</td>
<td>137</td>
<td>26</td>
<td>104</td>
</tr>
<tr>
<td>750 - 1000</td>
<td>8</td>
<td>33</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>500 - 750</td>
<td>8</td>
<td>63</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>300 - 500</td>
<td>12</td>
<td>101</td>
<td>6</td>
<td>102</td>
</tr>
<tr>
<td>200 - 300</td>
<td>9</td>
<td>127</td>
<td>5</td>
<td>116</td>
</tr>
<tr>
<td>100 - 200</td>
<td>6</td>
<td>428</td>
<td>7</td>
<td>440</td>
</tr>
<tr>
<td>50 - 100</td>
<td>6</td>
<td>800</td>
<td>6</td>
<td>843</td>
</tr>
<tr>
<td>25 - 50</td>
<td>6</td>
<td>961</td>
<td>4</td>
<td>1,008</td>
</tr>
<tr>
<td>&lt;25</td>
<td>3</td>
<td>539</td>
<td>2</td>
<td>515</td>
</tr>
<tr>
<td>No nodule detected</td>
<td>15</td>
<td>3,946</td>
<td>15</td>
<td>3,684</td>
</tr>
<tr>
<td>All participants</td>
<td>109</td>
<td>7,135</td>
<td>79</td>
<td>6,889</td>
</tr>
</tbody>
</table>

Definition of abbreviation: 95%CI = 95% confidence interval; ref = reference value.

† Volume of the largest non-calcified nodule in a participant in mm³, the interval includes the lower limit, not the upper limit.

‡ Probability of malignancy within two years after a CT scan. The difference in lung cancer risk with subjects without nodules was evaluated using Fisher’s exact test.

Table 1b. Probability of lung cancer diagnosis within two years after a screening test, by volumetry-based diameter of largest non-calcified nodule

<table>
<thead>
<tr>
<th>Max. diameter of largest nodule†</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Rounds 1 and 2</th>
<th>Lung cancer probability†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases n</td>
<td>All n</td>
<td>Cases n</td>
<td>All n</td>
</tr>
<tr>
<td>≥30</td>
<td>3</td>
<td>10</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>20 - 30</td>
<td>13</td>
<td>52</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>15 - 20</td>
<td>22</td>
<td>84</td>
<td>7</td>
<td>64</td>
</tr>
<tr>
<td>10 - 15</td>
<td>28</td>
<td>229</td>
<td>21</td>
<td>213</td>
</tr>
<tr>
<td>8 - 10</td>
<td>7</td>
<td>260</td>
<td>9</td>
<td>296</td>
</tr>
<tr>
<td>7 - 8</td>
<td>8</td>
<td>327</td>
<td>4</td>
<td>328</td>
</tr>
<tr>
<td>6 - 7</td>
<td>1</td>
<td>371</td>
<td>2</td>
<td>331</td>
</tr>
<tr>
<td>5 - 6</td>
<td>7</td>
<td>628</td>
<td>5</td>
<td>721</td>
</tr>
<tr>
<td>4 - 5</td>
<td>3</td>
<td>799</td>
<td>1</td>
<td>776</td>
</tr>
<tr>
<td>&lt;4</td>
<td>2</td>
<td>429</td>
<td>3</td>
<td>431</td>
</tr>
<tr>
<td>No nodule detected</td>
<td>15</td>
<td>3,946</td>
<td>15</td>
<td>3,684</td>
</tr>
<tr>
<td>All participants</td>
<td>109</td>
<td>7,135</td>
<td>79</td>
<td>6,889</td>
</tr>
</tbody>
</table>

Definition of abbreviation: 95%CI = 95% confidence interval; ref = reference value.

† Maximum diameter of the largest nodule in a participant in mm, the interval includes the lower limit, not the upper limit. Estimates based on diameters assessed using semi-automated volumetry. Manually measured diameters are less accurate and will overestimate nodule size, which corresponds with lower lung cancer probabilities than presented in this table.

‡ Probability of lung cancer within two years after a CT scan. The difference in lung cancer risk with subjects without nodules was evaluated using Fisher’s exact test.
but did not significantly differ from the findings above. Lung cancer probability according to few categories of nodule volume and VDT is provided in Table 1 of the Appendix.

### Predicting lung cancer probability

We did logistic regression analyses to predict lung cancer probability: nodule diameter, volume, volume doubling time and multinodularity were used as potential predictors. All four candidate predictors were significant univariate predictors (data not shown). Nodule volume, nodule volume doubling time (Table 2 in Appendix), and multinodularity (Table 3a-b in Appendix) were also significant multivariate predictors. However, the relationship between multinodularity and lung cancer risk was ambiguous: for those participants whose nodules were growing and measured 50-500 mm³, the relative proportion of participants with lung cancer decreased as the numbers of nodules per participant increased (Figure 1a in Appendix). However, in the total study population, the proportion of lung cancers varied as the amount of nodules per participant increased (Figure 1b in Appendix). Therefore, we thought it appropriate to do further studies to

---

**Table 1c. Probability of lung cancer within two years by VDT of fastest growing nodule**

<table>
<thead>
<tr>
<th>VDT of fastest growing nodule in days†</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Rounds 1 and 2</th>
<th>Lung cancer probability+</th>
<th>percentage (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases n</td>
<td>All n</td>
<td>Cases n</td>
<td>All n</td>
<td>Cases n</td>
<td>All n</td>
</tr>
<tr>
<td>&lt;100</td>
<td>7 24</td>
<td>2 10</td>
<td>9 34</td>
<td>26.5 (14.4-43.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>100 - 200</td>
<td>3 40</td>
<td>3 16</td>
<td>6 56</td>
<td>10.7 (4.7-21.8)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>200 - 400</td>
<td>5 130</td>
<td>7 52</td>
<td>12 182</td>
<td>6.6 (3.7-11.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>400 - 600</td>
<td>3 92</td>
<td>4 81</td>
<td>7 173</td>
<td>4.0 (1.8-8.3)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>600 - 800</td>
<td>0 56</td>
<td>0 74</td>
<td>0 130</td>
<td>0.0 (0.0-3.4)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>800 - 1000</td>
<td>0 45</td>
<td>1 63</td>
<td>1 108</td>
<td>0.9 (0.0-5.6)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>≥1000</td>
<td>5 171</td>
<td>2 542</td>
<td>7 713</td>
<td>1.0 (0.4-2.1)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Smaller or equal volume on 2nd CT</td>
<td>3 476</td>
<td>3 430</td>
<td>6 906</td>
<td>0.7 (0.3-1.5)</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Resolved on 2nd CT</td>
<td>0 135</td>
<td>0 70</td>
<td>0 205</td>
<td>0.0 (0.0-2.2)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>No follow-up CT, not referred</td>
<td>4 281</td>
<td>0 155</td>
<td>4 436</td>
<td>0.9 (0.3-2.4)</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>No follow-up CT, directly referred</td>
<td>3 5</td>
<td>2 6</td>
<td>5 11</td>
<td>45.5 (21.3-72.0)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

**All participants with largest nodule 50-500mm³**

| 33 1,455 | 24 1,499 | 57 2,954 | 1.9 (1.5-2.5) | <0.0001 |

**Definition of abbreviations:** VDT = volume doubling time; 95%CI = 95% confidence interval; ref = reference value

† Maximum VDT in subjects whose largest nodule measured 50-500 mm³, the interval for VDT includes the lower limit, not the upper limit.

+ Probability of lung cancer within two years after a CT scan. The difference in lung cancer risk with subjects without nodules was evaluated using Fisher's exact test.
unravel the association between multinodularity and lung cancer risk before inclusion of multinodularity in the prediction model and nodule management protocols, and so did not analyse multinodularity further in this study.

Figure 2 shows the combined effect of nodule volume and volume doubling time (with the final prediction model) on lung cancer probability; the interaction between volume and volume doubling time was not statistically significant (p = 0.95). Figure 2 shows

Table 2. Performance evaluation of simulated nodule management protocols for CT-detected nodules at the first screening round

<table>
<thead>
<tr>
<th>Screening result</th>
<th>Management protocol using volume</th>
<th>Management protocol using diameter*</th>
<th>Management protocol of the ACCP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>volume ≥300 mm³</td>
<td>diameter ≥10 mm</td>
<td>diameter ≥8 mm</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>volume ≥100 to ≤300 mm³</td>
<td>diameter ≥5 to &lt;10 mm³</td>
<td>diameter &gt;4 to &lt;8 mm³</td>
</tr>
<tr>
<td>Negative</td>
<td>volume &lt;100 mm³</td>
<td>diameter &lt;5 mm</td>
<td>diameter ≤4 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening test results</th>
<th>Percentage (n/n)</th>
<th>Percentage (n/n)</th>
<th>Percentage (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct referral due to positive result</td>
<td>4.7 (334/7,135)</td>
<td>5.3 (375/7,135)</td>
<td>8.9 (635/7,135)</td>
</tr>
<tr>
<td>Follow-up examination due to indeterminate result</td>
<td>7.8 (555/7,135)</td>
<td>22.2 (1586/7,135)</td>
<td>29.8 (2125/7,135)</td>
</tr>
<tr>
<td>- positive result after follow-up examination</td>
<td>1.2 (84/7,135)</td>
<td>5.5 (394/7,135)</td>
<td>4.7 (333/7,135)</td>
</tr>
<tr>
<td>- negative result after follow-up examination</td>
<td>6.6 (471/7,135)</td>
<td>16.7 (1192/7,135)</td>
<td>25.1 (1792/7,135)</td>
</tr>
<tr>
<td>Detected lung cancers</td>
<td>90.9 (60/66)</td>
<td>92.4 (61/66)</td>
<td>90.9 (60/66)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screen test parameters</th>
<th>Percentage (95%CI)</th>
<th>Percentage (95%CI)</th>
<th>Percentage (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>90.9 (81.2 - 96.1)</td>
<td>92.4 (83.1 - 97.1)</td>
<td>90.9 (81.2 - 96.1)</td>
</tr>
<tr>
<td>Specificity</td>
<td>94.9 (94.4 - 95.4)</td>
<td>90.0 (89.3 - 90.7)</td>
<td>87.2 (86.4 - 87.9)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>14.4 (11.3 - 18.1)</td>
<td>7.9 (6.2 - 10.1)</td>
<td>6.2 (4.8 - 7.9)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>99.9 (99.8 - 100.0)</td>
<td>99.9 (99.8 - 100.0)</td>
<td>99.9 (99.8 - 99.9)</td>
</tr>
</tbody>
</table>

Definition of abbreviation: 95%CI = 95% confidence interval (calculated using the Agresti-Coull method).

* In case of multiple nodules, the size of the largest nodule determines the screening result.

* Estimates based on diameters assessed using semi-automated volumetry. Manually measured diameters are less accurate and will overestimate nodule size. As a result, the performance of the presented nodule protocol using diameter will be worse when manually measured diameters are used to calculate nodule size and nodule VDT.

† Subjects with an indeterminate screening result should undergo a follow-up scan after three months to assess the VDT; a VDT<600 days is a positive screening result and leads to referral for diagnostic work-up.

‡ Subjects with an indeterminate screening result should undergo a follow-up scan after three months to assess the VDT; a VDT<400 days is a positive screening result and leads to referral for diagnostic work-up, according to the ACCP guideline (2013).

The test characteristics were estimated using the detection method; using a one-year interval plus all lung cancers detected in the same screening round (details are provided in the Appendix).
that in participants with nodules of 300 mm³ in size or larger, the lung cancer probability remained substantial (from 5.9% to >50%), even in case of slow nodule growth. In participants with nodules sized 100-300 mm³, lung cancer probability ranged from less than 3% to 20%, dependent on the volume doubling time.

**Evaluating management protocols for CT-detected nodules**

Two nodule volume or diameter thresholds based on lung cancer probability, or using the simulated ACCP management protocol, are presented in Table 2. After the first screening round (for a one year interval), the protocol that used nodule volume had a sensitivity of 90.9% (95% CI 81.2-96.1), and a specificity of 94.9% (95% CI 94.4-95.4). Due to its high specificity, relatively few patients would have had follow-up CT examinations (555

Abbreviations: VDT = volume-doubling time.
The risk isolines represent the percentage of NELSON participants that will be diagnosed with lung cancer within two years according to the volume of their largest nodule and VDT of the fastest growing nodule in the 50-500 mm³ range.
[8%] of 7,135) and additional diagnostic procedures (418 [6%] of 7,135) compared to the other protocols. The protocol that used (volumetry-based) nodule diameter had a lower specificity than the volume protocol (90.0% [95% CI 89.3-90.7]), which would have led to more follow-up examinations (1,586 [22%] of 7,135), and additional diagnostic procedures (769 [11%] of 7,135), but had a slightly higher sensitivity for lung cancer (92.4% [95% CI 83.1-97.1]). The simulated ACCP protocol had a sensitivity of 90.9% (95% CI 81.2-96.1), and the lowest specificity of the three evaluated protocols (87.2% [95% CI 86.4-87.9]), and would have led to the and additional diagnostic procedures (968 [14%] of 7,135). Performance of the lung cancer probability-based volume and diameter protocols in the second screening round with the same thresholds is provided in Table 4 of the Appendix.

DISCUSSION

In this analysis, we used NELSON trial data to calculate the probability developing lung cancer within two years after a low-dose CT scan, and stratified this risk by nodule volume, diameter, and volume doubling time. We used lung cancer probability to design and assess nodule management protocols. Our findings show that screened participants with nodules with volumes of 100 mm³ or smaller, or diameters of 5 mm or smaller, have a lung cancer risk that is not significantly different from that in participants without nodules and should not undergo additional CT examinations. Individuals with nodules of 100-300 mm³ in volume or 5-10 mm in diameter represent an indeterminate subgroup for whom assessment of volume doubling time is appropriate (<600 days warrants follow-up evaluation). Those participants whose largest nodules’ volume measured 300 mm³ or more, or had a diameter of 10 mm or more, should have immediate diagnostic evaluation.

In more than half of the included participants, no pulmonary nodules were detected. Their 2-year probability developing lung cancer was 0.4%, which suggests that a screening interval of at least 2 years might be safe to apply in these individuals.

Our findings support previous evidence that the probability of small nodules (volume <50 mm³ or diameter <4 mm) being, or developing into, lung cancer is low: 0.6% or lower, similar to the previously reported values of less than 1%.7,11,21-25 Moreover, the two-year probability of developing lung cancer in participants whose nodules measured 50-100 mm³ or 4-5 mm was also low, and did not significantly differ from that in participants without nodules. At present, guidelines recommend two to four follow-up scans for such nodules.8,13,26 Omission of these CT surveillance schedules for this patient population should be considered, because the risk of malignancy does not justify harms of ionising radiation (effective dose estimated at 10 mSv per full-dose CT),11 psychological distress (clinically relevant increase in lung-cancer-specific distress as shown by van den Bergh
and colleagues,\textsuperscript{14} and confusion, distress and frustration as reported by Wiener and colleagues\textsuperscript{27}, and associated pressure on financial resources.\textsuperscript{28,29}

Participants whose nodules measured 100-300 mm\textsuperscript{3} (or 5-10 mm in diameter) had a significantly higher two-year lung cancer risk than did participants without nodules, which, according to current guidelines,\textsuperscript{8,14,26} justifies additional CT examinations. Because lung cancer risk of participants with nodules between 5 mm and 8 mm is similar (0.9\% to 1.8\%),\textsuperscript{23} a uniform CT surveillance schedule could be applied, with volume doubling time assessed at CT surveillance used to reassess lung cancer probability. Participants with slowly growing (volume doubling time of ≥600 days), stable, shrunken or resolved nodules were at low risk of developing lung cancer, and could withdraw from intensified CT surveillance\textsuperscript{8} and return to regular screening.\textsuperscript{1,2} By contrast, participants whose nodules had a volume doubling time of less than 600 days had a significantly increased risk of lung cancer which justifies intensified CT surveillance\textsuperscript{8} and additional diagnostic procedures.\textsuperscript{1} Participants whose nodules had a volume doubling time of 400-600 days could be regarded as at intermediate risk, because their lung cancer probability was 4.0\% (95\% CI 1.8-8.3) over two years. Hence, a follow-up CT scan at short notice to reassess nodule size and growth might be a better initial option instead of more invasive diagnostic procedures.

These findings lend support to the notion that people with large nodules have a high probability of developing lung cancer, reported to be more than 10\% in previous studies\textsuperscript{8,21,24,30} and 8.9\% (95\% CI 5.6-13.7) or higher for volumes 300 mm\textsuperscript{3} or greater, or to 11.1\% (8.5-14.4) diameters 10 mm or greater in this study. Risk for these large nodules remained high even when they grew slowly (Figure 2). However, risk of developing lung cancer for participants with large nodules that had shrunken or resolved within 2 years was very low. Although classification of large slow-growing nodules as possibly malignant might add to overdiagnosis, the risk of large nodules (defined as those measuring ≥300 mm\textsuperscript{3} or ≥10 mm) being or developing into lung cancer is thought to be too high to delay diagnosis. Therefore, follow-up CT examinations to assess growth for large nodules provide little additional information, but may delay lung cancer diagnosis. Hence, immediate diagnostic work-up is suggested instead.

We did logistic regression analyses to predict lung cancer probability, and found that nodule diameter, volume, volume doubling time and multinodularity were significant univariate predictors. Nodule volume, nodule volume doubling time, and multinodularity were also significant multivariate predictors. The interaction between nodule volume and volume doubling time was not statistically significant; these two variables were included in the final lung cancer prediction model. The relationship between multinodularity and lung cancer risk was ambiguous; lung cancer probability varied as the number of nodules per subject increased. These findings contradict those of McWilliams and colleagues,\textsuperscript{25} who demonstrated an increased lung cancer risk for one, two, and three nodules per

\textsuperscript{161}
participant, and a decreased risk for more than four nodules per participant. Therefore, we thought it appropriate to do further studies to unravel the association between multinodularity and lung cancer risk before inclusion of multinodularity in the prediction model and nodule management protocols.

Based on these findings, we proposed and evaluated nodule management protocols, based on a two-step management approach as described above. Participants without nodules, or nodules smaller than the lower thresholds were to be classified as negative, and receive no additional diagnostic procedures. Participants whose nodules measured between the lower and upper thresholds were to be classified as indeterminate. Participants whose nodules are larger than the upper size threshold were to be classified as positive, and were directly referred for diagnostic work-up to diagnose or rule lung cancer. Participants who were classified as indeterminate were to undergo another low-dose CT examination to determine their final screening test result based on nodule growth using a single volume doubling time threshold. The advantage of nodule management protocols using a two-step approach compared to protocols that use just one nodule evaluation (e.g., as used in the ELCAP\textsuperscript{7} and the NLST\textsuperscript{4} trials) is a single low-dose CT examination is given at short notice (for example after three months) for indeterminate nodules, instead of 2-3 CT scans in two years.\textsuperscript{8} Further, this approach allows for a better risk stratification by nodule volume doubling time which is a strong lung cancer predictor.\textsuperscript{3,5,13}

The protocol that used lung cancer probability-based diameter thresholds was more sensitive than the simulated ACCP protocol\textsuperscript{8,15} and would have led to fewer CT examinations and additional diagnostic procedures. Nonetheless, these results imply that the simulated ACCP nodule management protocol performs well, but improvements are possible.

The protocol that used lung cancer probability-based thresholds for nodule volume had high specificity, and would have led to substantially fewer follow-up CT examinations and additional diagnostic procedures than would the simulated ACCP protocol. Moreover, this protocol was as sensitive as the simulated ACCP protocol. However, if manual diameter measurements had been used instead of volumetry-based measurements, as recommended in the ACCP protocol, it is unlikely that such high sensitivity values would have been reached due to the intrinsic unreliability of manual measurements.\textsuperscript{20} We believe that the advantages of an increase in specificity of the volume protocol indicate that lung cancer screening should be performed using volumetric software, despite the fact that volumetry demands more advanced CT equipment and takes more time than manual nodule measurements. Moreover, the use of volumetry enables reliable nodule growth assessment at short notice, which is not possible when manual nodule measurements are used, due to the lower sensitivity for actual nodule growth as a result of measurement error.
Analyses in this study were done at the participant level by using the largest and fastest growing nodule in participants with multiple nodules. This approach is recommended by the ACCP, and accounts for the fact that some interval cancers could not be matched to a nodule previously detected by screening. Lung cancer probability of the largest or fastest growing nodule in a participant could be a slight overestimate, as lung cancer was not always diagnosed in this nodule. Also, the presented lung cancer probabilities may be slightly overestimated due to advancing lung cancer diagnoses by screening in the 2-year follow-up. However, the probabilities may also be slightly underestimated because some lung cancers diagnosed as the two-year follow-up period may not have been present at the time of screening.

A limitation of this study is the inability of the LungCARE software to calculate volume of sub-solid nodules, and so we had to estimate some volumes based on manually measured diameters, which may have introduced some inaccuracies. Another limitation may be the length of follow-up, which was limited to two years. As a result, we cannot provide results to aid decision making for nodule management for periods longer than 2 years. Moreover, presented lung cancer probabilities may only be extrapolated to populations with a comparable prevalence of lung nodules (about 50%) and a comparable lung cancer risk (about 1.3% in 2 years).

Lastly, presented lung cancer probabilities, volume doubling times, and nodule protocols were all estimated and evaluated using a data set of nodule measurements that were mainly assessed using volumetry. Evaluation of two nodule management protocols using diameter was done under the assumption that nodule diameters measured using semi-automatic volumetry software were comparable to manually measured nodule diameters. However, measurement error of manual measurement of nodule diameter is larger than measurement error of the volumetry-based diameters we used in this study. Further, calculations of volume doubling time based on manually measured nodule diameters are less accurate than calculations of volume doubling time based on semi-automated volumetry. As a result, the relationship between nodule diameter and lung cancer probability may be weaker for manually measured nodule diameters. In addition, when results of this study are applied to manually measured diameters, presented sensitivities and specificities of protocols using diameter are likely to be too high, and the false-positive rate, number of follow-up CTs and diagnostic work-ups are likely to be too low. These discrepancies could be reduced by using the mean transverse nodule diameter instead of maximal nodule diameter. Nonetheless, the aforementioned theoretical discrepancies in lung cancer probability and performance characteristics are probably limited in practice, as our estimates of lung cancer probability are comparable to the probabilities published by the ELCAP, NLST, and the Pan-Canadian Early Detection of Lung Cancer Study, which used manual measurements of nodule diameters for analyses. Since our conclusions are restricted to volumetry-based diameter analysis, it remains unclear
whether the protocol using manually-measured diameters with the thresholds of 5 mm and 10 mm, can be applied to situations in which it is not possible to use semiautomatic volumetric software.

In the current study, nodule size and volume doubling time were used to determine an individual's lung cancer probability. Other nodule characteristics, such as nodule attenuation and multiplicity, and background characteristics, such as age and smoking history, may also affect lung cancer probability. Future studies need to determine whether we could include such characteristics in our prediction model to estimate an individual's lung cancer probability more accurately. Further, validation of presented lung cancer probabilities on a large, reliable data set would be valuable.

CONCLUSION

We designed improved management protocols for CT detected nodules, using thresholds for nodule size and VDT that are based on lung cancer probability. Subjects with nodules ≤100 mm³ or ≤5 mm have a lung cancer risk that is not significantly different from that in subjects without nodules and should not undergo additional CT examinations. Individuals with nodules 100-300 mm³ or 5-10 mm represent an indeterminate subgroup for whom assessment of VDT is appropriate (<600 days warrants follow-up evaluation). Lung cancer risk of subjects whose nodules measure >300 mm³ or >10 mm demands immediate diagnostic evaluation.
RESEARCH IN CONTEXT

Systematic Review
A systematic review was done as part of planning for this trial. To identify all relevant articles on management of solitary pulmonary nodules, we searched PubMed with the terms “lung neoplasms” [MeSH] AND “solitary pulmonary nodule” [MeSH] AND “tomography, x-ray computed” [MeSH] and “probability” [MeSH]; limits: humans, adults; published in the past 10 years, in English, in core clinical journals, or MEDLINE. To identify all articles of lung cancer CT screening trials that described pulmonary nodules, we used the terms “lung neoplasms” [MeSH] AND “early detection of cancer” [MeSH] AND “tomography, x-ray computed” [MeSH] AND “epidemiologic study characteristics as topic” [MeSH]. The search was limited to studies done in adults, and published from Jan 1, 2000, in English. Titles and abstracts of articles that were identified with these search terms were scanned to select articles relevant for this study. Reference lists of relevant articles were checked to identify more relevant articles. Current clinical practice guidelines on management of pulmonary nodules use thresholds for nodule diameter to determine appropriate follow-up strategy. In addition, use of prediction models to assess individual lung cancer risk is recommended by some guidelines. Data used to design current clinical practice guidelines is mainly obtained from published results of lung cancer screening cohort studies conducted in the 1990s.

Interpretation
Published probabilities of lung cancer stratified by nodule size were comparable to the probabilities estimated in our study. However, none of the published studies provided estimates for such small ranges of diameters, as in our study. Moreover, no estimates of lung cancer probability were published for nodule volume and nodule VDT. This retrospective analysis showed that the simulated ACCP guidelines performed well when volumetry-based diameter measurements were used, but also that improvements were possible. By small adjustments of thresholds for nodule size and growth rate, which were determined based on the associated lung cancer probability, sensitivity and specificity of the simulated ACCP protocol may be increased. Further, this study evaluated a nodule management protocol with lung cancer probability-based thresholds for nodule volume and volume doubling time, which yielded the same sensitivity as the simulated ACCP guideline and a substantially higher specificity. These results imply that use of lung cancer probability-based thresholds for nodule size and growth and volumetry in nodule management protocols can improve lung cancer detection, and reduce unnecessary follow-up CTs, invasive diagnostic procedures and costs.
ACKNOWLEDGEMENTS

We thank M. Quak, R. Faber, F. Santegoets, L. van Dongen, A. de Bruijn (Erasmus University Medical Center Rotterdam, the Netherlands), H. Ziengs (University Medical Center Groningen, the Netherlands), A. Hamersma, S. van Amelsvoort-van de Vorst (University Medical Center Utrecht, the Netherlands), L. Peeters (University Hospital Gasthuisberg Leuven, Belgium). Finally, we would like to thank the Dutch Cancer Registry for the data linkages that identified the interval lung cancers. The NELSON trial is supported by Zorg Onderzoek Nederland-Medische Wetenschappen (ZonMw) and KWF Kankerbestrijding. Roche diagnostics provided a grant for the performance of proteomics-research. Siemens Germany provided four digital workstations and LungCARE for the performance of 3D-measurements.

DECLARATION OF INTEREST STATEMENT

NH, HJdK, CMvdA, and KtH report grants from ZonMw, grants from KWF, grants from Roche diagnostics, and non-financial support from Siemens Germany during the conduct of the study. Additionally, HJdK and KtH report grants from National Cancer Institute/National Institutes of Health and grants from The Agency for Healthcare Research and Quality during the conduct of the study; grants from Sunnybrook Health Sciences and grants from Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen (RVVZ) outside the submitted work. J-WJL reports grants from the EU and grants from TiPharma outside the submitted work. KN reports grants from Belgian Foundation against Cancer and grants from Flemish Cancer League during the conduct of the study.
REFERENCES


Chapter 6


APPENDIX

NELSON nodule management protocol

Below is a more detailed description of the NELSON nodule management protocol. At the first detection of a pulmonary nodule, it is classified according to its size:

NODCAT 1:
- Only nodules with benign features (e.g. benign calcification patterns, fat component)

NODCAT 2:
- Solid nodules <50mm³
- Solid pleural based nodules <5mm in minimal diameter
- Part-solid nodules, non-solid component <8mm in mean diameter
- Part-solid nodules, solid component <50mm³
- Non-solid nodules <8mm in mean diameter

NODCAT 3:
- Solid nodules 50-500mm³
- Solid pleural based nodules 5-10mm in minimal diameter
- Part-solid nodules, non-solid component ≥8mm in mean diameter
- Part-solid nodules, solid component 50-500mm³
- Non-solid nodules ≥8mm in mean diameter

NODCAT 4:
- Solid nodules >500mm³
- Solid, pleural based nodules >10mm in minimal diameter
- Part-solid nodules, solid component >500mm³

If a nodule is detected at the second and later screenings, it is classified according to its growth rate. First the percentage volume change is calculated. If this percentage change is >25%, VDT is calculated, which categorizes the nodules as follows:

GROWCAT A
- VDT >600 days

GROWCAT B
- VDT 400-600 days

GROWCAT C
- VDT <400 days

Referral algorithm of the first screening round:
NEGATIVE:
- NODCAT 1
- NODCAT 2
• NODCAT 3 with GROWCATs A or B at follow-up examination
  POSITIVE:
  • NODCAT 3 with GROWCAT C at follow-up examination
  • NODCAT 4

Referral algorithm of the second screening round:

NEGATIVE:
• NODCAT 1
• NODCAT 2 with GROWCATs A or B at follow-up examination
• NODCAT 3 with GROWCATs A or B at follow-up examination

POSITIVE:
• NODCAT 2 with GROWCAT C
• NODCAT 3 with GROWCAT C
• NODCAT 4

The screening result could be negative (invitation for the next screen round), indetermi- nate (invitation for a repeat scan to determine the VDT), or positive (referral for diagnostic work-up). Nodule volume determined the screen result for newly detected nodules: <50mm³ was negative, 50-500mm³ was indeterminate, and >500mm³ was positive. For previously detected nodules, VDT was calculated and determined the screening result: >600days was negative, 400-600days was indeterminate and <400days was positive. The protocol allowed radiologists to adjust the screening result in case of inaccurate measurements by LungCARE, high suspicion of malignancy (e.g. new solid component in non-solid nodule), or high suspicion of benignancy (e.g. benign calcification patterns).

Framework for evaluating alternative nodule management protocols

The referral decisions made in the NELSON trial were based on the aforementioned formal NELSON protocol. Using the results of the NELSON trial, we can also assess how alternative nodule management protocols would have performed, if they had they been implemented in the NELSON trial. A complication in the analysis is that if an alternative protocol advised follow-up scanning to assess VDT, this VDT could only be calculated for subjects who received a follow-up scan in the NELSON trial. Below we describe the framework we used to estimate the lung cancer probabilities and the test characteristics of the evaluated nodule management protocols.

The evaluated protocols differ in several important ways from the original NELSON protocol. First, a single set of nodule size thresholds based on volume or diameter was used for all nodule types. Also, for nodules for which the volume could not be calculated using the volumetric software, the volume \( V \) was imputed using the maximal diameter \( D \) (formula:).
Optimisation of screening protocols

For part-solid nodules, only the solid component was used to determine the nodule size category. Finally, the criterion that the percentage volume change should be $>25\%$ before calculating the VDT was ignored.

Each evaluated protocol uses a nodule size threshold for a negative screening and a nodule size threshold for a positive screening. These two thresholds are based on either the volume or the diameter of a nodule. In each protocol, each detected nodule was classified as negative, indeterminate, or positive according to the following rules.

Negative: Nodules with benign features (e.g. benign calcification patterns, fat component; NODCAT 1 in the NELSON protocol) and nodules with volume/diameter below the nodule size threshold for a negative screening. The VDT is not relevant for these nodules since the participant is not referred even when the nodule is growing fast. Hence, when VDT was missing, it was not imputed.

Indeterminate: Nodules with volume/diameter above the threshold for a negative screening and below the threshold for a positive screening. For the participants with at least one indeterminate nodule and no positive nodules, the VDT determines whether the participant should be referred. For newly detected nodules, the VDT was calculated using a comparison of the volume on the initial scan and the first available follow-up scan in the same round; if no follow-up scan was available or if no growth was observed, the VDT could not be calculated. For nodules observed on the second round scan that had previously been seen on the baseline scan, we calculated the VDT by comparing the volumes on the baseline scan and the second round scan.

Positive: Nodules with volume/diameter above the threshold for a positive screening. The VDT is not relevant for these nodules since the participant should be referred, even in case of slow nodule growth. Hence, when VDT was missing, it was not imputed.

Participants with at least one positive nodule should be referred and participants with no nodules or only negative nodules should not be referred. For the remaining participants (i.e. participants with at least one indeterminate nodule and no positive nodules), the referral decision was based on the following rules:

I) For the evaluation of the simulated ACCP algorithm: participants with at least one indeterminate nodule with a VDT $\leq 400$ days are referred; participants in whom all indeterminate nodules have VDT $>400$ days are not referred. For the evaluation of the two new algorithms: participants with at least one indeterminate nodule with a VDT $\leq 600$ days are referred; participants in whom all indeterminate nodules have VDT $>600$ days are not referred.

II) If the VDT of a nodule could not be calculated because the nodule had not grown or was not visible on the follow-up scan, this did not lead to a decision to refer
the participant. If the VDT could not be calculated because no follow-up scan had been made in the NELSON trial, the decision to refer the patient was imputed using the referral decision made by the radiologists in the NELSON trial. This approach was necessary in approximately 15% of the subjects with the largest nodule in the 50-500 mm³ range, e.g. due to manual adjustments of the screening result by the radiologists.

Methods for estimating screening test characteristics

The nodule management algorithms that were evaluated in this study classified each scan result as positive, indeterminate, or negative. In all evaluated algorithms, subjects with an indeterminate screening result receive a second CT examination and the result of this scan was either positive (VDT <400 days) or negative (VDT ≥400 days). Summarizing, all scans have a ‘final’ screening result that was either positive or negative.

Next, whether a lung cancer was present at the time of the CT examination was determined as follows. A screening was classified as being done in the presence of lung cancer if:

I) The diagnostic work-up, which was initiated for a positive ‘final’ screening result, led to the diagnosis of lung cancer (true positive screening results).

II) A lung cancer diagnosis was made during the period from the first CT examination of the screening round to either the next screening round or one year later, whichever came first (false negative screening results).

Via linkages with the national cancer registry, which has complete national coverage, all lung cancer diagnoses made outside the screening trial were obtained. If the screening was not classified as being done in the presence of lung cancer, it was defined as being done in the absence of lung cancer.

Finally, definitions of the screening test parameters were defined as follows:

I) Sensitivity was estimated by dividing the number of true positive screens by the numbers of true positive and false positive screens (positive screens in the absence of lung cancer).

II) Specificity was estimated by dividing the number of true negative screens (negative screens in the absence of lung cancer) by the numbers of true negative and false negative screens.

III) The positive predictive value was estimated by dividing all subjects with a true positive screening by all subjects with positive screening.

IV) The negative predictive value was estimated by dividing all subjects with a true negative screening by all subjects with negative screening.

All screening test parameters were presented with 95% binomial confidence intervals (95%CI), which were calculated using the Agresti-Coull method.
Lung cancer diagnoses not confirmed by histological specimens

Lung cancer diagnoses in the first three rounds of the NELSON trial were based on histology or cytology in 174 out of 187 cases (93.0%). The basis for the diagnosis in the 13 participants without histology or cytology was:

I) Tumour in the right upper lobe, volume 1,502 mm³, PET-positive, cT1aN0M0, patient did not undergo thoracic surgery due to cardiac impairment.

II) Tumour in left lower lobe, volume 2,687 mm³, PET positive, cT1aN0M0, patient did not undergo thoracic surgery due to COPD stage IV.

III) Tumour in left lower lobe, volume 2,792 mm³, PET-positive, cT1aN0M0, patient did not undergo thoracic surgery due to COPD and renal failure.

IV) Tumour in right upper lobe, volume 580 mm³, PET-positive, cT1aN0M0, patient did not undergo thoracic surgery due to metastasized prostate carcinoma.

V) Tumour in right lower lobe, volume 2,793 mm³, PET-positive, cT1bN0M0, patient did not undergo thoracic surgery due to poor pulmonary function.

VI) Tumour in right upper lobe, volume 891 mm³, PET indeterminate, cT1aN0M0, and patient died due to bowel ischemia just before intended thoracic surgery.

VII) Tumour in right lower lobe, volume 731 mm³, PET-positive, cT1aN0M0, patient did not undergo thoracic surgery due to poor pulmonary function.

VIII) Tumour in left lower lobe, volume 108 mm³, VDT 125 days, PET-positive, cT1aN0M0, patient did not undergo thoracic surgery because he also participated in another study and was randomised to the radiotherapy treatment arm.

IX) Tumour in right upper lobe, volume 383 mm³, VDT 289 days, PET indeterminate, cT1aN0M0, patient did not undergo thoracic surgery because he refused; he was treated with stereotactic radiotherapy instead.

X) Tumour in left lower lobe, volume 1,108 mm³, PET positive, cT1aN1M0, patient did not undergo thoracic surgery due to poor pulmonary function.

XI) Tumour in left lower lobe, diameter 10 mm, PET positive, cT1aN0M0, and patient did not undergo thoracic surgery due to poor pulmonary function.

XII) Tumour in right upper lobe, diameter 13.2 x 11.6 mm, PET positive, cT1aN0M0, patient did not undergo thoracic surgery due to poor pulmonary function and general condition.

XIII) Tumour in right upper lobe, diameter 19.2 x 12.7 mm, PET positive, cT1bN0M0, patient did not undergo thoracic surgery due to poor general condition.
Figure 1a. Relationship multi-nodularity and lung cancer probability in all subjects with nodules

![Graph showing the ratio of proportion of subjects with lung cancer to proportion of subjects with n nodules.](graph1a.png)

Figure 1b. Relationship multi-nodularity and lung cancer probability in subjects whose largest measure 50-500mm³ and have a VDT>0

![Graph showing the ratio of proportion of subjects with lung cancer to proportion of subjects with n nodules.](graph1b.png)
Table 1. Two-year lung cancer probability by nodule volume and volume doubling-time

<table>
<thead>
<tr>
<th>Nodule volume</th>
<th>&lt;600 days</th>
<th>≥600 days</th>
<th>shrunk or resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mm³</td>
<td>7/199 (3.5%)</td>
<td>2/521 (0.4%)</td>
<td>0/4,803 (0.0%)</td>
</tr>
<tr>
<td>≥100 to &lt;300 mm³</td>
<td>19/207 (9.2%)</td>
<td>3/379 (0.8%)</td>
<td>0/525 (0.0%)</td>
</tr>
<tr>
<td>≥300 mm³</td>
<td>99/464 (21.3%)</td>
<td>3/51 (5.9%)</td>
<td>0/102 (0.0%)</td>
</tr>
</tbody>
</table>

Table 2. Multivariable logistic regression model for the probability to be diagnosed with lung cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule volume^</td>
<td>2.12 (1.64-2.75)*</td>
</tr>
<tr>
<td>Nodule VDT†</td>
<td>0.45 (0.35-0.60)*</td>
</tr>
<tr>
<td>Constant</td>
<td>1.35 (0.24-7.79)</td>
</tr>
</tbody>
</table>

In this model, only the participants in whom the largest detected nodule had a volume of ≥50 mm³ and <500 mm³ and who had at least two screenings were included. The dependent variable indicates whether a diagnosis of lung cancer has occurred during the follow-up period; the independent variables are volume, VDT, and a constant term. Hosmer-Lemeshow goodness-of-fit test: p = 0.7.

Abbreviations: VDT = volume-doubling time, 95% CI = 95% confidence interval using the Agresti-Coull method.

^ Linear effect: nodule volume was defined as the volume in mm³ divided by 100.
† Logarithmic effect: nodule VDT was defined as the natural logarithm of VDT in days.
* p-value < 0.001.
Table 3a. Multivariable logistic regression model for the probability to be diagnosed with lung cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule volume^</td>
<td>2.19 (1.69-2.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nodule VDT+</td>
<td>0.43 (0.32-0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multi-nodularity*</td>
<td>0.68 (0.55-0.85)</td>
<td>0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>5.00 (0.74-33.79)</td>
<td>0.099</td>
</tr>
</tbody>
</table>

In this model, only the participants in whom the largest detected nodule had a volume of ≥50 mm³ and <500 mm³ and who had at least two screenings were included. The dependent variable indicates whether a diagnosis of lung cancer has occurred during the follow-up period; the independent variables are volume, VDT, multi-nodularity, and a constant term. Hosmer-Lemeshow goodness-of-fit test: p = 0.8.

Abbreviations: VDT = volume-doubling time, 95% CI = 95% confidence interval using the Agresti-Coull method.
^ Linear effect: nodule volume was defined as the volume in mm³ divided by 100.
+ Logarithmic effect: nodule VDT was defined as the natural logarithm of VDT in days.
* Linear effect: multi-nodularity was defined as the number of nodule present at the scan.

Table 3b. Multivariable logistic regression model for the probability to be diagnosed with lung cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodule volume^</td>
<td>2.20 (1.69-2.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nodule VDT+</td>
<td>0.44 (0.33-0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multi-nodularity*</td>
<td>0.20 (0.10-0.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>3.60 (0.55-33.41)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

In this model, only the participants in whom the largest detected nodule had a volume of ≥50 mm³ and <500 mm³ and who had at least two screenings were included. The dependent variable indicates whether a diagnosis of lung cancer has occurred during the follow-up period; the independent variables are volume, VDT, multinodularity, and a constant term. Hosmer-Lemeshow goodness-of-fit test: p = 0.8.

Abbreviations: VDT = volume-doubling time, 95% CI = 95% confidence interval using the Agresti-Coull method.
^ Linear effect: nodule volume was defined as the volume in mm³ divided by 100.
* Logarithmic effect: nodule VDT was defined as the natural logarithm of VDT in days.
* Linear effect: multinodularity as binary variable (0 = 1 nodule, 1 = ≥ 2 nodules).
Table 4. Performance evaluation of simulated management algorithms for CT-detected nodules at the second screening round

<table>
<thead>
<tr>
<th>Screening result</th>
<th>Management protocol based on volumetry</th>
<th>Management protocol based on diameter*</th>
<th>Management protocol of the ACCP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>volume ≥300 mm³</td>
<td>diameter ≥10 mm</td>
<td>diameter ≥8 mm</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>volume ≥100 to ≤300 mm³ 🅱️</td>
<td>diameter ≥5 to &lt;10 mm</td>
<td>diameter &gt;4 to &lt;8 mm 🅱️</td>
</tr>
<tr>
<td>Negative</td>
<td>volume &lt;100 mm³</td>
<td>diameter &lt;5 mm</td>
<td>diameter ≤4 mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening test results</th>
<th>Percentage (n/n)</th>
<th>Percentage (n/n)</th>
<th>Percentage (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct referral due to positive result</td>
<td>4.1 (283/6,889)</td>
<td>4.7 (322/6,889)</td>
<td>9.0 (618/6,889)</td>
</tr>
<tr>
<td>Follow-up examination due to indeterminate result</td>
<td>8.1 (556/6,889)</td>
<td>24.3 (1676/6,889)</td>
<td>31.3 (2,156/6,889)</td>
</tr>
<tr>
<td>- positive result after follow-up examination</td>
<td>1.0 (72/6,889)</td>
<td>5.4 (370/6,889)</td>
<td>3.1 (314/6,889)</td>
</tr>
<tr>
<td>- negative result after follow-up examination</td>
<td>7.0 (484/6,889)</td>
<td>19.0 (1,306/6,889)</td>
<td>28.2 (1,942/6,889)</td>
</tr>
<tr>
<td>Detected lung cancers</td>
<td>83.1 (49/59)</td>
<td>86.4 (51/59)</td>
<td>88.1 (52/59)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screen test parameters</th>
<th>Percentage (95%CI)</th>
<th>Percentage (95%CI)</th>
<th>Percentage (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>83.1 (71.3 - 90.7)</td>
<td>86.4 (75.2 - 93.2)</td>
<td>88.1 (77.2 - 94.4)</td>
</tr>
<tr>
<td>Specificity</td>
<td>95.5 (95.0 - 96.0)</td>
<td>90.6 (89.9 - 91.3)</td>
<td>88.6 (87.8 - 89.3)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>13.8 (10.6 - 17.8)</td>
<td>7.4 (5.6 - 9.6)</td>
<td>6.3 (4.8 - 8.1)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>99.8 (99.7 - 99.9)</td>
<td>99.9 (99.7 - 99.9)</td>
<td>99.9 (99.8 - 99.9)</td>
</tr>
</tbody>
</table>

Definition of abbreviation: 95%CI = 95% confidence interval (calculated using the Agresti-Coull method).

* In case of multiple nodules, the size of the largest nodule determines the screening result.

* Estimates based on diameters assessed using semi-automated volumetry. Manually measured diameters are less accurate and will overestimate nodule size. As a result, the performance of the presented nodule algorithm based on diameter will be worse when manually measured diameters are used to calculate nodule size and nodule VDT.

* Subjects with an indeterminate screening result should undergo a follow-up scan after three months to assess the VDT; a VDT <600 days is a positive screening result and leads to referral for diagnostic work-up. Although the lung cancer probability of nodules with VDTs of 400-600 days is intermediate (4.1% in two years), it is not possible for this analysis to classify this subgroup as indeterminate because every participant must have a definite screening test results (positive or negative) to be able to determine whether lung cancer was detected by screening or not and to calculate the test characteristics of the screening algorithm. Semi-automatically assessed nodule diameters were used for calculation of the VDT. The use of manually measured nodule diameters for the calculation of the VDT is less accurate and will affect the sensitivity and specificity of the algorithm.

† Subjects with an indeterminate screening result should undergo a follow-up scan after three months to assess the VDT; a VDT <400 days is a positive screening result and leads to referral for diagnostic work-up, according to the ACCP guideline (2013).

The test characteristics were estimated using the detection method; using a one-year interval plus all lung cancers detected in the same screening round (details are provided in the data supplement).
Chapter 7

Evaluation of bronchoscopy

The role of conventional bronchoscopy in the work-up of suspicious CT screen-detected pulmonary nodules


Chest

August 2012
The role of conventional bronchoscopy in the work-up of suspicious CT screen-detected pulmonary nodules


**ABSTRACT**

Up to 50% of the participants in CT scan lung cancer screening trials have at least one pulmonary nodule. To date, the role of conventional bronchoscopy in the workup of suspicious screen-detected pulmonary nodules is unknown. If a bronchoscopic evaluation could be eliminated, the cost-effectiveness of a screening program could be enhanced and the potential harms of bronchoscopy avoided.

All consecutive participants with a positive result on a CT scan lung cancer screening between April 2004 and December 2008 were enrolled. The diagnostic sensitivity and negative predictive value were calculated at the level of the suspicious nodules. In 95% of the nodules, the gold standard for the outcome of the bronchoscopy was based on surgical resection specimens.

A total of 318 suspicious lesions were evaluated by bronchoscopy in 308 participants. The mean SD diameter of the nodules was 14.6 8.7 mm, whereas only 2.8% of nodules were <30 mm in diameter. The sensitivity of bronchoscopy was 13.5% (95% CI, 9.0%-19.6%); the specificity, 100%; the positive predictive value, 100%; and the negative predictive value, 47.6% (95% CI, 41.8%-53.5%). Of all cancers detected, 1% were detected by bronchoscopy only and were retrospectively invisible on both low-dose CT scan and CT scan with IV contrast.

Conventional white-light bronchoscopy should not be routinely recommended for patients with positive test results in a lung cancer screening program.
INTRODUCTION

Depending on the geographic region, 26% to 51% of participants in multi-detector computed tomography (CT) lung cancer screening trials showed at least one non-calcified pulmonary nodule on their CT scan. The likelihood of these nodules being malignant depends on their size. The Fleishner Society guideline recommends a recall CT scan, PET scan, or biopsy for nodules >8 mm detected on a CT scan but not by bronchoscopy. The American College of Chest Physicians (ACCP) guideline recommends only evaluation by bronchoscopy under the condition that an air bronchogram is present on CT scan or in centres with expertise in newer techniques. Literature on the role of newer techniques, such as ultrathin bronchoscopy, autofluorescence bronchoscopy, and CT scan-guided bronchoscopy in lung cancer screening settings is sparse. To our knowledge, a study by McWilliams et al is the only one to report on the role of autofluorescence bronchoscopy in a lung cancer screening trial. The diagnostic yield of bronchoscopy to evaluate solitary pulmonary nodules outside a CT scan screening program varies from 51% to 76% and highly depends on the size and location of the nodule.

The nodule management strategy of the Dutch-Belgian Randomised Lung Cancer Screening Trial (NELSON) is based on the size and the volume-doubling time (VDT) of nodules detected by CT scan, without the use of fine-needle aspiration, PET scan, or evaluation after antibiotics. Subjects with positive test results were referred for work-up of suspicious nodules, which included a physical examination, a standard CT scan with contrast, and bronchoscopy.

Recently, the U.S. National Lung Screening Trial (NLST) demonstrated a 20% mortality reduction with low-dose CT screening. In the low-dose CT group, 320 subjects (1.8% of all subjects with a positive test result) underwent bronchoscopy without biopsy or cytological testing, whereas 391 subjects (2.2% of all subjects with a positive test result) underwent bronchoscopy with biopsy or cytological testing. The investigators did not report on the diagnostic performance of bronchoscopy in their study. In Pan-Canadian Lung Cancer Screening Trial, all participants were offered an auto-fluorescence bronchoscopy to detect central airway lesions; 67% (378 of 561) actually underwent this procedure. Ideally, all subjects should have undergone bronchoscopy for this purpose. Four of 22 subjects (18%) bronchoscopy yielded a diagnosis of radiological occult lung cancer. In the Canadian trial, the purpose of bronchoscopy appears to have been inspection of the central airways. In about 45% (320 of 711) of cases, cytology or histology specimens were obtained. It is unclear to what extent the ACCP guidelines were followed. In both the Canadian trial and the NLST, no nodule criteria were specified before the decision to perform bronchoscopy.

So far, lung cancer screening trials have not provided specific recommendations on the use of bronchoscopy to evaluate suspicious CT-detected nodules, nonetheless...
a significant number of bronchoscopies have been performed.\textsuperscript{20} Screening detects more early-stage lung cancers, whereas advanced-stage lung cancers that are present as interval cancers amenable to bronchoscopy are excluded from analyses.\textsuperscript{1} Our hypothesis was that the diagnostic value of bronchoscopy in this workup process might be low as suspicious nodules are usually small and peripherally located.\textsuperscript{1,18,19} If this is true, bronchoscopic evaluation may be eliminated from the standard work-up of suspicious CT-detected nodules; which would enhance the cost-effectiveness of a lung cancer screening program and avoid the harms of bronchoscopy. Therefore, our objective was to prospectively investigate the diagnostic value of bronchoscopy in the NELSON trial and to evaluate the diagnostic yield of the various diagnostic techniques used during bronchoscopy.

**METHODS**

**Study Population**

The nodule management strategy of the NELSON trial has been published previously.\textsuperscript{16,23} Briefly, 15,822 individuals with at high risk for developing lung cancer were randomised to either four low-dose CT examinations (n=7,915) at baseline (first round), one year later (second round), three years later (third round), and five and a half years later, or no screening (n=7,907). All consecutive participants with a positive test result at the first, second, and third screening round from April 2004 to December 2008 were included in this study.

A test result was considered positive for pulmonary nodules with a volume of >500 mm\textsuperscript{3} (about 9.8 mm in diameter) and nodule with a volume doubling-time (VDT) of <400 days.\textsuperscript{1,16,21} For nodules with a solid component measuring ≥50 to ≤500 mm\textsuperscript{3} the test result was indeterminate, and a repeat scan was performed to assess the VDT of the nodule. When the VDT was <400 days at repeat scanning, the final test result was considered positive, otherwise, it was considered negative.\textsuperscript{1,16}

The NELSON trial was approved by the ethics committees of all participating centres, and all participants provided written informed consent (approval number IRB00001838).

**Bronchoscopy**

Conventional white-light bronchoscopies were performed by experienced pulmonologists working at the four screening sites in The Netherlands (Utrecht, Groningen, and Haarlem) and Belgium (Leuven).\textsuperscript{16} During bronchoscopy, bronchial washings were performed for cytology and culture; bronchial brushings and biopsy specimens were taken (52C-1 forceps) in the case of central lesions. In less than 1\% of the cases, biopsy was performed under fluoroscopic guidance. The bronchoscopists did not use CT scan fluoroscopic guidance or ultrathin bronchoscopes. A flexible Pentax video bronchoscope
Evaluation of bronchoscopy

(Pentax Medical Company) was used in Utrecht, whereas Groningen and Haarlem used the Olympus flexible video bronchoscope (Olympus America Inc), and in Leuven both types were used.

Endobronchial abnormalities were classified as visible tumour, constriction, or compression of the airways. Nodules within the inner third, middle, and outer third of the hilar-costal diameter on CT scan were classified as respectively central, intermediate, or peripheral.

If the bronchoscopy revealed cancer, the outcome of the procedure was considered positive; otherwise, it was considered negative. The gold standard for the outcome of the bronchoscopy was the pathology result of the surgical resection specimen of the suspicious lesion. If no surgical resection was performed, the presence or absence of cancer during a follow-up of at least two years after the first and second screening rounds and at least one year after the third round was used as the gold standard. Nodules with a VDT of >400 days at follow-up CT examinations were considered benign.

Data Analysis

Statistical analyses were performed using SPSS, version 17.0 (SPSS, Inc.) software. The sensitivity was defined as the ratio between the number of positive bronchoscopy results and the number of positive results according to the gold standard. The diagnostic sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated at the level of the suspicious nodules. Suspicious nodules that were not approached during bronchoscopy were excluded from the analysis.

Mann-Whitney U test was used for continuous variables, and chi²-test was used for binomial and categorical data. Binary logistic regression was used to determine the effect of the individual nodule characteristics on the diagnostic yield of bronchoscopy. In the multivariate analysis, the characteristics with a p-value ≤0.10 were included for a stepwise-forward procedure. P-values <0.05 were considered statistically significant.

RESULTS

Of the 415 participants with positive test results, 74.2% (308 of 415) underwent bronchoscopy to evaluate 318 suspicious pulmonary lesions; 25.8% (107 of 415) did not undergo bronchoscopy for several reasons (Fig 1). In 2.4% (10 of 415) of the cases, referral was based on non-nodular lesions on CT. Six bronchoscopies were performed (Fig 1) on these participants. No significant differences were found in participant characteristics and nodule characteristics between those who did and those who did not undergo bronchoscopy (Table 1); except for a sex difference and a difference in cancer detection rate of 22.4%
The average maximum diameter of the suspicious nodules was 14.6 mm; the maximum diameter varied from 5 to 68 mm (SD 8.7 mm), only 2.8% of the lesions measured >30 mm. Cancer was diagnosed by bronchoscopy in only 24 of 318 suspicious lesions. Suspicious nodules identified as cancer by bronchoscopy were significantly larger (odds ratio (OR) 1.07, 95% CI 1.02-1.13), and were more often visible during bronchoscopy (OR 87.6, 95% CI 4.9-564.9) compared to the cancer cases missed by bronchoscopy (Table 2).

Based on the gold standard used in this study, a total of 178 cancer cases were detected among the 318 lesions, including 167 lung cancer cases. In 77% (137 of 178) of cases the gold standard was based on surgical resection specimens, in 18.5% (33 of 178) of cases it was based on surgical biopsy specimens (mediastinoscopy, true-cut biopsy performed during surgery), and in 4.5% (eight of 178) of the cases it was based on the combination of a new and growing PET-positive lesion on CT scan.

In 24 of the 178 subjects with cancer, bronchoscopy yielded the diagnosis of cancer. Hence, the sensitivity of bronchoscopy to detect cancer was 13.5% (95% CI 9.0-19.6%), (24 of 107) in the group without bronchoscopy compared with 57.8% (178 of 308) in the bronchoscopy group (p<0.001) (Fig 1).

The average maximum diameter of the suspicious nodules was 14.6 mm; the maximum diameter varied from 5 to 68 mm (SD 8.7 mm), only 2.8% of the lesions measured >30 mm. Cancer was diagnosed by bronchoscopy in only 24 of 318 suspicious lesions. Suspicious nodules identified as cancer by bronchoscopy were significantly larger (odds ratio (OR) 1.07, 95% CI 1.02-1.13), and were more often visible during bronchoscopy (OR 87.6, 95% CI 4.9-564.9) compared to the cancer cases missed by bronchoscopy (Table 2).

Based on the gold standard used in this study, a total of 178 cancer cases were detected among the 318 lesions, including 167 lung cancer cases. In 77% (137 of 178) of cases the gold standard was based on surgical resection specimens, in 18.5% (33 of 178) of cases it was based on surgical biopsy specimens (mediastinoscopy, true-cut biopsy performed during surgery), and in 4.5% (eight of 178) of the cases it was based on the combination of a new and growing PET-positive lesion on CT scan.

In 24 of the 178 subjects with cancer, bronchoscopy yielded the diagnosis of cancer. Hence, the sensitivity of bronchoscopy to detect cancer was 13.5% (95% CI 9.0-19.6%), (24 of 107) in the group without bronchoscopy compared with 57.8% (178 of 308) in the bronchoscopy group (p<0.001) (Fig 1).
and the NPV was 47.6% (140 of 294; 95% CI 41.8-53.5%). Accordingly, 48.4% (154 of 318) of the bronchoscopic findings were false-negative (Table 3). As no false-positive diagnoses were made by bronchoscopy specificity and PPV were both 100%.

In 7.5% (23 of 308) of all bronchoscopies, an endobronchial abnormality was found, and in 47.8% (11 of 23) of the cases, the tumour was endobronchially visible. When an endobronchial tumour was visible, the sensitivity of bronchoscopy to detect cancer was 81.8% (95% CI 47.8-96.8%). In 2.6% of the 308 bronchoscopies, an endobronchial tumour was detected, which was not visible on CT scan, also in retrospect. This accounts for 4.5% (eight of 178) of all cancer cases detected by CT scan screening in this period. Of these eight additional cancer cases, only three were stage I, the remaining five were stage III or IV. When the diagnostic performance of bronchoscopy was limited to the suspicious nodules visible on CT scan, the sensitivity to detect cancer was 8.3% (14 of 168, 95% CI 4.8-13.9%), and the NPV was 47.6% (140 of 294, 95% CI 41.8-53.5%).
The sensitivities of the various diagnostic techniques used during bronchoscopy ranged from 7.9% for brush to 45.8% for endobronchial biopsy (Table 4).

During the bronchoscopies, minor complications (nose bleeding and mild bleeding after the biopsy) occurred in only 0.6% (2 of 308) of participants. There were no major complications.
DISCUSSION

In this study, the diagnostic value of conventional white-light bronchoscopy in the NELSON trial was prospectively evaluated.

The overall sensitivity was 13.5%, and the NPV was 47.6%. The sensitivity was only 8.3% when limited to CT-detected suspicious nodules. Of all cancers detected within the time frame of this study, 4.5% were identified by bronchoscopy only and were not visible on CT.

In non-screening studies, the sensitivity of conventional bronchoscopy varied from 51% to 76%,\textsuperscript{9–14} which is much higher than the 13.5% in the NELSON trial. This can be
explained by the fact that in the present study, only 2.8% of the nodules were >30 mm, whereas in non-screening studies, lesion size ranged from 48 to 72 mm.\textsuperscript{9,10,13,14} Further, fewer lesions were endobronchially visible in the current study compared to the literature (7.3\% vs. 8-64\%).\textsuperscript{10-12} Both nodule size and endobronchial visibility were independent predictors for high diagnostic yield in the present study.

As far as we know, only Kanemoto et al\textsuperscript{24} retrospectively evaluated the diagnostic value of bronchoscopy in a selected study population in which 108 suspicious pulmonary nodules had been detected by mass screening (chest radiography or CT scan). All nodules were ≤20 mm and 42\% of the nodules were malignant; based on fluoroscopy-guided bronchoscopy or lung biopsy specimens. The drawback of that study is the selection bias of the study population and the absence of a gold standard for the outcome of the bronchoscopy. As a result, the investigators were unable to provide data on the diagnostic performance of bronchoscopy in this screening program.

According to current guidelines, bronchoscopy is recommended only for the evaluation of nodules with an air bronchogram\textsuperscript{6,25,26} without a standard position in the routine workup of suspicious pulmonary nodules. Although we did not evaluate whether the presence of an air bronchogram increased the diagnostic yield of bronchoscopy, the results clearly demonstrate that bronchoscopy is not justified for the evaluation of CT-detected pulmonary nodules, because of its very low sensitivity and NPV.

The use of more advanced bronchoscopic techniques is not yet recommended by the ACCP\textsuperscript{6}. Nevertheless, we believe that electromagnetic-navigated or peripheral endobronchial ultrasound-guided bronchoscopy may play a role in the evaluation of small, peripheral CT-detected nodules, since their sensitivity is respectively 59-74\%\textsuperscript{27-30} and 49-80\%\textsuperscript{27,31-34}. In addition, ultrathin bronchoscopy may play a role in the future for diagnostic evaluation of peripheral pulmonary nodules.\textsuperscript{35,36}

Because of the poor diagnostic performance, we do not recommend the routine use of conventional bronchoscopy for patients with suspicious CT-detected nodules, even though bronchoscopy yielded the detection of eight cancers that were not visible on CT. Only one-third of these cancers was early stage and may be treated with curative intent. It is arguable what percentage missed lung cancers is acceptable. We believe that this depends on the setting, lung cancer screening, or daily practice. In lung cancer screening trials, vast numbers of subjects are exposed to invasive procedures, which are accompanied by morbidity, anxiety and costs. Therefore, we consider the benefit of bronchoscopy too small. Moreover, only 38\% of these radiologically occult cancers were stage I. The reason that the eight cancers detected by bronchoscopy were not visible on CT may be the use of low-dose CT examinations, without the use of intravenous contrast. The lesions were, in retrospect, visible on the standard-dose CT with intravenous contrast performed in the workup of these participants. Other investigators reported that 1\%\textsuperscript{37} to 5\%\textsuperscript{6} of CT
occult tumours was detected by white-light bronchoscopy, whereas 18% was detected with autofluorescence bronchoscopy.\textsuperscript{21}

Additional diagnostic techniques, such as brush and biopsy, should only be used to evaluate visible endobronchial tumours. In the present study, we found sensitivity of >80% for brush and biopsy.

The strength of the present study lies in the fact that it was prospectively conducted and that for the majority of the suspicious nodules, histologic conformation was obtained by either surgical resection or biopsy specimen. So far, the diagnostic value of a conventional bronchoscopy has not previously been evaluated properly in a CT screening trial which included asymptomatic, high-risk participants from the general population. In addition, we were able to evaluate the diagnostic value of bronchoscopy based on individual nodule level. Despite this, our study also has its limitations. The proportion of women and the cancer detection rate in the group that did not undergo bronchoscopy was lower than in those who underwent bronchoscopy. Because sex was not associated with a higher diagnostic yield in the study, this did not introduce selection bias. The cancer detection rate in the group without bronchoscopy was lower because 20% (21 of 107) of cases were referred for non-nodular lesions or because the suspicious nodule had disappeared on the diagnostic CT scan with contrast. If all participants with positive test results had undergone bronchoscopy, the sensitivity may have been even lower, which further strengthens the present conclusions. In the workup protocol, bronchoscopy only was performed on participants with positive test results. To date, it is not known what the performance of conventional bronchoscopy is, when it is used as a screening tool, instead of as diagnostic tool. This is currently under investigation in the Pan-Canadian lung cancer screening trial.\textsuperscript{38}
CONCLUSION

In conclusion, routine use of conventional bronchoscopy in patients with suspicious CT-detected pulmonary nodules in a lung cancer screening program is not recommended.

SUPPORT STATEMENT

We thank Siemens Germany for providing four digital workstations, Roche Diagnostics for providing an unrestricted research grant, and Tom and Josephine Rijke for their legacy gift.

CONFLICTS OF INTEREST

The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. The unrestricted financial support of the sponsors provided for the costs of CT screening. The sponsors had no role in analysing or interpreting the data or in preparation of the manuscript.

ACKNOWLEDGEMENTS

We thank Roel Faber and Frank Santegoets for their assistance as information and communication technology scan managers as well as the data managers of the four screening sites: Henk Pruiksma (Haarlem), Liesbet Peeters (Leuven), Saskia van Amelsvoort-van de Vorst (Utrecht), and Ria Ziengs (Groningen).
REFERENCES


Chapter 8

Evaluation of surgical procedures

Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial


European Journal of Cardio-Thoracic Surgery
September 2012
Complications following lung surgery in the Dutch-Belgian randomized lung screening trial


ABSTRACT

To assess the complication rate in participants of the screen group of the NELSON lung cancer screening trial who underwent surgical resection and to investigate, based on a literature review, whether the complication rate, length of hospital stay, re-thoracotomy and mortality rates after a surgical procedure were different from those of the non-screening series, taking co-morbidity into account.

Between April 2004 and December 2008, 198 subjects underwent thoracic surgery. Co-morbid conditions were retrieved from the medical records. Postoperative complications were classified as minor and major.

In total, 182 thoracotomies, 5 thoracotomies after video-assisted thoracoscopic surgery (VATS), and 11 VATS procedures were performed. 36% of the participants had chronic obstructive lung disease, 16% coronary artery disease, 14% diabetes mellitus and 11% peripheral vascular disease. Following thoracotomy, 47% (88/187) had ≥1 minor (7-57% in literature) and 10% (18/187) ≥1 major complication (2-26% in literature); following VATS, 38% (6/16) had ≥1 minor complication, but no major complications. Seventeen percent (3/18) of major complications and 21% (20/96) of minor complications were observed in subjects operated for benign disease. The re-thoracotomy rate was 3%, there was no 30-day mortality after thoracotomy or VATS (0-8.3% in literature). The mortality rate of 0% after surgical procedures is low compared to non-screening series (0-8.3%); the rate of complications (53%) was within the range of published non-screening series (8.5-58%).

In conclusion, mortality rates after surgical procedures were lower in the NELSON lung cancer screening trial than in non-screening series. The rate of complications was within the same range as in non-screening series.
INTRODUCTION

It has been shown that lung cancer screening by low-dose multi-detector computer tomography (CT) can detect lung cancer at an early stage. Before considering implementation of CT screening, a reduction in lung cancer mortality has to be demonstrated by randomised clinical trials, and the balance between the benefits and harms of screening has to be evaluated thoroughly. Important aspects to be taken into account are the effects of CT screening on health-related quality of life, and the occurrence of complications associated with the work-up and treatment of participants with a positive test result.

Patient-related factors, such as a poor general health status, age and co-morbidity, contribute to the risk of postoperative pulmonary complications. Screening populations usually consist of heavy current and former smokers at an advanced age and at high risk for co-morbid disease. In several studies, it has been demonstrated that co-morbidity is predictive of morbidity and mortality related to surgical procedures. Hence, to be able to make a fair comparison with the mortality and complication rates reported in non-lung cancer screening series, the co-morbidity of the screened population should be assessed.

Our objective was to assess the complication rate in participants in the screen group of the Dutch-Belgian lung cancer screening trial (NELSON) who underwent a surgical resection, and to investigate, based on a literature review, whether the complication rate, length of stay and re-thoracotomy and mortality rates after a surgical procedure were different from those in non-screening series.

METHODS

Inclusion criteria and work-up

NELSON trial participants were current and former smokers at high risk for developing lung cancer. Detailed information on the inclusion and exclusion criteria have been reported previously. Briefly, current and former smokers aged 50–75 with a smoking history of >15 cigarettes per day during >25 years or >10 cigarettes per day during >30 years (quit ≤10 years ago) were invited. Subjects with a moderate or bad self-reported health, subjects who were unable to climb two flights of stairs and persons with a body weight ≥140 kg were excluded, as were those with a history of cancer.

The prospective screening study was approved by the Ministry of Health and by the Medical Ethical Boards of each of the four participating hospitals. Written informed consent was obtained from all participants.

In the NELSON trial, 7,557 subjects underwent a CT scan at baseline, the second screening round (1 year after baseline) and the third screening round (2 years after the second round). Subjects with a positive test result were referred for work-up to a pul-
monologist and, depending on the outcome of this work-up, a resection of the suspicious lesion was performed. The standard non-invasive work-up included a physical exam, pulmonary function test, bronchoscopy, FDG-PET-scan and a standard-dose CT scan with intravenous contrast of the chest and upper abdomen.

**CT data acquisition and image reading**

Data acquisition and image reading were as described previously. In brief, all four participating screening sites used 16-detector CT scanners (Sensation-16, Siemens Medical Solutions, Forchheim, Germany Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH, USA). Scan data were obtained in a spiral mode, with $16 \times 0.75$ mm collimation and 1.5 pitch. No contrast was administered. Data acquisition and scanning conditions were standardized and equal for baseline and repeat screening. Digital workstations (Leonardo*, Siemens Medical Solutions, Erlangen, Germany) were used in all screening sites with commercially available software for semi-automated volume measurements (LungCare*, Siemens Medical Solutions, version Somaris/5: VA70C-W).

**Nodule management and diagnostic work-up**

At baseline, a scan was considered positive if any non-calcified nodule had a solid component $>500$ mm$^3$ (about $>9.8$ mm in diameter) and indeterminate if the volume of the largest solid nodule or the solid component of a partially solid nodule was 50-500 mm$^3$ (about 4.6-9.8 mm in diameter), or $>8$ mm in diameter for non-solid nodules. Subjects with an indeterminate result underwent a follow-up scan after three months to assess nodule growth. Significant growth was defined as a change in volume between the first and second scan of $\geq 25\%$. Subjects with positive screening tests were referred to a chest physician for work-up and diagnosis. If lung cancer was diagnosed, the participant was treated for the disease and no longer underwent screening; if no lung cancer was found the regular second-round CT scan was scheduled twelve months after baseline scan. For participants with one or more new nodules on the second-round scan, the result (positive or negative) was based on the size of the nodule, as for round one; in the case of an indeterminate result, a follow-up scan was performed 6 weeks later. For participants with previously existing nodules, the second-round result was based on the volume doubling-time (VDT). If there was no growth, or if the VDT was $>600$ days, the scan was classified negative. If the VDT was $<400$ days, or if a new solid component had emerged in a previously non-solid nodule, the scan was considered positive. When the VDT was 400-600 days, the test was classified indeterminate and follow-up scanning was performed one year after the second round. For nodules with a VDT of $<400$ days, the final result was considered to be positive. If both new and existing nodules were present, the nodule with the largest volume or fastest growth determined the screening test result.
All participants with a negative second-round result were invited to undergo the third screening two years after the second round.

Work-up and staging were standardized for all screening sites according to national and international guidelines and included a physical exam, a standard CT scan with contrast of the chest and upper abdomen, FDG-PET scan and a bronchoscopy. Subjects with a negative non-surgical work-up were referred for surgery to obtain histology of the suspicious nodule. Bronchoscopies were done in accordance with Dutch national guidelines in order to evaluate the central airways and (if possible) to diagnose lung cancer or benign disease. Pulmonologists and thoracic surgeons were not blinded for the result of the positron emission tomography (PET) examination. All subjects with suspected lung cancer were discussed in multidisciplinary tumour boards, which included a thoracic surgeon, before progressing to surgery; all imaging studies were available during these meetings. National and international pathology review panels evaluated all cytological and histological specimens.

Operative details

All resections were performed at one of the four screening centres, of which three were academic institutions and one a peripheral hospital. In Groningen, three experienced thoracic surgeons were involved, in Haarlem two, in Louvain three and in Utrecht eleven. Participants with a benign diagnosis after non-surgical work-up were scheduled for the next screening round. In the remaining test-positive subjects, the suspicious nodules were removed either by VATS or thoracotomy with wedge resection and frozen section. A preoperative tissue biopsy was not routine. Lobectomies were performed only for central nodules that could not be approached by wedge resection, meaning limited resections were performed for benign lesions. If lung cancer was diagnosed by VATS, the procedure was converted to an open thoracotomy with sampling of lobar, interlobar, hilar and mediastinal lymph nodes. This is because VATS resection for lung cancer was not yet fully implemented in daily practice in the Netherlands at the time of the present study. A mediastinoscopy was performed before proceeding to VATS or thoracotomy in subjects with mediastinal lymph nodes larger than 10 mm in the short-axis and/or FDG-PET positive mediastinal lymph nodes. No specific strategies were employed to prevent prolonged air leak, such as reinforced staple lines. The chest tube was removed if there was no air leak and the fluid production was 200 ml or less per 24 hours.

Data collection and co-morbidity scoring

The date, nature, number and outcome of all adverse events related to all diagnostic and treatment procedures between April 2004 and 31 December 2008 were entered into an web-based database ‘the NELSON Management System’ by investigators at the four screening sites after completion of the diagnostic work-up and therapeutic procedures.
In addition, a hard copy of the medical records of all subjects referred for work-up and treatment was centrally stored at the data centre of Erasmus MC Rotterdam in order to review for complications.

Co-morbid conditions were retrieved from the medical records based on the medical history at the time of referral because of a positive screening test result. Subjects were defined as having chronic obstructive pulmonary disease (COPD) when the forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) ratio was <0.70 and/or the medical history mentioned COPD and the participant used inhaled steroids and/or bronchodilators. Coronary artery disease included a history of myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty or angina pectoris. Peripheral vascular disease included a history of intermittent claudication, abdominal aneurysm, percutaneous transluminal angioplasty or bypass grafting of the peripheral arteries.

**Literature search**

A review of the literature was performed using a Pubmed search up to February 2011. The search string consisted of a combination of medical subject headings [MeSH] and keywords including 'Lung Neoplasms', 'Postoperative Complications', 'Co-morbidity', 'Mortality', 'Thoracotomy', 'Thoracic Surgery, Video-Assisted' and related synonyms. We summarised the main results of the literature study and the current study with regard to co-morbidity and adverse events following thoracotomy in forest plots. This was not done for VATS procedures in view of the low number of VATS procedures in the current study. Lack or incomplete reporting of comorbidity was not used as an exclusion criterion. Studies in which all participants had previously received chemotherapy and/or radiotherapy were excluded. For studies without classification of complications, complications were scored according to our definitions of minor and major complications, provided that a complete overview of all complications was reported. In addition, in the case of studies that graded complications based on the Common Terminology Criteria for Adverse Events, grade 4–5 events were considered major complications.

**Definitions of complications**

Postoperative mortality was defined as death within 30 days after the operation or within the same hospital admission. According to EuroSCORE⁶ and Birim et al.⁷ major complications included bleeding requiring re-operation, empyema, pneumonia (Center for Disease Control and Prevention definition of nosocomial pneumonia)², myocardial infarction, renal failure requiring temporary or permanent dialysis, postoperative stroke, critical arrhythmia (ventricular fibrillation, ventricular tachycardia) and pulmonary embolism. Additional major complications included respiratory failure requiring ventilator support for >48 hours⁸ and postoperative heart failure with pulmonary oedema.⁹ We
classified a chylothorax, haemothorax and gastro-intestinal complications requiring operative re-intervention (re-thoracotomy) or laparotomy as major complications. Non-life threatening complications were classified as minor complications. All minor and major complications were scored for each VATS and thoracotomy procedure.

**Statistical analysis**

Data were analysed using SPSS (version 17.0, SPSS, Inc., Chicago, IL, USA). A two-tailed Mann–Whitney U-test was used to analyse continuous data in the absence of normal distribution. Chi²-test was used for binomial or categorical data and Fisher's exact test for small groups. Statistical significance was defined as a p-value <0.05. Asymmetric confidence intervals (CI) were calculated for the literature study data presented in Figures 1 and 2 using log-linear regression, where we estimated the observation as the log of a β; a weighted standard error (SE) was calculated for this β and subsequently the CI was obtained.

**RESULTS**

**Background and treatment characteristics**

A total of 415 subjects had a positive test result following CT screening between April 2004 and December 2008. The role of FDG-PET in the work-up of these test-positive participants has been described elsewhere. In seventeen of the participants surgical procedures consisted of a mediastinoscopy only; fifteen were subsequently diagnosed with lung cancer, which was at an early stage in two, who were inoperable because of co-morbidity (Figure 3). In 178 participants, the final benign diagnosis was based on FDG-PET, CT with intravenous contrast or biopsies. Transthoracic biopsies were only performed in 5% (22/415) of test-positive participants.

In twenty-two participants cancer was diagnosed but the subjects did not undergo resection because of: advanced stage disease (n=13) or co-morbidity (n=9), the latter group was treated with stereotactic radiotherapy. In the twenty-two subjects, diagnosis was based on biopsy (n=15) cases, or imaging studies (n=7). In 198 participants, non-surgical work-up showed lung cancer or was inconclusive. These subjects underwent a resection either via thoracotomy (n=182), VATS converted to thoracotomy (n=5), or wedge resection by VATS (n=11) (Figure 3).

The characteristics of the subjects who underwent a resection are presented in Tables 1 and 2. The most frequent comorbid conditions were COPD (36%), coronary artery disease (16%), diabetes mellitus (14%) and peripheral vascular disease (11%) (Table 2). Table 1 shows the clinical and pathological lung cancer stages. Three subjects with clinical stage III (T4N0M0) were operated and a microscopic complete resection could
be achieved. Five subjects had pathological stage IV lung cancer after surgery. Two of them had an indeterminate preoperative FDG-PET result, which in retrospect appeared to be metastatic lesions. In two patients the preoperative FDG-PET was false-negative for distant metastasis. In one subject, no preoperative FDG-PET was made due to an
Figure 2. Prevalence of complications and mortality in subjects undergoing thoracotomy

Complication and mortality rates after thoracotomy in the NELSON lung cancer screening trial in comparison with non-screening series from the literature.

administrative error; the postoperative FDG-PET scan showed distant metastasis. Of eight patients with pathological stage III disease, this was due to unforeseen N2 disease in seven patients and due to a bronchoalveolar carcinoma in the middle lobe, which was resected in one patient; a second suspicious upper lobe nodule could not be found during surgery. The clinical stage at that time was cT1N0M1. One month later the upper lobe
nodule showed rapid growth and mediastinal lymphadenopathy was noted (clinical stage T1N2M0); mediastinoscopy showed metastasis of a large cell carcinoma.

Table 1. Characteristics of participants who underwent surgery after a positive screening test

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lung surgery n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>35 (18)</td>
</tr>
<tr>
<td>Age - mean(range)</td>
<td>61 (50-74)</td>
</tr>
<tr>
<td>Pack-years - mean(range)</td>
<td>46 (21-133)</td>
</tr>
<tr>
<td>COPD</td>
<td>71 (36)</td>
</tr>
<tr>
<td>GOLD I</td>
<td>38 (19)</td>
</tr>
<tr>
<td>GOLD II</td>
<td>20 (10)</td>
</tr>
<tr>
<td>GOLD III</td>
<td>6 (3)</td>
</tr>
<tr>
<td>GOLD stage unknown</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>4 (2)</td>
</tr>
<tr>
<td>(Bi)lobectomy</td>
<td>137 (70)</td>
</tr>
<tr>
<td>True cut biopsy, segment/wedge resection</td>
<td>56 (26)</td>
</tr>
<tr>
<td>Sternotomy</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td>139 (70)</td>
</tr>
<tr>
<td>Other cancer</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Benign abnormalities</td>
<td>47 (24)</td>
</tr>
<tr>
<td>Clinical lung cancer stage a</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>117 (84)</td>
</tr>
<tr>
<td>II</td>
<td>18 (13)</td>
</tr>
<tr>
<td>III</td>
<td>3 (2)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pathological lung cancer stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>112 (81)</td>
</tr>
<tr>
<td>II</td>
<td>11 (8)</td>
</tr>
<tr>
<td>III</td>
<td>11 (8)</td>
</tr>
<tr>
<td>IV</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>198 (100)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: COPD = Chronic Obstructive Pulmonary Disease, GOLD = Global initiative for chronic Obstructive Lung Disease.

a Sixth edition of TNM classification for lung cancer.
Complications after surgery

Tables 3 and 4 present all complications observed. Following thoracotomy, 47% (88/187) had at least one minor and 10% (18/187) at least one major complication. Thirty-eight percent (6/16) of the VATS procedures was complicated by at least one minor complication, but no major complications have been observed. As 5% had both minor and major complications, the proportion of participants with any complication was 53%. Seventeen percent (3/18) of major complications and 21% (20/96) of minor complications were seen in subjects operated for benign disease.

The overall median length of hospital stay was 13 days (2-51 days) after thoracotomy and 8 days (4-12 days) after VATS. In subjects with minor complications, this was 15 days (6-51 days) and 9 days (7-12 days), respectively. In the case of major complications following thoracotomy, the median length of stay was 21 days (range 8-51 days). The re-thoracotomy rate was 3% after thoracotomy and 0% after VATS. Re-admissions occurred in 5% of those who underwent a thoracotomy (eight after minor complications and one after a major complication), but were absent after VATS. There was no 30-day mortality after thoracotomy or VATS in the NELSON trial.

Table 5 shows that a higher rate of minor complications was seen in the case of more extensive resections. Limited resections (true-cut biopsies, and wedge and segment resections) had lower rates of minor complications (OR 0.51, 95% CI 0.26-1.03, p-value 0.06) compared to bilobectomy, lobectomy and pneumonectomy. No significant correlation could be established between type of resection and risk of major complications.

Five subjects were re-admitted because of minor complications: three subjects with chest pain and one with dyspnoea a pulmonary embolism could be excluded; in one
### Table 3. Minor complications following thoracotomy and VATS procedures

<table>
<thead>
<tr>
<th>Minor complication</th>
<th>Thoracotomy n (%)</th>
<th>VATS n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air-leakage &gt;5 days</td>
<td>42 (23)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>17 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>16 (9)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Diaphragm paralysis</td>
<td>10 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Chest tube &gt;5 days</td>
<td>8 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>8 (4)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Drop hand</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Delirium</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>2 (2)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Persistant ptosis</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Paralysis serratus anterior muscle</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Ileus</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Pleuritic effusion</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: VATS = video-assisted thoracoscopic surgery; COPD = Chronic Obstructive Pulmonary Disease.*

### Table 4. Major complications following thoracotomy

<table>
<thead>
<tr>
<th>Major complication</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Empyema</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Bleeding, re-operation</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Chylothorax, re-operation</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Bowel perforation</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>
subject with pleural effusion an empyema was excluded; no repeat chest tube placement or thoracocentesis was necessary (Table 3). Atelectasis was diagnosed by chest radiograph in nine subjects; in five subjects bronchoscopy was performed.

Table 5. Complications according to type of surgery

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Thoracotomy n (%)</th>
<th>Minor complications</th>
<th>Major complications</th>
<th>VATS n (%)</th>
<th>Minor complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total 187 (100)</td>
<td>53 31 88 (47)</td>
<td>127 16 2 18 (10)</td>
<td>20 16 (100)</td>
<td>4 1 1 6 (38)</td>
</tr>
<tr>
<td>True cut biopsy</td>
<td>6 (3)</td>
<td>2 0 2 (33)</td>
<td>2 0 0 (0)</td>
<td>0 0 (0)</td>
<td>0 0 0 0 (0)</td>
</tr>
<tr>
<td>Wedge resection</td>
<td>35 (19)</td>
<td>8 3 11 (31)</td>
<td>14 3 0 3 (9)</td>
<td>3 16 (100)</td>
<td>4 1 1 6 (38)</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>4 (2)</td>
<td>1 0 1 (25)</td>
<td>1 0 0 (0)</td>
<td>1 0 (0)</td>
<td>0 0 0 0 (0)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>131 (70)</td>
<td>40 26 69 (53)</td>
<td>101 11 2 13 (10)</td>
<td>15 0 (0)</td>
<td>0 0 0 0 (0)</td>
</tr>
<tr>
<td>Bilobectomy</td>
<td>5 (3)</td>
<td>1 2 4 (80)</td>
<td>8 0 0 (0)</td>
<td>1 0 (0)</td>
<td>0 0 0 0 (0)</td>
</tr>
<tr>
<td>Sleeve resection</td>
<td>1 (1)</td>
<td>0 0 0 (0)</td>
<td>0 0 0 0 (0)</td>
<td>0 0 (0)</td>
<td>0 0 0 0 (0)</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>4 (3)</td>
<td>1 0 1 (25)</td>
<td>1 0 0 0 (0)</td>
<td>0 0 (0)</td>
<td>0 0 0 0 (0)</td>
</tr>
<tr>
<td>Sternotomy</td>
<td>1 (1)</td>
<td>0 0 0 (0)</td>
<td>0 0 0 0 (0)</td>
<td>0 0 (0)</td>
<td>0 0 0 0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>187 (100)</td>
<td>53 31 88 (47)</td>
<td>127 16 2 18 (10)</td>
<td>20 16 (100)</td>
<td>4 1 1 6 (38)</td>
</tr>
</tbody>
</table>

Data from the literature review

Literature search revealed sixteen studies on thoracotomy and twelve studies on both thoracotomy and VATS which met the selection criteria (Appendix Table 1). The prevalence of comorbidity in the literature on thoracotomy ranged from 43% to 80%3,7 (Appendix Table 1). Figure 1 shows the prevalence of co-morbidities in subjects who underwent a thoracotomy in non-lung cancer screening studies. The most frequently reported co-morbid conditions were COPD (10–52%), coronary artery disease (10-52%), diabetes mellitus (7-19%) and peripheral vascular disease (6-26%). The number of lobectomies performed during thoracotomy procedures varied from 40% to 100%.22 (Suemitsu et al. 2009), while pneumonectomies were performed in 0-27%10,14 (Pagni et al. 1998). The percentage of stage I disease in the thoracotomy group was 69.0% (median, range 31-100%).10,11 Mortality rates reported after thoracotomy varied from 0% to 8% (Figure 2). The National Emphysema Treatment Trial (NETT) found a 90-day mortality of 5% following lung volume reduction surgery in subjects with severe emphysema (mean FEV1 0.7 l; 26% of predicted).12 Figure 2 shows major and minor complications after thoracotomy, ranges varied respectively from 4-26% and 7-57%. The median length of hospital stay after thoracotomy reported in the literature was 5–22 days13 (Boffa et al, 2008). The reported re-thoracotomy rates after a thoracotomy varied from 0% to 9%.7,13

In the majority of the studies on VATS, lobectomies were performed. Complications after VATS were reported in 9-51% (Kim et al. 2010, Petersen et al. 2010) and major
complications in only 0-12%\(^\text{17}\) (Jaklitsch et al. 1996, Petersen et al. 2010). The median length of stay after a VATS reported in the literature was 4-23 days\(^\text{13}\) (Villamizar et al. 2009). The reported re-operation rate after a VATS varied from 1% to 5%\(^\text{13}\) (Paul et al. 2010), with a mortality rate of 0-4%\(^\text{21}\) (Handy et al. 2009).

**Figure 3. Flowchart of surgical procedures and outcomes**

![Flowchart](image)

*Surgical procedures and outcomes in 415 screen positives of the NELSON randomised lung cancer screening trial.*
DISCUSSION

Our study compared the complications rates, length of hospital stay, rethoracotomy and mortality rates of participants of the NELSON trial who underwent thoracic surgery with data from non-screening series. The comparison with non-screening series could be made because we demonstrated that the age range and co-morbidity level of the NELSON trial participants who underwent a surgical resection was the same as those in the non-screening series.

Literature review and complications
The studies included in our literature review displayed a large heterogeneity with respect to the definition, classification and way in which data on complications have been collected so far. For example, prolonged air leak has been defined as >5 days\(^7\) and >7 days.\(^{13}\) In addition, chest-tube management with regard to output differs in studies or is not defined. Few authors make a distinction between minor and major complications, and complication data are collected by reviewing individual patient charts, based on ICD-9 codes\(^{14}\) or on claims in Medicare files.\(^3\) The latter methods may lead to underreporting of complications, especially for minor complications. Probably because we screened all individual patient files, our minor complication rates are in the higher range of what has been reported before. The most important observation was the relatively low rate of major complications and the absence of postoperative mortality after the thoracotomy and VATS procedures performed in the screen group of the NELSON trial. This could probably be explained by the fact that screening participants were asymptomatic individuals, screen-detected tumours are usually smaller\(^{15,16}\) and that pneumonectomies were less often required in the NELSON compared to published studies, wherein more complex resections with a higher expected complication rate were performed. Nevertheless, the proportion of stage I disease was in the same range of what has been reported in our literature review of the non-screening series.

Lung cancer-screening studies and complications
In a recent study, Infante et al.\(^{17}\) report on the outcome of surgical procedures in the DANTE trial. A total of 59 subjects underwent a thoracotomy procedure. Three died following the thoracotomy and a total of twenty complications were noted, which were major complications in nine subjects. No major complications or postoperative deaths were seen in subjects diagnosed with benign disease. Fifteen subjects underwent a VATS procedure; no postoperative deaths or major complications were noted in this subset of patients. The postoperative mortality rate in the DANTE study was higher than expected. All subjects had central tumours of stage IIA or higher, two had co-morbid conditions and two had undergone a pneumonectomy. Veronesi et al.\(^{18}\) reported that 25% of subjects
developed complications following thoracotomy and VATS procedures, which were serious in 6% and required re-operation in 2%. No postoperative complications or mortality was noted in the subjects with benign disease. While only two subjects underwent a pneumonectomy in this study, pneumonectomies were performed on four subjects in our study. Infante et al. performed a relatively high number of pneumonectomies, in seven subjects in total, which may explain the higher mortality rate. The rate of major complications in lung cancer screening studies is at the lower limit of the range published in the literature. Mortality rates are also at the lower limit, however with more extensive resections the rate may be the same as in the literature. An important observation to make is that no major complications and no deaths were seen in subjects operated for benign disease. However, in our study 17% (3/18) of major complications and 21% (20/96) of minor complications were observed in subjects operated for benign disease.

**Length of stay after VATS and thoracotomy**

Despite these observations, the length of stay (LOS) after thoracotomy and VATS procedures was not shorter for NELSON participants than the average. This can be explained by the fact that patients in the Netherlands and Belgium usually stay in the surgery or pulmonary medicine department and do not routinely go to a short-stay facility after surgery. It has been shown that LOS decreases when the use of skilled nursing facilities increases. Another possible explanation may be that in the Netherlands and Belgium it is socially much less accepted to discharge patients home after three or four days. None of the participants in the NELSON study went to a long-term nursing facility. Prolonged air leak has been described as the most important factor for prolonged hospital stay, this was not the case in the current study, presumably because of less severe emphysema.

**Type of resection**

In the NELSON trial, VATS procedures were only performed for wedge resections, whereas in the majority of studies VATS was used to perform lobectomies, which is a major difference. This is due to the fact that VATS lobectomy had only recently been introduced in the Netherlands at the time of the study. The proportion of lobectomies in the thoracotomy group was comparable with the literature. Therefore, and because of the low number of VATS procedures in the current study, the comparison we made between the VATS results in the NELSON screening trial and the non-screening series from the literature should be interpreted with caution. There is general consensus in the literature that morbidity and mortality rates after VATS are lower than after thoracotomy, and that patients have a better postoperative physical functioning and a shorter postoperative length of stay. In addition, the oncological validity of VATS resections for lung cancer has been proved as 5-year survival rates are similar to those after thoracotomy. We therefore believe that lung cancer screening sites should be equipped to perform VATS
procedures, especially in view of the substantial risk of false-positive test results and resections for benign disease.¹

SUMMARY

In the NELSON lung cancer screening trial, the rate of minor complications after thoracotomy and VATS was in the upper range of what has been reported for the non-screening series, while the rate of major complications was in the lower range. The postoperative length of stay was not shorter than in the literature. The re-thoracotomy rate for complications such as a haemothorax requiring re-intervention in the NELSON trial was in the range reported in the literature, but no re-thoracotomies were performed after VATS. No postoperative deaths were observed after the thoracotomy and VATS procedures.

To our knowledge, this is the first report on the prevalence of co-morbidity and of complications in a lung cancer screening population. Veronesi et al. presented data on complications as an abstract without information on co-morbidity.¹⁸ Their results support our encouraging data, which demonstrate that participants are at low risk of major complications or postoperative death following thoracotomy or VATS lung cancer screening. Nonetheless, the high rate of resection for benign disease and associated morbidity continues to be a concern. Seventeen percent of the major complications and 21% of the minor complications were seen in subjects operated for benign disease. The use of FDG-PET²⁴ and combination of FDG-PET and VDT²⁵ may help to reduce the number of resections for benign disease.

In conclusion, mortality rates after surgical procedures were lower in the NELSON lung cancer screening trial than in non-screening series. The rate of minor and major complications is within the range of non-screening series.
SUPPORT STATEMENT

The NELSON trial is financially supported by Zorg Onderzoek Nederland-Medische Wetenschappen (ZonMw), KWF Kankerbestrijding, Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen (RvvZ), G. Ph. Verhagen Foundation, Rotterdam Oncologic Thoracic Study Group (ROTS), Erasmus Trust Fund, Stichting tegen Kanker (Belgium), Vlaamse Liga tegen Kanker and LOGO Leuven and Hageland. We also wish to thank Tom and Josephine De Rijke for their legacy gift.

CONFLICTS OF INTEREST

Roche Diagnostics provided a grant for the performance of proteomics research. Siemens Germany provided four digital workstations and LungCARE for the performance of 3D measurements.

ACKNOWLEDGEMENTS

We thank the surgeons at the four screening sites who performed the surgeries on participants in the NELSON study. Groningen: D.J. Drenth, T.J. Klinkenberg and Y.N. Drijver; Haarlem: H. Rijna and H.L.F. Brom. Louvain: G. Decker and E. Internullo and Utrecht: J. Kluin, P.F.A. Bakker-de Wekker, R.C.A. Meijer and E.Z. Ramjankhan. We thank Harry de Koning (Department of Public Health, Erasmus MC Rotterdam), Matthijs Oudkerk (Department of Radiology, UMC Groningen), Willem Mali (Department of Radiology, UMC Utrecht) and Frederik Thunnissen (Department of Pathology, VUMC Amsterdam) for their critical review of the manuscript and their comments, which have been appreciated. Our thanks to René Vernhout (Department of Pulmonology, Erasmus MC Rotterdam) for developing the database used to register complications and data management support. We thank Roel Faber, ICT manager, for his assistance, and Linda van Dongen for her support in data management; and also the local data managers: Henk Pruiksma (Haarlem), Liesbet Peeters (Louvain), Saskia van Amelsvoort-van de Vorst (Utrecht) and Ria Ziengs (Groningen). Finally, our thanks to Caspar Looman for his assistance in statistics.
REFERENCES


## APPENDIX

Table 1. Outline studies on thoracotomy and studies on thoracotomy and VATS

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Participants</th>
<th>Age*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagni</td>
<td>1971-1996</td>
<td>385</td>
<td>75 (70-96)</td>
</tr>
<tr>
<td>Thomas</td>
<td>1975-1996</td>
<td>500</td>
<td>74 ± 3</td>
</tr>
<tr>
<td>Moro</td>
<td>1979-2003</td>
<td>588</td>
<td>63 (33-86)</td>
</tr>
<tr>
<td>Igai†</td>
<td>1982-2008</td>
<td>37</td>
<td>82 ± 2.3</td>
</tr>
<tr>
<td>Bach</td>
<td>1985-1996</td>
<td>2,118</td>
<td>≥ 65</td>
</tr>
<tr>
<td>Sirbu</td>
<td>1986-2001</td>
<td>273</td>
<td>73 (70-88)</td>
</tr>
<tr>
<td>Memtsoudis</td>
<td>1988-2002</td>
<td>512,758</td>
<td>62 (1-91)</td>
</tr>
<tr>
<td>Birim</td>
<td>1989-2001</td>
<td>125</td>
<td>74 (70-82)</td>
</tr>
<tr>
<td>Harpole</td>
<td>1991-1995</td>
<td>3,516</td>
<td>64 (22-91)</td>
</tr>
<tr>
<td>Birim</td>
<td>1996-2001</td>
<td>205</td>
<td>64 (29-82)</td>
</tr>
<tr>
<td>Sueumitsu</td>
<td>1996-2006</td>
<td>756</td>
<td>20-90</td>
</tr>
<tr>
<td>Yang†</td>
<td>1996-2003</td>
<td>508</td>
<td>52 (23-79)</td>
</tr>
<tr>
<td>Matsuoka</td>
<td>1997-2004</td>
<td>40</td>
<td>82 (80-88)</td>
</tr>
<tr>
<td>Sugiuara†</td>
<td>1997-1998</td>
<td>22</td>
<td>61 ± 9</td>
</tr>
<tr>
<td>Meguid</td>
<td>1998-2003</td>
<td>26,310</td>
<td>66</td>
</tr>
<tr>
<td>Handy†</td>
<td>1998-2007</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Whitson†</td>
<td>1998-2005</td>
<td>88</td>
<td>65</td>
</tr>
<tr>
<td>Allen</td>
<td>1999-2004</td>
<td>1,023</td>
<td>68 (23-89)</td>
</tr>
<tr>
<td>Berry†</td>
<td>1999-2007</td>
<td>119</td>
<td>76 ± 0.2</td>
</tr>
<tr>
<td>Boffa</td>
<td>1999-2006</td>
<td>9,033</td>
<td>67 (20-94)</td>
</tr>
<tr>
<td>Scott†</td>
<td>1999-2004</td>
<td>686</td>
<td>68 ± 9</td>
</tr>
<tr>
<td>Villamizar†</td>
<td>1999-2008</td>
<td>382</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Little</td>
<td>2001</td>
<td>11,668</td>
<td>67</td>
</tr>
<tr>
<td>Mishra</td>
<td>2001-2005</td>
<td>597</td>
<td>69 (63-74)</td>
</tr>
<tr>
<td>Flores†</td>
<td>2002-2007</td>
<td>343</td>
<td>67 (35-89)</td>
</tr>
<tr>
<td>Cattaneo†</td>
<td>2002-2005</td>
<td>82</td>
<td>76 (70-89)</td>
</tr>
<tr>
<td>Paul†</td>
<td>2002-2007</td>
<td>1,281</td>
<td>65 ± 12</td>
</tr>
<tr>
<td>NELSON</td>
<td>2004-2008</td>
<td>187</td>
<td>62 (50-74)</td>
</tr>
<tr>
<td>Infante†</td>
<td>2001-2009</td>
<td>59</td>
<td>64 (64.0-64.7)</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: VATS = video-assisted thoracoscopic surgery.

* Median (range) or, mean ± standard deviation.
† Thoracotomy arm.
Table 2. Outline of studies on VATS and studies VATS and thoracotomy

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Participants</th>
<th>Age*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igai†</td>
<td>1982-2008</td>
<td>58</td>
<td>83 ± 2.4</td>
</tr>
<tr>
<td>McKenna</td>
<td>1992-2004</td>
<td>1,100</td>
<td>71 (16-94)</td>
</tr>
<tr>
<td>Walker</td>
<td>1992-2001</td>
<td>178</td>
<td>66 (43-85)</td>
</tr>
<tr>
<td>Congregado</td>
<td>1993-2006</td>
<td>237</td>
<td>61 (12-79)</td>
</tr>
<tr>
<td>Yang†</td>
<td>1996-2003</td>
<td>113</td>
<td>54 (9-77)</td>
</tr>
<tr>
<td>Sugiura†</td>
<td>1997-1998</td>
<td>22</td>
<td>62 ± 12</td>
</tr>
<tr>
<td>Handy†</td>
<td>1998-2007</td>
<td>49</td>
<td>63</td>
</tr>
<tr>
<td>Whitson†</td>
<td>1998-2005</td>
<td>59</td>
<td>67</td>
</tr>
<tr>
<td>Berry†</td>
<td>1999-2007</td>
<td>219</td>
<td>76 ± 0.2</td>
</tr>
<tr>
<td>Scott†</td>
<td>1999-2004</td>
<td>66</td>
<td>71 ± 9.7</td>
</tr>
<tr>
<td>Villamizar†</td>
<td>1999-2008</td>
<td>697</td>
<td>67± 10</td>
</tr>
<tr>
<td>Nakanishi</td>
<td>2000-2006</td>
<td>58</td>
<td>70 (52-90)</td>
</tr>
<tr>
<td>Cattaneo†</td>
<td>2002-2005</td>
<td>82</td>
<td>76 (70-88)</td>
</tr>
<tr>
<td>Flores</td>
<td>2002-2007</td>
<td>328</td>
<td>67 (36-90)</td>
</tr>
<tr>
<td>Paul†</td>
<td>2002-2007</td>
<td>1,281</td>
<td>65 ± 12.1</td>
</tr>
<tr>
<td>Kim</td>
<td>2003-2008</td>
<td>704</td>
<td>57 (12-86)</td>
</tr>
<tr>
<td>Petersen</td>
<td>2005-2008</td>
<td>197</td>
<td>65 (44-85)</td>
</tr>
<tr>
<td>Belgers</td>
<td>2006-2008</td>
<td>70</td>
<td>66 (41-85)</td>
</tr>
<tr>
<td>Infante†</td>
<td>2001-2009</td>
<td>15</td>
<td>64 (64.0-64.7)</td>
</tr>
<tr>
<td>NELSON</td>
<td>2004-2008</td>
<td>16</td>
<td>61(52-72)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: VATS = video-assisted thoracoscopic surgery.

* Median (range) or, mean ± standard deviation.
† VATS arm.
Part IV

Evaluation of effectiveness
Chapter 9

Endpoint determination

Uniform and blinded cause of death verification in a lung cancer CT screening trial.

Horeweg N,
van Klaveren RJ,
Groen HJM,
Lammers JWJ,
Weenink C,
Nackaerts K,
Mali W,
Oudkerk M,
de Koning HJ

Lung Cancer
September 2012
Uniform and blinded cause of death verification in a lung cancer CT screening trial


**ABSTRACT**

Disease-specific mortality is the final outcome of a lung cancer screening trial, therefore cause of death verification is crucial. The use of death certificates for this purpose is debated because of bias, inaccurate completion and incorrect ante mortem diagnoses. A cause of death evaluation process was designed to ensure a uniform and unbiased determination of the graduation of certainty that lung cancer was the underlying cause of death. An independent clinical expert committee will review the medical files of all deceased participants once diagnosed with lung cancer and will make use of a flow chart and predetermined criteria. A pilot study of fifty cases was conducted to determine the performance of this process and to compare the outcome with the official death certificates. The independent review has shown an agreement of 90% (kappa 0.65), which demonstrates a uniform classification. The sensitivity and specificity of the death certificates for lung cancer specific mortality were 95.2 and 62.5%. This demonstrates a limited distinctive character of the death certification process in lung cancer patients. Our results imply that the final outcome of a lung cancer screening trial cannot reliably be established without predetermined criteria and an independent review of blinded cases.
INTRODUCTION

Lung cancer is the first cause of cancer-related death in males and the second in females globally, accounting for 1.4 million deaths per year. Despite treatment advances, survival has not improved substantially over the past 30 years, mainly because the majority of the patients have distant metastasis at the time of diagnosis. The early detection of lung cancer by screening asymptomatic smokers with low dose computer tomography (CT) scanning is a promising strategy to reduce lung cancer mortality, since the results of the National Lung Screening Trial (NLST) were published.

Disease-specific mortality is the outcome of lung cancer screening; therefore, cause of death (CoD) verification is crucial. The use of death certificates for this purpose is debated for several reasons. Firstly, two forms of bias especially affect death certification in screening trials. Sticky-diagnosis bias; because lung cancer is more likely to be diagnosed in the screen arm, deaths are more likely to be attributed to lung cancer compared to the usual care arm. Slippery-linkage bias; deaths as a result of interventions for lung cancer may be difficult to trace back to screening and could easily be certified as death due to other causes. Secondly, the merit of death certificates depends on the accuracy of the certifying clinician and nosologist and the establishment of a correct ante mortem diagnosis. Common reasons for misclassification are coinciding malignancies, considerable comorbidity and death after a surgical procedure. Finally, the sensitivity and specificity of the death certificate has been reported to range from 84.5 to 99.7% of screening and 91.3 to 99.7%; causing an error that tends to reduce the effect of screening.

To overcome these problems clinical expert committees (CEC), reviewing the medical files of the deceased participants to determine the cause of death, are frequently employed in cancer screening trials. The additional value of a CEC depends on the use of predetermined criteria and a thorough and independent evaluation of all cases with lung cancer blind towards each arm, to prevent an unbalanced outcome between the study arms.

We hypothesized that a clinical expert committee cannot reliably establish the outcome of a lung cancer screening trial, unless they are independent and review the medical files blinded and with predetermined criteria and flowcharts. The aim of this study is to develop a CoD review process protocol that will be used in the Dutch-Belgian lung cancer CT screening trial (NELSON). The performance of the protocol has been tested in a pilot and the outcomes will be compared with the official death certificates.
METHODS

Study design and subjects for the NELSON trial
Details of the design and conduct of the Dutch-Belgian lung cancer screening trial have been reported elsewhere.\textsuperscript{15,16} Briefly, randomly assigned eligible participants underwent CT screening at baseline (first round), 1 year later (second round), 3 years later (third round) and 5.5-year later (fourth round) or no screening. The purpose of the trial is to determine whether at 10 years after randomisation, CT screening will have reduced mortality from lung cancer by at least 25%.\textsuperscript{16} The trial was approved by the Dutch Minister of Health and the ethics board at each participating centre.\textsuperscript{4} All participants provided written informed consent for the evaluation of personal data from hospital charts and national registers. The CoD evaluation process of the NELSON trial was designed to ensure a uniform and unbiased determination of the primary cause of death in participants with lung cancer.

Identification of subjects for the CoD review and data collection
The causes of death of all participants of the NELSON trial that are diagnosed with lung cancer (during their lifetime or at autopsy) are subject of the ‘review process’ to ensure a valid determination of the primary outcome measure of the screening trial. The lung cancer cases are identified by linkages with the national cancer registries of the Netherlands and Belgium and by checking all official death certificates for the diagnosis lung cancer, which are obtained from Statistics Netherlands and the Flemish Agency for Care and Health. For all identified cases, the diagnosis of lung cancer is verified by a pathology panel\textsuperscript{17} or clinical experts for cases without cytology or histology. This verification process of the lung cancer diagnosis was performed separately from the CoD-verification process in the NELSON-trial and will not be addressed in this manuscript.

After the identification of the subjects, all relevant medical information will be collected and blinded for the participant’s identity and study arm by an individual who is not otherwise involved in the trial. The medical files include: information provided by the general practitioner, discharge, outpatient visit letters, reports of radiology, nuclear medicine, pathology and microbiology, laboratory results, and autopsy reports.

Formation of the clinical expert committee
All cases will be reviewed and classified separately by the three members of the CEC, who are no employees of the screening trial. The committee is formed by a pulmonologist–oncologist and pathologist specialised in lung oncology and a clinical epidemiologist specialised in screening. For a random sample of 10%, cases with disagreement and all intervention related deaths the committee will meet. An international committee will be consulted in case no consensus is reached.
The cause of death evaluation process protocol

The evaluation process performed by the experts will be guided by the use of a flowchart (Figure 1a-d in Appendix) and a detailed list of criteria (Table 1 in Appendix). The product of the evaluation is the classification of the cause of death of the participant in one of the six categories which define graduation of certainty that lung cancer was the primary cause of death (Table 1).

Table 1. Classification of the cause of death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely lung cancer death</td>
<td>Death certainly as a direct result of (second primary) lung cancer, a paraneoplastic syndrome or a diagnostic or therapeutic intervention, including euthanasia and palliative sedation. No clear other cause of death is present.</td>
</tr>
<tr>
<td>Probable lung cancer death</td>
<td>Participants with (second primary) lung cancer with evidence of loco-regional or distant disease progression or a paraneoplastic syndrome. It is uncertain whether this is the final direct cause of death. No clear other cause of death is present.</td>
</tr>
<tr>
<td>Possible lung cancer death</td>
<td>Participants with (second primary) lung cancer with evidence of loco-regional or distant disease progression or a paraneoplastic syndrome and one or more coinciding malignancies. It is not possible to determine which malignancy was the primary cause of death.</td>
</tr>
<tr>
<td>Unlikely lung cancer death</td>
<td>Participants with (second primary) lung cancer, but without evidence of loco-regional or distant disease progression, a paraneoplastic syndrome or death as a result of an intervention for lung cancer. No clear other cause of death is present.</td>
</tr>
<tr>
<td>Definitely no lung cancer death</td>
<td>The cause of death is definitely not a direct or indirect result from (second primary) lung cancer, a paraneoplastic syndrome or an intervention for lung cancer. Another cause of death is present.</td>
</tr>
<tr>
<td>Intercurrent death with lung cancer as contributing factor</td>
<td>Only use this option when the cause of death cannot be classified as listed above. The cause of death is definitely not a direct result from (second primary) lung cancer. Another cause of death is present and lung cancer contributed to the death of the patient.</td>
</tr>
</tbody>
</table>

Design and subjects of the CoD pilot

Before the implementation of the protocol we decided to perform a pilot study by ourselves with a limited number of cases to test its user-friendliness and performance compared with the official death certificates. Therefore, we included the first fifty consecutive deceased participants diagnosed with lung cancer. In contrary to the CEC of externals to be formed for the review of all lung cancer deaths, a medical doctor (N.H.) and a clinical epidemiologist (H.J.d.K), internals of the NELSON-trial formed the committee for the pilot study. The collection and blinding of the medical files and the review process itself was performed as described. After the completion of the evaluation of the cases by
both reviewers separately, the reviewers met and discussed the cases with disagreement. Two of the pulmonologist–oncologists of the NELSON trial (H.J.M.G. and J.-W.J.L.) were consulted in case of persistent disagreement. After that, the final outcome of the pilot study was compared with the primary cause of death on the official death certificate.

**Analysis**

The primary cause of death is defined as 'the disease that initiated the chain of morbid events directly leading to death'. Lung cancer mortality, the primary endpoint of the study, is defined as “definitely” or “probable lung cancer death” (Table 1). “Possible”, “unlikely” and “definitely no lung cancer death” and “intercurrent death with lung cancer as a contributing factor” are considered as death due to other causes (Table 1).

The agreement between the two reviewers of the CoD pilot is assessed by means of kappa statistics. A kappa of 1 and 0, respectively indicates a perfect agreement and no agreement.

The cause of death, as assigned by the review committee of the pilot after consensus meeting, is considered as the gold standard. The sensitivity and specificity of the official death certificates were defined as the proportion of lung cancer deaths assigned by both sources and as death due to other causes.

Because it is not yet allowed to analyse the data by study arm, no absolute numbers of lung cancer deaths per arm are disclosed. Therefore, it is not possible to determine if the CoD review process enhances or attenuates the effect of screening.

**RESULTS**

The baseline characteristics, base for the diagnosis of lung cancer and the disease stage of the fifty subjects that were included in the pilot are displayed in Table 2. The separate classification of the cause of death by the reviewers is shown in Table 3. In thirty-eight of the fifty participants (76%) the reviewers reached a concordant conclusion. The twelve remaining cases with disagreement had; significant comorbidity (n=3), multiple malignancies (n=2), death after an intervention (n=3) and death indirectly caused by lung cancer (n=4), such as death due to post-obstruction pneumonia or paraneoplastic pulmonary embolism. However, when clustering all “definitely” and “probable” lung cancer deaths into one group and “possible”, “unlikely” and “definitely not” lung cancer death and “intercurrent death” into another, the differences were minimal; agreement in 45 cases (90%) resulting in a kappa of 0.65.

The comparison between the results of the CoD review, after consensus meeting, and the primary cause of death on the official certificates is displayed in Table 4. The sensitivity and specificity of the death certificates are 95.2% (95% confidence interval:}
84.2-98.7%) and 62.5% (95% confidence interval: 30.6–86.3%), respectively. Disagreement was observed in 10% (5 of 50 individuals) with the following causes of death: adult respiratory distress syndrome after lobectomy, rupture of an abdominal aneurysm during chemotherapy, another malignancy besides lung cancer in two cases (breast carcinoma and acute myeloid leukaemia) and small cell lung carcinoma diagnosed after the person’s death by autopsy.

Autopsy was performed in 3 (6%) of the cases. Five of the 41 (12%) lung cancer deaths involved euthanasia or palliative sedation. The place of death was in the hospital in 48%, in a hospice or nursing home in 10% and at home in 42% of the subjects. In 65% of the

### Table 2. Characteristics of the fifty subjects of the pilot study

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean: 62.6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range: 51-73 years</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 42/50 (84%)</td>
</tr>
<tr>
<td></td>
<td>Female: 8/50 (16%)</td>
</tr>
<tr>
<td>Base for the diagnosis of lung cancer</td>
<td>Surgical resection of primary tumour: 16/50 (32%)</td>
</tr>
<tr>
<td></td>
<td>Histology or cytology of primary tumour: 15/50 (30%)</td>
</tr>
<tr>
<td></td>
<td>Histology or cytology of lymph node metastasis: 6/50 (12%)</td>
</tr>
<tr>
<td></td>
<td>Histology or cytology of distant metastasis: 8/50 (16%)</td>
</tr>
<tr>
<td></td>
<td>Autopsy: 1/50 (2%)</td>
</tr>
<tr>
<td></td>
<td>Clinical picture and imaging techniques: 4/50 (8%)</td>
</tr>
<tr>
<td>Disease stage at diagnosis</td>
<td>Ia: 12/50 (24%)</td>
</tr>
<tr>
<td></td>
<td>Ila: 2/50 (4%)</td>
</tr>
<tr>
<td></td>
<td>IIb: 1/50 (2%)</td>
</tr>
<tr>
<td></td>
<td>IIIa: 6/50 (12%)</td>
</tr>
<tr>
<td></td>
<td>IIIb: 3/50 (6%)</td>
</tr>
<tr>
<td></td>
<td>IV: 26/50 (52%)</td>
</tr>
</tbody>
</table>

**a** Age at the inclusion in the NELSON trial.

**b** TNM staging system for lung cancer 7th edition.

### Table 3. Outcome of the separate review of the cause of death

<table>
<thead>
<tr>
<th>Lung cancer death</th>
<th>Review 1</th>
<th>Review 2</th>
<th>Level of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n of 50 (%)</td>
<td>n of 50 (%)</td>
<td>kappa</td>
</tr>
<tr>
<td>Definitely or probable</td>
<td>41 (82)</td>
<td>42 (84)</td>
<td>0.65</td>
</tr>
<tr>
<td>- definitely</td>
<td>33 (66)</td>
<td>41 (82)</td>
<td>0.60</td>
</tr>
<tr>
<td>- probable</td>
<td>8 (16)</td>
<td>1 (2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Possible</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Unlikely</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Definitely not</td>
<td>3 (6)</td>
<td>7 (14)</td>
<td>0.56</td>
</tr>
<tr>
<td>Contributory to other CoD</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**Definition of abbreviation:** CoD = cause of death.
cases, the reviewers indicated the letters of the pulmonologist as the most valuable source of information.

**DISCUSSION**

In this pilot study, we have presented the principles of the CoD review process that will be used in the NELSON trial. The pilot study of fifty cases has shown an agreement of 90% (kappa 0.65) between the two reviewers, which demonstrates a reasonable classification. We expect an increase of the level of agreement for the actual review process, performed by clinical experts, with the number of cases they evaluate; the so-called ‘learning-effect’.

When comparing to the CoD process, the sensitivity and specificity of the official death certificates for lung cancer specific mortality were 95.2 and 62.5%, respectively. Despite the lack of a ‘gold standard’ for the cause of death of lung cancer participants, this still demonstrates, in our opinion, a limited distinctive character of the official cause of death certification in lung cancer patients for scientific purposes.

Potential limitations of the present study relate to the sample size and the selection of subjects of the pilot study. We have taken the first fifty consecutive deceased participants that were diagnosed with lung cancer. This has introduced a selection bias of individuals with a high lung cancer disease stage at diagnosis (Table 2) compared with the screen-arm of the trial. In the pilot study, most deaths were due to lung cancer. It is plausible that death due to other causes than lung cancer plays a bigger part when the files of all NELSON participants will be reviewed. Hence, the figures demonstrated in the pilot could differ from those of the entire study.

No other lung cancer CT screening trial has published results of their methodology of CoD evaluation yet, to our knowledge. In the chest X-ray screening trials, such as the Mayo Lung Project, Hopkins and Sloan-Kettering Lung Trials and the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, an expert review panel determined the CoD. Lung cancer mortality was 5–6% overestimated in the intervention

---

**Table 4. The causes of death by the reviewers and the official certificates**

<table>
<thead>
<tr>
<th>CoD review</th>
<th>Death certificates</th>
<th>Other CoD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LC death n (%)</td>
<td>Other CoD n (%)</td>
<td>Total n (%)</td>
</tr>
<tr>
<td>LC death</td>
<td>40 (80)</td>
<td>2 (4)</td>
<td>42 (84)</td>
</tr>
<tr>
<td>Other CoD</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Total</td>
<td>43 (86)</td>
<td>7 (14)</td>
<td>50 (100)</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CoD = cause of death; LC = lung cancer.

*Cause of death after consensus meeting of the reviewers.*

---

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
arm and 2\% underestimated in the usual-care arm by the death certificates in these trials.\textsuperscript{11,18} In this initial pilot, the misestimate is 10\%.

**CONCLUSION**

Our and other studies’ results imply that the outcome of a lung cancer screening trial cannot reliably be established without a concordance analysis between vital statistics and a CoD review of blinded cases. Moreover, the principles and flowcharts presented here aim to provide one of the essential tools to make data pooling with other CT screening trials in the future possible.
CONFLICTS OF INTEREST STATEMENT

Roche diagnostics provided a grant for the performance of proteomics-research. Siemens Germany provided four digital workstations and LungCARE for the performance of 3D measurements.

ACKNOWLEDGEMENTS

We thank the Central Bureau for Genealogy, Statistics Netherlands, the Flemisch Agency for Care and Health, the Dutch Cancer Registry, the Belgian Cancer Registry and the co-operating general practitioners in the Netherlands for providing the required data. Furthermore, we thank our data manager R.M. Vernhout and we thank S.J. Schop (medical student Maastricht University, Netherlands) for blanking and scanning the medical documents.

The NELSON trial is supported by: “Zorg Onderzoek Nederland-Medische Wetenschappen” (ZonMw), “KWF Kankerbestrijding”, “Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen” (RvvZ), “G. Ph. Verhagen Foundation”, “Rotterdam Oncologic Thoracic Study Group” (ROTS) and “Erasmus Trust Fund”, “Stichting tegen Kanker”, “Vlaamse Liga tegen Kanker” and “LOGO Leuven and Hageland”.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118.
REFERENCES

APPENDIX

Figure 1a. Cause of death evaluation flowchart part I

Definition of abbreviations: LC = lung cancer; CoD = cause of death.
Figure 1b. Cause of death evaluation flowchart part II

Definition of abbreviations: LC = lung cancer; CoD = cause of death.
Figure 1c. Cause of death evaluation flowchart part III

Definition of abbreviations: LC = lung cancer; CoD = cause of death.
Table 1. The cause of death evaluation process protocol

1. Death as a result of an intervention of lung cancer? (Figure 1a in appendix)

Death certainly as a direct result of a diagnostic intervention (for example: intravenous contrast or radiopharmacon (CT, Magnetic Resonance Imaging (MRI) or Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET)), endoscopic interventions (transbronchial biopsy, endoscopic ultrasound (EUS) or endobronchial ultrasound (EBUS)), transthoracic puncture or biopsy, pleural puncture or drainage, puncture of distant metastases or mediastinoscopy) or a therapeutic intervention (such as: surgery (in-hospital mortality and 30-day mortality), chemotherapy, radiotherapy, combined modality treatment, pleural drainage, endobronchial and endoesophageal interventions and brachytherapy, medication, euthanasia, palliative sedation) performed for (second primary) lung cancer or a paraneoplastic syndrome.

2. Evidence for progressive, recurrent or new metastasis present? (Figure 1b in appendix)

To answer these two questions the following criteria are used:

I. Pathology

- Proof of relapse, progression or a second primary lung cancer:
  - Histological/cytological proof of lung cancer relapse, progression or 2nd primary

II. Radiology (X-ray, CT scan, MRI)[17]

- Proof of relapse, progression or a second primary lung cancer:
  - Growth of primary tumour (≥20% increase in largest diameter or unequivocal progression if not measurable)
  - Recurrence (short axis >10mm) or progressive pathologically enlarged lymph nodes (≥20% increase in short axis or unequivocal progression if not measurable)
  - Recurrence or progressive growth of previously existing intrapulmonary tumours (≥20% increase in largest diameter or unequivocal progression if not measurable)
  - Recurrence or progressive growth of previously existing distant metastases (≥20% increase in diameter or unequivocal progression if not measurable)
  - The appearance of any new malignant lesion (intrapulmonary or at distant sites) or pathologically enlarged lymph nodes (short axis >10mm)
  - Increase of pleural or pericardial effusions from ‘trace’ to ‘large’
  - Increase of lymfangitis carcinomatosa from ‘localised’ to ‘widespread’

III. Nuclear scans (FDG-PET scan, bone scintigraphy)

- New positive lesion(s) in case of a previously negative scan

IV. Bronchoscopy

- New, recurrent or progressive visible endobronchial tumour
- New, recurrent or progressive compression of the airways by tumour mass

V. Laboratory

- Findings suggestive of relapse, progression or a second primary lung tumour, which must be confirmed by additional testing:
  - Hypercalcaemia
  - Progressive liver chemistry abnormalities
  - Increase in alkaline phosphatase
  - Increase in tumour markers (carcinoembryonic antigen, neuron-specific enolase, cytokeratin 19 fragments (CYFRA))

VI. Clinical picture

- Physical exam: vena cava superior syndrome, pathologically enlarged lymph nodes ≥10mm.[17]

Findings suggestive of relapse, progression or a second primary lung tumour, which must be confirmed by additional testing:

- Physical exam: brain metastases, abdominal masses or organomegaly, pleura or pericardial effusions, ascites, skin metastases.
- Anamnesis: decline in WHO-performance status, weight loss >10% in past 3 months, progressive dyspnoea, bone pain
4. Evidence for paraneoplastic syndrome present? (Figure 1d in appendix)

To answer this question the following criteria are used:

I. Angiography

Proof of a paraneoplastic syndrome:
- Deep venous thrombosis (DVT): contrast venography (intraluminal filling defect in two or an abrupt cut-off of a deep vein)[18]
- Pulmonary embolism (PE): pulmonary angiography (intraluminal filling defect in two views and or an occluded pulmonary artery with or without a trailing edge)[18-19]

II. Radiology

Proof of a paraneoplastic syndrome:
- DVT: ultrasound (compression technique, duplex or colour flow imaging)[18-19]
- DVT: MRI (intravascular filling defect or occlusion of a vessel)[18]
- PE: spiral CT scanning (intravascular filling defect or occlusion of a vessel)[18-19]
- PE: MRI (intravascular filling defect or occlusion of a vessel with a 'trailing embolus' sign)[18]
- Nonbacterial thrombotic endocarditis: thoracic or transoesophageal echocardiography (evident valve vegetation)

Findings suggestive of a paraneoplastic syndrome, which must be confirmed by additional testing:
- PE: chest X-ray (no abnormalities, atelectasis, pleural effusion, pulmonary infiltrates, elevation of a hemidiaphragm, Hampton's hump, Westermark's sign)[18]
- PE: thoracic or transoesophageal echocardiography (emboli in the main, right or left pulmonary artery, right ventricular dysfunction)[18-19]
- PE: using transthoracic ultrasound (peripheral wedge-shaped opacities)[19]

III. Nuclear scans

Proof of a paraneoplastic syndrome:
- PE: (ventilation-)perfusion scanning ((sub)segmental perfusion defect)[18-19]

IV. Electrocardiography (ECG)

Findings suggestive of a paraneoplastic syndrome, which must be confirmed by additional testing:
- PE: P-wave pulmonale, axis deviation, right bundle branch block, S1 Q3 T3 pattern, ST segment abnormalities, T-wave changes.[18]

V. Laboratory

Proof of a paraneoplastic syndrome:
- Hypercalcaemia of malignancy (elevated total serum calcium corrected for albumin and low intact parathyroid hormone (PTH) and elevated PTH-related protein)
- Syndrome of inappropriate Antidiuretic Hormone (ADH) secretion (low serum sodium and elevated ADH and elevated urine osmolality)
- Ectopic Adrenocorticotropic Hormone (ACTH) secretion causing Cushing's syndrome (elevated ACTH (>20pg/ml) and a negative corticotrophin-releasing hormone simulation or dexamethasone suppression test and no central step-up at inferior petral sinus sampling)
- Neurologic paraneoplastic syndrome; always in combination with corresponding clinical picture (antibodies: anti-Hu, anti-Ri, anti-Tr, anti-Crossveinless-2/anti-Collapsin response mediator protein-5, anti-Ma1, anti-Ma2, anti-ampiphysin, anti-Zic 4, anti-neuronal nuclear antibody-3, purkinje cell antibody-2, anti-Voltage-gated calcium channel, anti-Nicotinic acetylcholine receptors)
- Disseminated intravascular coagulation: microangiopathic changes on the peripheral blood smear and increased fibrinolysis (e.g. elevated fibrinogen-fibrin degradation products and D-dimer)
- Thrombotic microangiopathy: haemolytic anaemia, thrombocytopenia, increased turnover of platelets, normal level of coagulation components and little or no prolongation of prothrombine time or activated partial thromboplastin time.

Findings suggestive of a paraneoplastic syndrome, which must be confirmed by additional testing:
- PE (hypoxemia in arterial blood gas analysis and positive D-dimer)[18-19]

VI. Clinical picture

Findings suggestive of a paraneoplastic syndrome, which must be confirmed by additional testing:
- DVT: limb pain, tenderness or swelling, Homans' sign.[18]
- PE: unexplained dyspnoea, pleuritic chest pain, haemoptysis, tachypnea, tachycardia, syncope, hypoxemia. [18]
Chapter 9

- Hypercalcaemia: constipation, fatigue, polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness.
- Syndrome of inappropriate ADH secretion: fatigue, headache, oedema, nausea, vomiting, altered mental status, coma.
- Cushing's syndrome: muscle weakness, weight loss, hypertension, hirsutism.
- Severe paraneoplastic syndrome of the central nervous system (e.g. Lambert-Eaton myasthenic syndrome, cerebellar degeneration, pandysautonomia): focal neurological signs, autonomic dysfunction.
- Disseminated intravascular coagulation: signs of bleeding, acute organ failure (renal, liver, lungs), shock, thromboembolism, central nervous system dysfunction.
- Thrombotic microangiopathy: signs of anaemia, bleeding, acute renal failure, central neurologic abnormalities.
- Nonbacterial thrombotic endocarditis: acute ischemic cerebrovascular accident or acute peripheral arterial thromboembolism.

5. Clear cause of death present, other than lung cancer? (Figure 1a in appendix)

In the last step of the flowchart (Fig. 1a), no evidence for death related to interventions, (second) primary or metastatic lung cancer or a paraneoplastic syndrome is present. In case no other clear cause of death is known, the case is categorised as "unlikely lung cancer death".
Part V

Implications for implementation
Chapter 10

State of the art in lung cancer screening

The importance of screening for lung cancer

Horeweg N, de Koning HJ

Expert review in Respiratory Medicine
August 27th 2014
THE IMPORTANCE OF SCREENING FOR LUNG CANCER


**ABSTRACT**

Lung cancer is a major public health problem since it causes most cancer-related deaths worldwide. As the disease often causes no symptoms at early stages, diagnosis at advanced stages, wherein cure is no longer possible, is common.

Improvements in lung cancer treatment have been made, but yielded only modest improvement in survival over the last decades. Continuous efforts should be made to force back exposure to causative agents of lung cancer, tobacco smoking in particular. However, this is not expected to reverse the lung cancer epidemic in the next decades.

The U.S. National Lung Cancer Screening Trial has demonstrated that lung cancer screening using low-dose computed tomography can reduce morbidity and mortality by detecting lung cancer at an early and curable stage. Effectiveness of a screening program is a prerequisite for implementation. In addition, the benefits of a screening program should outweigh the harms the program induces.

The currently available literature on all relevant aspects of LDCT screening for lung cancer was reviewed to determine whether the benefits of LDCT screening outweigh the harms. Next, it was determined whether LDCT screening meets the World Health Organisation criteria for screening.

Initial estimates of many harms and benefits of screening have been made, suggesting that the benefits of LDCT screening outweigh the harms. Nonetheless, the success of an implemented screening program will be determined by the benefit it yields for public health.
LUNG CANCER SCREENING: STATE OF THE ART

On November 4\textsuperscript{th} 2010, the U.S. National Cancer Institute announced that lung cancer screening using low-dose computed tomography (LDCT) reduced mortality from lung cancer by 20%, compared to screening using chest radiography.\textsuperscript{1} This impressive result was achieved in the U.S. National Lung Screening Trial (NLST), which is the world's largest randomised lung cancer screening trial.\textsuperscript{2} As lung cancer is the leading cause of cancer-related death in the U.S. and beyond,\textsuperscript{3,4} the impact of a significant lung cancer mortality reduction was directly recognised.

In this review, the World Health Organisation (WHO) criteria for screening (Box 1) were used as a guide for the literature search through all relevant aspects of LDCT screening for lung cancer. Hence, the ten WHO criteria for screening will be discussed, followed by a series of general conclusions on LDCT screening for lung cancer. Ultimately, the author’s current and five year view on lung cancer screening will be presented.

Box 1. Modern screening criteria proposed by the World Health Organisation

| I) | The screening programme should respond to a recognized need. |
| II) | The objectives of screening should be defined at the outset. |
| III) | There should be a defined target population. |
| IV) | There should be scientific evidence of screening programme effectiveness. |
| V) | The programme should integrate education, testing, clinical services and programme management. |
| VI) | There should be quality assurance, with mechanisms to minimize potential risks of screening. |
| VII) | The programme should ensure informed choice, confidentiality and respect for autonomy. |
| VIII) | The programme should promote equity and access to screening for the entire target population. |
| IX) | Programme evaluation should be planned from the outset. |
| X) | The overall benefits of screening should outweigh the harm. |

I) The screening programme should respond to a recognised need

A lung cancer screening programme responds to a recognised need, since lung cancer is a major public health problem. Lung cancer is currently the most prevalent cause of cancer-related death.\textsuperscript{3,4} Considering the ongoing global tobacco epidemic, lung cancer is expected to stay an important cause of death over the next decades.\textsuperscript{5} Screening could be
a valuable addition to clinical care, primary and tertiary prevention in the fight against lung cancer.

II) The objectives of screening should be identified at the outset

The objective of screening should be reducing morbidity and mortality from lung cancer. Earlier detection of cancer should not be the objective of screening, since a prolonged disease course without a reduced burden of disease or a lower risk of lung cancer death is not beneficial (Table 1). Increasing survival should also not be the objective of screening, since estimates of survival in a screening setting are distorted by lead-time bias, length-time bias and overdiagnosis.

![Table 1. Benefits and harms of cancer screening](image-url)

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less persons dying from lung cancer</td>
<td>Undergoing screening test and awaiting result - psychological distress</td>
</tr>
<tr>
<td>Less persons suffering from advanced lung cancer</td>
<td>Radiation-induced cancers - morbidity and mortality</td>
</tr>
<tr>
<td>Less persons receiving intensive or mutilating primary treatment</td>
<td>False positive results - psychological distress, morbidity and mortality due to subsequent diagnostic procedures</td>
</tr>
<tr>
<td>Possible positive effects on smoking cessation</td>
<td>False negative results - false reassurance, delayed diagnosis once symptoms occur</td>
</tr>
<tr>
<td></td>
<td>Overdiagnosis - psychological distress, morbidity and mortality due to overtreatment</td>
</tr>
<tr>
<td></td>
<td>Persons receiving the diagnosis of lung cancer earlier</td>
</tr>
<tr>
<td></td>
<td>Possible negative effects on smoking cessation</td>
</tr>
</tbody>
</table>

III) There should be a defined target population

The significant mortality reduction in the NLST made many medical societies recommend the NLST inclusion criteria as the definition of the optimal target population for screening (Table 2). The National Cancer Comprehensive Network (NCCN) and the American Association of Thoracic Surgery (AATS) recommended an extended or modified versions of the NLST inclusion criteria. Remarkably, two New England Journal of Medicine publications by the NLST pointed out that the trial's inclusion criteria were suboptimal.

The first article demonstrated that the use of a lung cancer prediction model, (including age, race, education, body-mass index, chronic obstructive pulmonary disease, personal and family history of cancer, smoking status, intensity duration and quit time) yielded a higher sensitivity and an equal specificity for lung cancer compared to the NLST inclu-
sion criteria. The second article demonstrated that screening was most effective and least harmful in the NLST participants at the highest risk of lung cancer mortality. In the participants at a relatively low 5-year risk of lung cancer death (lowest risk quintile 0.15-0.55%), the benefit of screening (1% of prevented lung cancer deaths) was small compared to the numbers needed to screen (5276:1) and the false-positive screenings (97.0%).

Table 2. Inclusion criteria of randomised controlled trials on LDCT screening for lung cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST2,21</td>
<td>male or female 55-74 ≥30 pack-years</td>
</tr>
<tr>
<td>NELSON29,33</td>
<td>male or female 50-75 ≥15 per day for 25 years or ≥10 per day for 30 years ≤10 yrs</td>
</tr>
<tr>
<td>DLST34</td>
<td>male or female 50-70 ≥20 pack-years</td>
</tr>
<tr>
<td>MILD40</td>
<td>male or female ≥49 ≥20 pack-years</td>
</tr>
<tr>
<td>LUSI58</td>
<td>male or female 50-70 ≥15 per day for 25 years or ≥10 per day for 30 years ≤10 yrs</td>
</tr>
<tr>
<td>UKLS44,55</td>
<td>male or female 50-75 ≥5% risk of lung cancer in 5 years ≤10 yrs</td>
</tr>
<tr>
<td>ITALUNG56</td>
<td>male or female 55-70 ≥20 pack-years</td>
</tr>
<tr>
<td>DANTE57</td>
<td>male 60-75 ≥20 pack-years</td>
</tr>
</tbody>
</table>

*Age range up to, but not including upper limit.

The CISNET lung cancer working group assessed benefits and harms of LDCT screening for lung cancer for the U.S. Preventive Services Task Force (USPSTF). Five modelling groups independently evaluated 576 screening scenarios to determine the optimal target population. Eligibility criteria were: age at begin and end of screening, minimum number of pack-years, and maximum number of years since smoking cessation. Their analyses identified a range of possible 'optimal' target populations, including the set of eligibility criteria for screening which were adopted by the USPSTF (Table 3).

The latter study provided solid evidence for optimal target populations for lung cancer screening. Future studies will provide more insight in the value of prediction models.
for selecting eligible subjects for screening, and optimal inclusion criteria for Asian and other specific populations. Since all prominent medical associations have published their guidelines on lung cancer screening in the past two years, none of them incorporates all currently available evidence on this subject. Possibly, the next generation of guidelines will recommend definitive criteria for the optimal target population for lung cancer screening.

IV) There should be scientific evidence of screening programme effectiveness
The NLST has demonstrated 20% lung cancer mortality reduction by screening using LDCT compared to screening using chest radiograph (Table 4).\(^1\) When the CISNET lung cancer working group evaluated hundreds of screening scenarios, mortality reductions were also estimated.\(^14\) Estimates for twenty-six selected efficient screening scenarios ranged from 4.6-21.2%, which demonstrates the strong correlation between the benefit of a screening programme and its design and target population. The USPSTF eligibility criteria (Table 3) with annual screening was estimated to yield a 14.0% lung cancer mortality reduction, which corresponds with 497 lung cancer deaths averted and 5250 life-years gained per the 100,000-member cohort.\(^14\) Lung cancer mortality reductions in several European trials are still awaited (Table 4). Since the outcomes of European trials combined have enough statistical power to affect the significant mortality reduction of the NLST, no definitive conclusion can be drawn on the magnitude of the mortality reduction to date.

<table>
<thead>
<tr>
<th>Trial*</th>
<th>Lung cancer deaths per 100,000 py(^{20})</th>
<th>Relative risk(^{20}) (95%CI)</th>
<th>All deaths per 100,000 py(^{20})</th>
<th>Relative risk(^{20}) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>NLST(^1)</td>
<td>247</td>
<td>309</td>
<td>0.80 (0.73-0.93)</td>
<td>1142</td>
</tr>
<tr>
<td>DLST(^4)</td>
<td>154</td>
<td>112</td>
<td>1.37 (0.63-2.97)</td>
<td>625</td>
</tr>
<tr>
<td>MILD(^2)</td>
<td>216</td>
<td>109</td>
<td>1.99 (0.80-4.96)</td>
<td>558</td>
</tr>
<tr>
<td>DANTE(^5)</td>
<td>527</td>
<td>637</td>
<td>0.83 (0.45-1.54)</td>
<td>1212</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: py = person-years; RR = relative risk; 95%CI = 95% confidence interval.
*Trial included with results published before July 2014.

V) The programme should integrate education, testing, clinical services and programme management
Since LDCT screening has been recommended by several U.S. medical associations,\(^6\)-\(^8\) these implementation-related aspects of screening have become relevant. So far, little has been published about lung cancer screening programme management, clinical services,
education, and testing. Nonetheless, recommendations on these aspects have been made by several medical associations.

I) Multi-disciplinary approach: is recommended by all guidelines.\textsuperscript{6-11,15,16} Hence, radiologists, pulmonologists and thoracic surgeons should have regular meetings wherein screening cases are discussed. However, close cooperation with other specialties is also warranted: nuclear medicine experts and pathologists for the assessment of respectively nuclear scans and small biopsies of CT-detected nodules, and medical and radiation oncologists for the treatment of screen-detected lung cancer.

II) Process management: all subsequent steps from the candidate’s first attendance to the screening clinic to the treatment of screen-detected lung cancer should be orchestrated before screening is implemented. Two steps of this process have been described in lung cancer screening guidelines; a defined algorithm for scan interpretation,\textsuperscript{6-8,15-17} and a diagnostic algorithm for suspicious CT-detected nodules.\textsuperscript{6-8,10,11,15,16} Clinical guidelines on the management of incidentally-detected pulmonary nodules may be complementary, since many recommendations are based on data from lung cancer screening studies. Furthermore, logistics of the screening programme should be coordinated to prevent drop-outs and limit waiting times.

III) Facilities: the availability and quality of radiological, surgical, and other facilities is essential for a screening programme’s effectiveness and safety. A number of screening guidelines emphasise that screening should be performed in ‘centres similar to those wherein the NLST was conducted.’\textsuperscript{6-8} This suggest that screening should be performed in large centres which comply with the NLST minimum equipment standards,\textsuperscript{2} and have specialised thoracic radiologists and board-certified thoracic surgeons on staff.

Detailed descriptions of radiological requirements are provided in the AATS guideline and are expected from the International Association for the Study of Lung Cancer (IASLC) Radiology Working Group,\textsuperscript{15,18} and the Radiological Society of North America (RSNA) / American College of Radiology (ACR) collaboration.\textsuperscript{17} The use of volumetry to assess nodule size and growth is currently only recommended by IASLC\textsuperscript{15} and AATS guidelines.\textsuperscript{11}

Specific recommendations for surgical management of suspicious nodules are only provided by the IASLC and the AATS. Both recommend lobectomy with systematic lymph node sampling as preferred procedure for suspected or confirmed early stage lung cancer.\textsuperscript{15,16} Segmentectomies with sampling of N1 and N2 lymph node stations are only recommended by the IASLC for sub-solid nodules smaller than 2cm, and in individuals with limited pulmonary reserve or multiple lesions.\textsuperscript{15} Wedge resections should only be used for diagnostic purposes according to the IASLC,\textsuperscript{15} however according to the AATS, wedge resections could also be used as therapeutic procedure for lung cancers appearing
as sub-solid nodules on CT. The preferred approach to perform these procedures is video-assisted thoracoscopic surgery (VATS), because of the lower post-operative mortality compared to thoracotomy.

The integration of a smoking cessation programme along with screening is recommended by all guidelines. Besides the ethical necessity of this recommendation, smoking cessation will also increase the benefits of a screening programme.

VI) There should be quality assurance, with mechanisms to minimise potential risks of screening

Screening bears the risk of several harms (Table 1), which can be minimised by adequate quality assurance. This aspect of lung cancer screening is still under development. Many useful lessons could be learned from successfully implemented screening programmes, such as breast cancer screening. However, the implementation of lung cancer screening will give rise to new challenges. Besides screening trials, screening demonstration projects are also useful for the development of quality metrics and minimum standards for lung cancer screening. CT quality controls are currently already recommended. Moreover, a LDCT-screening quality standards act and independent quality assurance units that collect and collate data about the performance and outcomes of screening programmes and organise quality assurance visits would enforce quality assurance.

VII) The programme should ensure informed choice, confidentiality and respect for autonomy

Persons, who consider undergoing LDCT screening, should be informed on harms and benefits of screening (Table 1). Currently, many harms have been identified and some risk estimates of these harms have been published. Education of screening candidates is recommended in almost all guidelines. However, minimum requirements for the harms and benefits that should be discussed, and the level of knowledge of counsellors have not been published. Naturally, the individual’s choice on participation after education on the harms and benefits should be respected. By no means, fear of cancer should be used to convince subjects to undergo screening. Once eligible screening candidates are informed and voluntarily agree to undergo LDCT screening, written informed consent should be obtained. In case data from their screening will be used for research purposes, explicit permission should be requested.

VIII) The programme should promote equity and access to screening for the entire target population

The benefit of lung cancer screening for public health depends on the participation rate in the target population. The applied recruitment method influences the population that
will attend to screening. Recruitment through the media attracts younger individuals who are more often ex-smokers with better education and higher social economic status, compared to the entire target population. The latter is not desirable since subjects at high risk for developing lung cancer are most predominantly represented in lower social-economic groups.

Henceforth, recruitment should effectively reach out to the lower educated proportion of the population. The population participating in the Dutch-Belgian lung cancer screening trial was slightly lower educated, smoked more heavily, had a worse general health and a higher prevalence of malignancies, but had the same age, percentage current smokers, and BMI as the general population. Recruitment for this trial was performed by determining eligibility for screening first (via an initial mailing which did not contain any information on the trial), followed by a second mailing only to eligible subjects, with information and the invitation to participate in lung cancer screening. Although lower educated groups can be recruited with this method, it will be difficult to obtain information on eligibility from the target population without informing them on lung cancer screening outside a clinical trial nowadays. Unfortunately, no other screening trial, that used a population-based recruitment strategy wherein anyone in the target age range received a mailing with an invitation for screening and a questionnaire to determine eligibility, also investigated participation bias especially by educational level.

Besides difficulties with recruitment of lower educated groups, reaching out to minorities and ethnic groups other than Caucasians is also challenging. The NLST institutions were encouraged to identify regional minorities and develop plan for targeted recruitment. Seven institutions were selected and received funding to implemented their proposals, which were diverse; advertising in minority-specific media, distribution of culturally adapted and translated brochures, outreach programs via general practitioners, face-to-face interaction and word-of-mouth dissemination. The success of the aforementioned strategies varied, and no single strategy was successful among all institutions. Nonetheless, recruitment of local minorities increased from 9.3% to 15.2% in the seven institutes using any strategy. Knowledge on local cultural and ethnic diversity and cooperation with local stakeholders and minority organisations are probably vital for developing suitable recruitment strategies and successful implementation.

Concluding, recruiting the higher educated, health-concerned part of the population for lung cancer screening will probably be successful. However, making the lower educated and minority groups aware of the availability and advantages of lung cancer screening will be more difficult. It will require social responsibility of health policy makers to put effort and resources in the recruitment of these subgroups. Since the subjects at high risk for developing lung cancer are predominantly represented in these subgroups, the success of lung cancer screening for public health will partly depend on it.
IX) Programme evaluation should be planned from the outset

As for all health care programmes, evaluation and feedback with the objective to detect deficiencies and improve care should be planned from the outset. Current guidelines on lung cancer screening do not explicitly mention programme evaluation, but registry/data collection is recommended.\textsuperscript{7,8,11,15,16} Collected data could be used to monitor and improve performance, as well as collate with quality standards, as described at criterion VI.

X) The overall benefits should outweigh the harm

One of the most important criteria for screening. Determining whether the benefits of a screening programme outweigh the harms is complex. The benefits of screening can be expressed as the number of quality-adjusted life-years (QALYs) gained, which should be estimated using the number of deaths prevented and the number of advanced stage disease prevented by screening. The number of life-years gained can be estimated with data from randomised controlled trials and micro-simulation modelling. Next, the life-years gained should be corrected for quality of life using utility estimates.\textsuperscript{26} Further, the same should be done for the harms of screening; estimating the number of QALYs lost by screening using data from trials, implemented programmes, registries and modelling studies. Once this has been established, it can be determined whether the benefits of lung cancer screening outweigh the harms. An example of such a calculation has recently been published for prostate cancer screening.\textsuperscript{27}

Currently, only the gain in quality-adjusted life-years for NLST participants in whom death was prevented has been estimated: 21.7 QALYs per 1000 screened individuals.\textsuperscript{28} The gain QALYs for those in whom advanced stage disease was prevented by LDCT screening should be added to obtain an estimate for the total benefit of screening. Moreover, the estimate would become more reliable if data from other screening trials, such as the largest European trial,\textsuperscript{29} was added. The CISNET lung cancer working group estimated that per 100,000-person cohort screened with the recommended regimen (Table 4) 497 subjects would not die from lung cancer and 550 no longer needed treatment for advanced lung cancer.

Estimates for numbers of QALYs lost due to screening have not been published yet. However, some estimates of the magnitude of many harms have been published to date, briefly:

I) Undergoing screening test: could be accompanied by psychological distress, however neither clinically relevant, nor statistically significant negative effects on physical health, mental health, self-reported health, generic anxiety, lung cancer-specific distress and on the impact of event scale were demonstrated.\textsuperscript{30} Further, undergoing the screening test leads to exposure to ionising radiation.\textsuperscript{31} The harmful effect of radiation related to both the screening examination and the subsequent diagnostic procedures for positive screenings have been estimated for
the participants of the NLST; it was estimated that cancer for every 2,500 screened subjects, one subject would die from radiation-induced cancer.\textsuperscript{7,8} The CISNET lung cancer working group estimated the number of radiation-related lung cancer deaths for a range of screening scenarios; per a 100,000-person cohort followed from ages 45 to 90, 24 deaths were expected both with the screening strategy most similar to the NLST eligibility criteria (Table 2), and the screening strategy adopted by the USPSTF (Table 3).

II) Awaiting screening test result: led to discomfort in 46.0-51.3\% of the screened subjects of the NELSON trial.\textsuperscript{32} Awaiting the follow-up scan after an initial indeterminate screening result led to a clinically relevant increase in lung cancer-specific distress; which recovered in case of a negative follow-up scan and remained in case of a positive follow-up scan.\textsuperscript{30}

III) False-positive screenings: a positive screening in subjects without lung cancer. The proportion of all screening results that is false-positive depends on the definition of a positive screening (i.e. threshold for nodule size or growth), and to a lesser extent to the technique that is used to review the screening examination (i.e. manual measurements semi-automated volumetry). In the NLST, a relatively low threshold of ≥4 mm for manually measured nodule diameter was applied, and a high percentage of false-positive screenings (23.3\%) was observed.\textsuperscript{1} In comparison, in the NELSON trial a higher threshold of 500 mm\textsuperscript{3} for semi-automatically assessed nodule volume (about 9.8 mm in diameter) was applied, and a relatively low percentage of false-positive screenings was observed (1.2\%).\textsuperscript{33} False-positive screenings lead to unnecessary diagnostic procedures and psychological distress in subjects without lung cancer. The magnitudes of the psychological distress and their long-term effects have not been investigated in any of the randomised lung cancer screening trials. Invasive diagnostic procedures for false-positive screenings were performed in 0.4-1.3\% of the participants of lung cancer screening trials.\textsuperscript{33-38} The CISNET lung cancer working group modelled that 67,550 persons would have a false-positive result and 910 would undergo invasive diagnostic procedures for benign nodules per 100,000-person cohort screened annually from age 55 to 80.\textsuperscript{14} Data on the incidence of morbidity and mortality as a result of complications of the invasive procedures for false-positive screenings were not published.

IV) False-negatives: a negative screening result in a subject with (early) lung cancer could lead to delayed diagnosis through false reassurance once symptoms emerge. In the randomised lung cancer screening trials, 0.0-6.3\% of the lung cancers was not detected through screening.\textsuperscript{29,35,38-41} Estimates of the delay to diagnosis caused by the false negative screening result were not provided.

V) Overdiagnosis: estimates of the amount of overdiagnosis for a range of hypothetical screening programmes were made by the CISNET lung cancer working group in a
comparative modelling study. The screening strategy as applied in the NLST was estimated to have led to 8.7% overdiagnosis. The slightly adjusted screening algorithm that was recommended from this study after weighing several harms and benefits of screening (Table 3) would yield 9.9% overdiagnosis. This corresponds with 190 persons with an overdiagnosed lung cancer per 100,000-person cohort. The associated harms consist of the physical harms induced by diagnostic procedures and overtreatment, and mental harms caused by distress due to the aforementioned interventions and anxiety of having a cancer diagnosis; none of these have been quantified to date.

VI) Prolonged disease course: effective screening programmes advance diagnosis of lung cancer. For some screenees, this will lead to cure from lung cancer, however in most screenees screening will not prevent lung cancer death. In these subjects the course of disease was longer because of the earlier diagnosis, but there was no health benefit; which is a harmful side-effect of screening. It was estimated by that 1,970 persons per 100,000-person cohort would receive the diagnosis of lung cancer earlier when annual screening from the age of 55 to 80 is implemented. Estimates of the harms and duration of the lead time in these persons have not been published.

VII) Negative impact on life-style: another potential harm of lung cancer screening is that the screened population considers the LDCT examination as a substitute for smoking cessation; the so-called health certificate effect. In two screening trials, this was investigated and no differences were found in the cessation rate and the number of quit attempts between subjects who received screening and those who received no screening. However, in one study smoking abstinence was significantly higher for participants receiving no screening compared to participants who received LDCT examinations. The difference in smoking abstinence between the screened group and the control group was 4.6% (OR 1.40, 95% CI 1.01-1.92). Henceforth, it cannot be precluded that LDCT screening does not have a negative impact on life-style. Effective smoking cessation programmes implemented along with LDCT screening may compensate for any harmful effect of screening on life-style.
CONCLUSIONS ON LDCT SCREENING FOR LUNG CANCER

I) The screening programme should respond to a recognised need
Lung cancer screening responds to a recognised need as lung cancer is a major public health problem.

II) The objectives of screening should be defined at the outset
The objectives of lung cancer screening are reducing morbidity and mortality from lung cancer.

III) There should be a defined target population
Although evidence for an optimal target population for lung cancer screening has been published, discussions are ongoing.

IV) There should be scientific evidence of screening programme effectiveness
Effectiveness of lung cancer screening has been demonstrated in one study, future results of a pooled analysis of all lung cancer screening trials will provide definite conclusions.

V) The programme should integrate education, testing, clinical services and programme management
Current lung cancer screening guidelines provide some useful recommendations on the integration of education, testing, clinical services and management in lung cancer screening programmes, however substantial gaps remain.

VI) There should be quality assurance, with mechanisms to minimise potential risks of screening
Since LDCT screening is already (recommended to be) implemented and adequate quality assurance is still under development, the population undergoing screening is exposed to several risks.

VII) The programme should ensure informed choice, confidentiality and respect for autonomy
Although any lung cancer screening guideline recommends informing screening candidates on the harms and benefits of screening and respecting their autonomy, no minimum requirements on screening information and knowledge of the counsellor are defined.

VIII) The programme should promote equity and access to screening for the entire target population
Successful implementation of LDCT screening depends on the benefit the programme yields for public health, therefore effective methods need to be developed to reach out to the lower educated and minority groups.
IX) Programme evaluation should be planned from the outset
Data collection from lung cancer screening programmes is recommended by several guidelines, and should at least be used for evaluation and quality assurance, which is not recommended yet.

X) The overall benefits of screening should outweigh the harm
Initial estimates of many harms and benefits of screening have been made, suggesting that the benefits of LDCT screening outweigh the harms.

AUTHOR’S VIEW ON LUNG CANCER SCREENING

Screening a population at high risk of developing lung cancer using low-dose computed tomography examinations is a promising technique to reduce morbidity and mortality from lung cancer. A significant reduction in lung cancer mortality by screening using LDCT examination has been demonstrated in one large, high-quality randomised trial.1 Future pooled analysis of multiple randomised lung cancer screening trials will provide definitive evidence for the effectiveness of LDCT screening.29 Initial estimates of many harms and benefits of screening have been made using data from the U.S. lung cancer screening trials.14 It is unknown to what extent these estimates apply to other screening strategies, such as the volumetry-based nodule protocols of the European trials.29,34,38,44 Available evidence suggests that LDCT screening can be beneficial if applied as in the NLST.7,20 However, it is uncertain whether LDCT screening for lung cancer screening is beneficial when implemented in different settings without established safety and quality assurances.

The success of any screening programme is determined by the benefits it yields for public health. Ma et al. estimated that if the screening regimen adopted in the NLST was fully implemented among the 8.6 million screening-eligible U.S. population, 12,250 lung cancer deaths could be averted per year.45 If the optimal screening scenario according to the USPSTF (Table 4) is implemented in the U.S., 10.5 million individuals will be eligible for screening.14 The yield, assuming 100% adherence to screening, is estimated at 18,000 deaths avoided per year, which corresponds with a 25% lung cancer mortality reduction in the eligible population and 14% overall lung cancer mortality reduction.14 Clearly, the projected benefits of LDCT screening for public health are significant. Implementation of LDCT screening programmes that reach out to the entire target population will be essential in realising the potential benefit for public health.

Continued efforts and advances in lung cancer treatment, primary prevention, and tertiary prevention are also expected to reduce the burden of lung cancer in the future. However, each of these methods solely will not be able to reverse the lung cancer epi-
Therefore, screening using LDCT should be regarded as a valuable new tool in the fight against lung cancer.

AUTHOR'S FIVE-YEAR VIEW ON LUNG CANCER SCREENING

Implementation of LDCT screening for lung cancer has only recently become an issue. Hence, the next five years will be important for its success. Many remaining uncertainties and discussions are likely to be addressed within five years.

Hence, final results of all randomised lung cancer screening trials have become available. Meta-analyses of lung cancer and all-cause mortality reduction will provide definitive conclusions on the efficacy of LDCT screening. Further, data from lung cancer screening trials and implemented screening programmes will give insight in the magnitude and impact of the harms associated with LDCT screening. With this data, more comprehensive calculations of the balance between harms and benefits of screening can be made. This will eventually also facilitate the performance of more integral cost-effectiveness analyses.

In the next five years, some lingering questions surrounding LDCT screening will probably be answered. Among these are probably: the value of lung cancer prediction models for the selection of eligible subjects; the optimal screening method, including insight in the added value of volumetry and the use of imaging biomarkers for the interpretation and accuracy of screening examinations; and the optimal diagnostic work-up from positive screening result to diagnosis for any type of screen-detected pulmonary nodule.

Finally, a number of issues will become more relevant in the next five years than they have been so far, as a result of the recommended implementation of LDCT screening. Examples are: recruitment of elderly, lower educated and minority groups for screening; shared decision-making; management systems for screening programmes; quality assessment and performance indicators; non-surgical treatments for screen-detected lung cancer; follow-up regimens for curatively treated screen-detected lung cancers, and patient-centred research.
REFERENCES


Chapter 11

General discussion
In this thesis, the harms and benefits of lung cancer screening using low-dose computed tomography were investigated. Data of the Dutch-Belgian NELSON trial were used to quantify its harms and benefits and develop strategies to improve the balance between them. If the NELSON trial demonstrates that low-dose CT screening is an effective method to reduce mortality from lung cancer, balance between harms and benefits is a perquisite for the implementation of a lung cancer screening program.

In the General Discussion, this thesis is evaluated to determine its implications. Firstly, the research objectives of this thesis are summarised. Secondly, background information necessary for the interpretation of the results is provided. Thirdly, the main and sub research questions of this thesis are evaluated for each chapter consecutively. The sub research questions are used to present and interpret the main results in each chapter. All sections on the interpretation of results conclude by answering a sub research question. The main research question of each chapter is answered in the conclusion section. Fourthly, a list of general conclusions based on the conclusions of each chapter are presented. Finally, general recommendations for further research and clinical practice are presented.

**THIS THESIS**

As the design of an effective and feasible screening algorithm is crucial for the implementation of screening, the evaluation of screening trials may provide valuable knowledge. Topic of this thesis is the evaluation of the screening algorithm of the Dutch-Belgian lung cancer screening trial; the NELSON trial. Hence, aims of this thesis were to estimate test characteristics (sensitivity, specificity and predictive values), number of required follow-up CT examinations and additional diagnostic tests, to determine whether improvements to the screening algorithm were possible by identifying failures and unnecessary procedures, and to estimate the performance of improved hypothetical screening algorithms. Ideally, the evaluation of the performance of the screening algorithm also considers effectiveness, which is reduction in lung cancer mortality. However, these analyses are planned at ten years after randomisation, which is outside the scope of this thesis. Nonetheless, this thesis contributed to these mortality analyses by developing the protocol for endpoint verification.

**BACKGROUND**

A screening algorithm is the management protocol of a screening programme or trial. The algorithm should define each possible screening test result and recommend an ap-
appropriate management strategy. Since low-dose computed tomography examination of the chest (LDCT) is used as a screening test, there are numerous options to define the screening test result. Therefore, many different screening algorithms have been designed and applied in lung cancer screening trials.

Although the interpretation of the LDCT examination differs substantially between lung cancer screening trials, three screening test outcomes have been defined quite consistently. Firstly, in case the screening LDCT examination did not show any abnormality, the screening test result is usually defined as ‘normal’ or ‘negative’ and the recommended management is not to perform any additional diagnostic tests. Secondly, in case the screening LDCT examination showed an abnormality that required immediate medical care, for example a large aortic aneurysm, screening is usually put on hold and adequate medical care is arranged. After this, an assessment is made to determine whether continuation of screening and consequential diagnostic testing is still appropriate. Finally, in case abnormalities suspicious for advanced lung cancer are detected on the screening LDCT examination, the screening test result is usually defined as ‘positive’, and the recommended management is to perform a work-up for diagnosis and staging followed by treatment according to (inter)national guidelines. In all other cases (thus cases wherein abnormalities not suspicious for advanced lung cancer were visible and no acute medical care was indicated) lung cancer screening trials use various definitions for screening test results and recommend opposing management strategies.

Although a variety of different abnormalities may be detected on the LDCT screening examination, the screening test result is determined by those abnormalities that are suspicious for (pre)cancerous lesions, which are lung nodules or masses. Pulmonary nodules are defined by the Fleischner Society as rounded or irregular opacities, that are well or poorly defined and measure up to 3 cm in diameter.\(^1\) Masses are defined as pulmonary, pleural, or mediastinal lesions that are seen as an opacity greater than 3 cm in diameter, and are usually solid or partly solid.\(^1\) Traditionally, the visual characteristics and size of the lung nodules or masses detected on the LDCT screening examination determines the screening test result.

In the first lung cancer screening cohort studies, such as the U.S. Early Lung Cancer Action Project (ELCAP study), all detected lung nodules which did not show a benign calcification pattern, were classified as a suspicious for lung cancer and the screening test result as ‘positive’. Usually, the recommended management strategy was to perform series follow-up CT scans for a period of two years for small nodules (<6 mm in diameter) and invasive diagnostic procedures, such as transthoracic biopsy, for larger nodules and lung masses. From this first generation of lung cancer CT screening algorithms we learned that the majority of these small non-calcified pulmonary nodules were not malignant.\(^2\) As a result, the predictive value of a ‘positive’ screening test results was very low.\(^2\) This led to vast amounts of follow-up CT examinations and diagnostic procedures for benign
nodules. Another important lesson we learned from these studies is that the size of the nodule is highly correlated with the probability of malignancy.3

The next generation of lung cancer screening studies, such as the U.S. National Lung Screening Trial (NLST) used the knowledge from previous studies. Hence, these studies applied screening algorithms that did not classify all non-calcified pulmonary nodules as suspicious for lung cancer, but used the size of the nodule to determine whether the screening test result was ‘positive’ or not.4 A threshold for nodule size that was commonly used to define ‘suspicion of lung cancer’ was a nodule diameter of 4 mm.5 Hence, subjects with nodules smaller than 4 mm would not receive follow-up CT scans or diagnostic tests. While subjects with nodules of 4 mm or larger were considered as suspicious for lung cancer and were recommended to undergo series of follow-up CT examinations or additional diagnostic tests (often depending on clinical judgement of the referring physician).4 From these studies we learned that the sensitivity for lung cancer of such screening algorithms is high, which means that it is safe to perform no additional CTs for nodules smaller than 4 mm in diameter.6,7 Nonetheless, the predictive value of a ‘positive’ screening test result was still low due to a moderate specificity of these screening algorithms.6,7

The next generation of lung cancer screening studies, such as the NELSON trial, aimed to achieve both a high sensitivity for lung cancer and a high specificity. To achieve this, another nodule feature that is highly predictive of malignancy was included in the screening algorithms: nodule growth.8-11 Unfortunately, the traditional manual or visual assessment of nodule diameter was not accurate enough to determine the growth rate of small non-calcified nodules at short notice. Therefore, these studies used semi-automatic volumetric software to assess the differences in nodule size on subsequent screening examinations.8-11 Hence, the screening protocols used a two-step approach to determine which of the detected non-calcified nodules were suspicious of lung cancer. First, nodules under a certain size threshold (smaller than 50 mm³ in the NELSON trial) were classified as not suspicious or ‘negative’, and nodules larger than a certain size threshold (larger than 500 mm³ in the NELSON trial) were directly classified as suspicious for lung cancer or ‘positive’. Next, the nodules with a size between these thresholds were classified as ‘indeterminate’ and were scheduled for another LDCT screening examination at short notice to determine nodule growth. Only the indeterminate-sized nodules that demonstrated malignant growth were classified as suspicious for lung cancer or ‘positive’ (in the NELSON trial defined as a percentage volume change of ≥25% combined with a volume-doubling time shorter than 400 days). Summarising, only nodules above a certain size threshold and intermediate-sized nodules growing faster than a certain threshold are classified as suspicious for lung cancer or ‘positive’ and additional diagnostic testing is recommended. Hypothetically, the use of follow-up CT scans in these screening algorithms will lead to more targeted and economical use of additional diagnostic tests, which will improve specificity and will still yield a high sensitivity for lung cancer.
The series of diagnostic tests performed after a positive screening test result are called the diagnostic work-up, and have the objective to either diagnose or rule out lung cancer. In general, the diagnostic work-up is not coordinated by the screening trial. Referring physicians use (inter)national guidelines for the management of pulmonary nodules to assist them with decision-making in the diagnostic work-up for suspicious screen-detected nodules. Despite the fact that this process is not incorporated in most screening trials, the performance evaluation of a screening protocol should also consider the diagnostic work-up. This is because performing and interpreting a screening test only identifies persons who are suspected of having lung cancer. The work-up is the next essential step in diagnosing lung cancer. Medical tests, other than LDCT examinations, are used to distinguish persons who actually have lung cancer from those who had a false-positive screening test result. The sensitivity of a screening programme will be affected when the diagnostic work-up does not effectively pick out all subjects with lung cancer.

Once the diagnosis of lung cancer has been made, the next essential step is the treatment of lung cancer. This might seem trivial, but diagnosing lung cancer earlier by LDCT screening does not affect lung cancer mortality. It is only a prerequisite that enables the early treatment of lung cancers. Only in case the treatment of early diagnosed lung cancers has a higher cure rate than in lung cancers diagnosed through symptoms, mortality from lung cancer can be reduced by screening. Therefore, the performance evaluation of a screening algorithm should also consider the lung cancer mortality reduction. To determine the mortality reduction of a screening program, a randomised controlled trial is indispensable. The NELSON trial is the largest randomised trial wherein screening using low-dose CT is compared to no screening.

RESEARCH QUESTIONS

Research question I

Chapter 2. Predictive value of screening test results

Volumetric computer tomography screening for lung cancer: three rounds of the NELSON trial.

European Respiratory Journal

Main research question

What was the screening performance of the nodule management protocol of the NELSON trial?
Sub research questions
a) What were the detection rates, test characteristics and numbers needed to screen of the nodule management protocol of the NELSON trial?
b) What was the incidence of invasive diagnostic procedures for false-positive screening test results?
c) What were participant’s probabilities of false-positive screening results and lung cancer after baseline and subsequent screening test results?

Main results
a) In the first three rounds of the NELSON trial a total of 24,354 CT scans were performed. 89.4% of the scans were a regular scans and 10.6% performed to assess the VDT of indeterminately sized nodules, the so-called ‘follow-up scans’. The screening test result was negative in 87.2%, indeterminate in 10.8% and positive in 2.0% of the scans. The positive scans eventually led to the diagnosis of lung cancer in 200 persons (cumulative lung cancer detection rate: 2.6%). Hence, the predictive value of a positive screening test result was 40.6% and 59.4% of the positive screening test results was false-positive. Overall, 1.2% of all 24,354 CT scans had a false-positive result. Finally, the number needed to screen for the diagnosis of one lung cancer was 92-133 per round.
b) Across the three screening rounds, 6.0% of the participants received one or more positive screening result. As 59.4% of the positive screening test screening results was false-positive, 3.6% of all participants had one or more false-positive screening result. 24.5% of the subjects with a false-positive screening result underwent an invasive diagnostic procedure. Hence, invasive diagnostic procedures for false-positive screening results were performed in 0.9% of all participants.
c) The probabilities of receiving a false-positive screening result or being diagnosed with lung cancer depend on the result of the baseline and subsequent screening tests. The estimated risk of a false-positive screening result within the next 5.5 years was respectively 1.3%, 8.8% and 54.2% for the individuals with a negative, indeterminate or positive baseline scan. Moreover, the estimated 5.5-year risk of screen-detected lung cancer was only 1.0% for the individuals with a negative baseline scan result, 5.7% for subjects with an indeterminate baseline result and 48.3% for those with a positive baseline.

Interpretation of results
a) The majority of the LDCT screening examinations in the NELSON trial had a negative result. Only in about one in ten screening tests an additional follow-up LDCT examination had to be performed. Moreover, only 2% of the LDCT screening examinations were positive. These results are comparable to the results of the
Danish lung cancer screening trial (DLCST), which also has a ‘third generation’ volumetry-based screening algorithm.\textsuperscript{9,12} However, the number of positive screening tests results was substantially lower than the 24.2\% positive screening test results in the NLST, wherein a second-generation screening algorithm using a single nodule size criterion of 4mm is used to define suspicion for lung cancer.\textsuperscript{13}

Despite the lower percentage of positive screenings, the cumulative lung cancer detection rate of 2.6\% was slightly higher than in the NLST (2.4\%),\textsuperscript{13} but lower than in the DLCST (3.4\%).\textsuperscript{9,12} The latter is probably due to the two additional screening rounds that have been completed in the DLCST.

The predictive value of a positive screen result was higher in the NELSON trial (40.6\%) than in both the DLCST (34.8\%) and the NLST (3.6\%).\textsuperscript{9,12,13} As a result of this and the low percentage positive screening test result, the proportion of false-positive scans out of all scans is slightly lower in the NELSON trial (1.2\%) compared to the DLCST (1.3\%), substantially better than in the NLST (23.3\%).\textsuperscript{9,12,13}

Finally, the number needed to screen for the detection of one lung cancer was 92-133 per round in the NELSON trial, which is a little less than in the other trials (97-147 in the NLST and 116-180 in the DLCST).\textsuperscript{9,12,13}

Concluding, the detection rate, positive predictive value and number needed to screen of the screening algorithm of the NELSON trial compare favourably to other lung cancer screening trials. Nonetheless, before an eventual implementation of lung cancer screening, efforts should be made to reduce the proportion of indeterminate screening test results without loss of efficacy.

b) The percentage of participants with one or more positive scan (6.0\%) was low in our trial compared to the NLST (39.1\%).\textsuperscript{13} Therefore, also the percentage of participants that had one or more false-positive screening tests was lower in the NELSON trial (3.6\%) compared to the NLST (25.8\% in round one, 27.2\% in round two and 15.9\% in round three).\textsuperscript{5,7}

Despite this, more invasive diagnostic procedures for false-positive screening results were performed in the NELSON trial (0.9\%) than in the NLST (0.6\%). Apparently, a more cautious approach to positive screening test results was applied in the United States than in the Netherlands and Belgium. Probably, suspicious screen-detected nodules were more often followed up using serial CT examinations, instead of directly proceeding to invasive procedures.\textsuperscript{14}

Concluding, invasive procedures for false positive screening test results cannot be eliminated because biopsy or surgery is sometimes the only way to distinguish lung cancer from a benign nodule. Nonetheless, this study showed that the incidence of these ‘unnecessary’ procedures could be lower than observed in the NELSON trial, as it is lower in the NLST (corrected for the difference in percentage positive screening tests). Therefore, efforts should be made to investigate what the causes of
the slightly higher rate of invasive procedures in the NELSON trial were. Examples are: insufficient guidance of referring clinicians, lack of a national guideline on the management pulmonary nodules, unavailability of tools to estimate lung cancer probability of screen-detected nodules or inexperience with CT-detected nodules. Once the causes have been identified, targeted interventions should be developed, evaluated and if successful implemented before lung cancer screening is implemented.

c) This study demonstrated that participants with a negative, indeterminate or positive first screening test had very distinct risks of false-positive screening results and lung cancer. Analyses showed a significant increase in age and number of pack-years in participants with respectively negative, indeterminate and positive screening test result, which are all well known risk factors for developing lung cancer. The presented results could aid clinicians when counselling individuals comparable to NELSON study participants when LDCT examinations are interpreted in the same fashion as in the NELSON trial.

Concluding, the result of the LDCT screening test adequately stratifies participants by their risk of lung cancer. Moreover, the predictive value of screening results lasts up to 5.5 years. As the screening test result is based on the size and growth rate of pulmonary nodules, these variables are probably very strong predictors of lung cancer risk. Hence, future studies should assess whether it is possible to build a reliable lung cancer prediction model that uses nodule size and growth rate in addition to individual characteristics such as age, gender, smoking status and smoking history. Once a reliable lung cancer prediction model has been built and validated, it should be investigated how the model can be made useful for clinicians who are confronted with the management of CT-detected pulmonary nodules. Such a lung cancer prediction tool may help identifying the malignant nodules and may reduce unnecessary diagnostic procedures for benign nodules.

**Conclusion**

The screening algorithm of the NELSON trial adequately stratified participants according to their lung cancer risk. The NELSON screening algorithm yielded a limited number of follow-up LDCT scans for indeterminate screening test results and a low number of diagnostic work-ups for positive screening test results. Although the predictive value of screening test results compared favourably to other studies, perhaps too many invasive diagnostic procedures for benign nodules were performed.
Research question II

Chapter 3. Characteristics of screen-detected lung cancer

Characteristics of lung cancers detected by computer tomography screening in the randomized NELSON trial.

*American Journal of Respiratory and Critical Care Medicine*

Main research question
What was the effect of screening using low-dose computed tomography on the characteristics of screen-detected lung cancer?

Sub research questions
a) What were the tumour characteristics of lung cancers detected by low-dose CT screening?
b) What was the effect of screening round and gender on the characteristics of screen-detected lung cancer?
c) To what extent was screening able to detect lung cancer before the onset of symptoms?

Main results
a) In the first three screening rounds of the NELSON trial, a total of 209 lung cancers in 200 persons were detected via screening. The most common histological type was adenocarcinoma (51.2%), followed by squamous cell carcinoma (16.3%), large cell carcinoma (8.1%), bronchoalveolar carcinoma (5.3%) and small cell carcinoma (3.8%). The majority of the screen-detected lung cancers were detected at a limited stage (70.8% at stage I), a minority was detected at a locally advanced stage (21.1% at stage II and IIIA) and few at an advanced disease stage (8.1% at stage IIIB and IV). Most screen-detected lung cancers were localised in the right lung (65.6% whereof 45.0% in the right upper lobe). The cancers were also predominantly localised in the periphery of lungs; 62.2% in the outer one-third of the costal-hilar diameter; adenocarcinomas in particular (82.2% vs. 17.8%, p=0.001).
b) The lung cancers detected in round 1 had a slightly higher disease stage (stage IA 59.5%, stage IV 6.8%) than in later rounds (round 2: stage IA 74.1%, stage IV 3.4%, and round 3: stage IA 64.9%, stage IV 3.9%), but this was not statistically significant. Also, the proportion histological type and localisation of the screen-detected lung cancers was not significantly different across the screen rounds.
None of the histological subtypes of lung cancer were unevenly distributed between the sexes. Also, the localisation of the lung cancers was not significantly different between the sexes: neither for the left lung versus right lung localisation nor for peripheral versus central localisation. However, cancer stage at diagnosis was significantly lower in women than in men (p=0.005). After correction for the sex differences in age, number of pack-years and BMI, women still had a statistically significant lower cancer stage than men (p=0.028).

c) 189 of the 200 (94.5%) participants who were diagnosed with lung cancer through screening had no symptoms suspicious of lung cancer. The remaining eleven participants (5.5%) had symptoms suspicious of lung cancer before they were diagnosed. In five of them symptoms emerged before the screening scan was made; however, none of them had symptoms at randomisation. Three subjects experienced suspicious symptoms for the first time in the period between the positive scan and the first consultation, and three subjects had reported the symptoms in the period between the first consultation and the diagnosis date.

**Interpretation of results**

a) The stage distribution of the screen-detected lung cancers in the NELSON trial (70.8% at stage I and 8.1% at stage IIIB/IV) is considerably more favourable than the stage distribution of clinically diagnosed lung cancers (28% at stage I and 18% at stage IIIB/IV). Moreover, the stage distribution appears also to be relatively favourable compared with the other lung cancer screening trials (on average: 64.7% at stage I and 10.9% at IIIB–IV).

This study demonstrated that the disease stage at diagnosis strongly correlated with the histological subtype of the lung cancer. On the one hand, LDCT screening detected many relatively slow growing, peripherally localised adenocarcinomas an early stage. On the other hand, LDCT screening detected only a few small cell lung cancers and all were diagnosed at stage III-IV. This finding could imply that LDCT screening is not, or is less, capable of early detection in some fast-growing histological subtypes of lung cancer. Therefore, future studies should include all lung cancers in screened participants, not only the screen-detected lung cancers, to complete the picture of lung cancer characteristics.

This study also demonstrated that most screen-detected lung cancers were localised in the periphery of the lungs, which is probably a result of the detection of many adenocarcinomas and the use of low-dose, unenhanced CT scans which can have limited image quality in hilar regions and the mediastinum. The finding that 45.0% of all lung cancers were localised in the right upper lobe is known from patients with non-small cell lung cancer. This phenomenon may be explained by the fact that the airflow at the beginning of the breath is the largest toward the right
upper lobe bronchus.\textsuperscript{90,91} As a result, the deposition of particles in tobacco smoke and their carcinogenic effects are the largest in the right upper lobe.\textsuperscript{92,93}

Concluding, the tumour characteristics of the lung cancers detected by low-dose CT screening in the NELSON trial are typically described as early stage adenocarcinomas localised in the periphery of the right upper lobe. Although the stage distribution of the screen-detected lung cancers suggests a stage shift as a result of LDCT screening, a comparison of all lung cancers diagnosed in the screening group with all lung cancers diagnosed in the control group is the only valid method to determine this.

b) Analyses showed no significant effect of screening round on cancer stage, histology, or tumour localisation. However, a decrease in advanced-stage lung cancers was observed at the second screening round (stage IV dropped from 6.8 to 3.4%). This was probably not statistically significant because of the low absolute number of advanced-stage lung cancers. In the third screening round, no evident increase in stage IV lung cancers was observed (3.9%), despite the screening interval of 2 years.

The differences in lung cancer characteristics between men and women have been studied extensively. In general, studies found that women are, in general, diagnosed at an earlier age,\textsuperscript{94,95} at a more favourable cancer stage,\textsuperscript{95-97} and are more often diagnosed with adenocarcinomas than are men.\textsuperscript{94,98,99} This study was the first trial to report on sex differences in lung cancer in a screening setting and also demonstrated that women were diagnosed at a significantly more favourable cancer stage compared to men. However, the histological subtype and localisation of the lung cancers were not significantly different between the sexes. In 2013, a post hoc analyses using data from the NLST was published. The investigators did not specifically analyse sex differences in lung cancer characteristics, however they showed that women benefitted more from LDCT screening than men.\textsuperscript{20} This is in line with the more favourable stage distribution in women as demonstrated in the current study of the NELSON trial.

Concluding, no effect of screening round on lung cancer characteristics could be demonstrated in the NELSON trial. The gender of the participants only affected the disease stage at diagnosis of the screen-detected lung cancer, but no effect on histological subtype or localisation has been observed. Because of the more favourable in stage distribution and higher effectiveness of LDCT screening in women, post hoc analyses of the effectiveness of LDCT screening in the NELSON trial stratified by gender should be performed in the future.

c) Almost all (94.5%) screen-detected lung cancers were diagnosed before the onset of symptoms. In 5.5% of the participants, lung cancer was diagnosed after the first symptoms emerged. In 3.0% the participants reported that the symptoms had started in the interval between the LDCT screening test and the date of diagnosis.
General discussion

It cannot be excluded that these symptoms were actually present for a longer time, but only recognised as serious by the participant after a suspicion of lung cancer was raised by the screening examination and subsequent tests.

Concluding, LDCT screening in the NELSON trial was able to detect lung cancer before the onset of symptoms in the large majority of the participants.

Conclusion

This study suggests that screening using low-dose computed tomography leads to a stage shift towards earlier diagnosis, more in women than in men, and a shift in histology towards slower growing and more peripherally localised subtypes of lung cancer.

Research question III

Chapter 4. Epidemiological evaluation


*Lancet Oncology*

Main research question

How can knowledge on the lung cancers not detected by low-dose computed tomography screening be used to improve the performance of the screening strategy?

Sub research questions

a) What were the detection rates and test characteristics of the nodule management protocol of the NELSON trial?
b) Were there any differences in the characteristics between the participants diagnosed with screen-detected lung cancer and the participants diagnosed with an interval cancer?
c) What were the tumour characteristics of the lung cancers not detected by low-dose computed tomography screening?
d) What were causes of the failure to detect the interval cancers?

Main findings

For this study, all Dutch participants who received at least one screening in the first three rounds (n=7,155) were included. Data on all lung cancers diagnosed from the first screening round to the last screening in round three, plus an additional two years of follow-up
were obtained from the Dutch Cancer Registry. The Belgian participants (n=935) were excluded as a linkage with the Belgian Cancer Registry was not yet possible.

a) In the first three screening rounds, a total of 187 participants were diagnosed with lung cancer through screening. Another 34 subjects were diagnosed with lung cancer between screening rounds. Hence, per 1000 screened subjects, 26.1 lung cancers were detected by screening, and 4.8 lung cancers were not (ratio 5.5:1). Across the three screening rounds, the ratio between the detected and missed lung cancers decreased from the first to the second round from 12.4:1 to 2.9:1, and increased from round two to round three to 7.2:1.

The test characteristics for the three screening rounds combined were: sensitivity 84.6% (95% confidence interval (CI) 79.9-89.3%), specificity 98.6% (95% CI 98.5-98.8%), PPV 40.4% (95% CI 35.9-44.7%), and NPV 99.8% (95% CI 99.8-99.9%). When only the first year of the interval between the screening rounds was considered, the performance was: sensitivity 90.8% (95% CI 86.4-94.5%), specificity 98.7% (95% CI 98.5-98.8%), positive and negative predictive values respectively, 40.4% (95% CI 35.9-44.7%) and 99.9% (95% CI 99.9-99.9%). Across the three screening rounds, the sensitivity and specificity were respectively: 92.5% and 98.3% in the first round, 73.6% and 99.0% in the second round, and 87.8% and 98.7% in the third screening round.

b) The participants diagnosed with either screen-detected lung cancer or interval lung cancer were significantly older than the subjects without lung cancer, however no differences were observed in the gender, or number of pack-years smoked. Only participants diagnosed with an interval cancer were significantly more often current smokers than those without lung cancer. Analyses between the participants with interval cancer and participants with screen-detected lung cancer showed that there was only a significant difference in smoking status.

c) The cancer stage at diagnosis of the lung cancers not detected by screening was as follows: 8.6% was diagnosed at stage IA, 8.6% at stage IIB, 8.6% at stage IIIA, 5.7% at stage IIIB, and 68.6% at stage IV. This disease stage distribution was significantly less favourable than the stage distribution of the screen-detected lung cancers. The interval cancers diagnosed within the first year of the screening interval had a significantly higher disease stage than in the interval cancers diagnosed in the second year of the interval.

The distribution over the histological subtypes of lung cancer was as follows for the interval cancers: 25.7% adenocarcinomas, 20.0% small cell carcinomas, 17.1% squamous cell carcinomas, 17.1% large cell carcinomas, the remaining 20.0% were other rarer subtypes and lung cancers of unknown histopathological subtype. The interval cancers were significantly more often small cell carcinomas, and signifi-
cantly less often adenocarcinomas compared to screen-detected cancers. The other histological subtypes were equally distributed.

Finally, the localisation of both the interval cancers and screen-detected cancer was equally distributed across the lungs.

d) Re-evaluation of the CT examinations of the 34 participants with an interval cancer learned that no lung cancer was present at the last screening examination in 35.3%. In the remaining 64.7% an abnormality suspicious for lung cancer could, in retrospect, be identified on the screening CT examination. In the majority of these cases, the suspicious abnormality was missed. The causes of the failure to detect these lung cancers were: detection errors (38.2%), interpretation errors (5.9%) and human error (5.9%). In the remaining cases, the abnormality was actually detected, but lung cancer was not diagnosed because of: participant non-compliance (5.9%), not classified as suspicious by the protocol (2.9%), and manually classified as not suspicious by the radiologist due to a negative diagnostic work-up at a previous screening round (5.9%).

Interpretation of results

a) This study demonstrated that the detection rate was high at 26.1 per 1000 screened subjects for three screening rounds. Since the NELSON trial has screening intervals of more than one year from the second round onwards, only the detection rates of the first round and the first year of the second round may be compared to other screening trials with a one-year screening interval. Henceforth, the detection rate for the first screening round was 8.69 per 1000 screened in the NELSON trial, which was lower than in the U.S. National Lung Screening Trial (NLST): 10.3 per 1000 screened. This difference may be explained by the lower lung cancer risk of the NELSON participants compared to the NLST participants, and the slightly lower sensitivity in the NELSON trial (92.5%) than in the NLST (93.8%). The incidence of interval cancers between the first and second round was comparable in the two trials (0.70 per 1000 screened in NELSON and 0.68 per 1000 in NLST). This might indicate that the majority of lung cancers not detected at baseline in the NELSON trial, did not become symptomatic in the one-year interval and were diagnosed through screening in the second round. This explanation is supported by the observation that the lung cancer detection rate in the second screening round was higher in the NELSON trial (7.69 per 1000) than in the NLST (6.80 per 1000). In the first year of the screening interval after the second round scan, substantially more interval cancers were diagnosed in the NELSON trial (1.02 per 1000) than in the NLST (0.40 per 1000). This probably results from the difference in sensitivity in the second round (NELSON 88.3% versus NLST 94.4%).
The sensitivity and specificity of NELSON screening algorithm were respectively 92.5% and 98.3% in round one, 73.6% and 99.0% in round two, and 87.8% and 98.7% in round three. Whether the sensitivity is sufficient to obtain a significant lung cancer mortality reduction can only be determined by the final mortality analyses of the NELSON trial, which are planned ten years after randomisation. It is likely that the specificity is sufficient to obtain cost-effectiveness.

Since the NELSON trial has screening intervals of more than one year from the second round onwards, only the detection rates of the first round and the first year of the second round may be compared to other screening trials with a one-year screening interval. Henceforth, the sensitivity of 92.5% in the first round and 88.3% in the second round is slightly lower than in the NLST (93.8% in the first round and 94.4% in the second round). The specificity of 98.3% in the first round and 99.0% in the second round is substantially higher than in the NLST (73.4% in the first round and 72.6% in the second round).

Concluding, the detection rate for the first three screening rounds of NELSON trial was 26.1 per 1000 participants. Simultaneously, 4.8 lung cancers per 100 participants were not detected by screening. The test characteristics for the first three screening rounds combined were: sensitivity 84.6%, specificity 98.6%, PPV 40.4%, and NPV 99.8%. These detection rates and test characteristics are promising for the cost-effectiveness of the NELSON screening trial. Nonetheless, the results of the mortality analysis and subsequent cost-effectiveness analysis should be awaited.

b) All participants of this study were at substantial risk of developing lung cancer as they were at least 50 years old and had smoked ten or more cigarettes a day for over 30 years, or fifteen or more cigarettes a day for over 25 years. Even within this population, older age and being a current smoker were still significant risk factors for developing lung cancer. Remarkably, being a current smoker is only associated with an increased risk of being diagnosed with an interval lung cancer. This may be because continued smoking promotes the development of lung cancer subtypes that grow faster and are less perceptible by LDCT screening, such as small cell carcinomas. This finding reinforces the urgency of smoking cessation in individuals undergoing lung cancer screening.

Concluding, subjects diagnosed with an interval cancer were significantly more often current smokers than the participants with screen-detected lung cancer; no differences in age, gender and number of pack-years smoked were observed.

c) This study demonstrated, not surprisingly, that screen-detected lung cancers are diagnosed at a notable more favourable cancer stage than interval cancers. More noticeable was the finding that the disease stage of the interval cancers diagnosed in the first year since screening was significantly higher than the stage of those diagnosed in the second year.
This study also demonstrated that interval cancers are different in histopathology compared to screen-detected lung cancers. Interval cancers were significantly less often adenocarcinomas and not a single interval cancer was a bronchoalveolar carcinoma. Interval cancers were slightly more often large cell carcinomas and squamous cell carcinomas, and significantly more often small cell carcinomas than screen-detected lung cancers.

The differences in tumour characteristics are both caused by the earlier diagnosis of screen-detected lung cancer as a result of screening asymptomatic individuals, and by the more aggressive nature of interval lung cancers compared to detected cancers. This study revealed that 35.3% of the interval cancers newly developed during the screening interval, all these interval cancers were diagnosed at stage III/IV. Hence, these cancers grew from undetectable to incurable cancers in less than one or two years. This observation suggests an enormous growth and metastatic potential. This suits with the finding that these interval cancers were significantly more often small cell carcinomas than the interval cancers that did not arise during the screening interval (41.7% versus 8.7%, p=0.03).

This study is the first to present the cancer stage distribution of both the screen-detected and the interval cancers of the NELSON trial. Hence, 61.9% of all lung cancers were diagnosed at stage I, and only 17.8% at stage IIIB/IV. In the NLST, 59.0% of the lung cancers was diagnosed at stage I, and 22.9% at stage IIIB/IV, which is not significantly different (p=0.20). Thus, despite longer screening intervals, slightly lower sensitivity, and fewer female participants in the NELSON trial, lung cancer was diagnosed as early as in the NLST.13 This finding is encouraging for the effectiveness of lung cancer screening regimens using biannual screening after an initial annual screening round.

Concluding, the lung cancers not detected by CT screening were characterised by a higher cancer stage at diagnosis; more than 70% of the interval cancers were diagnosed at an incurable stage (IIIB/IV). Further, the interval cancers were most frequently of the adenocarcinoma subtype, followed by small cell, squamous cell carcinomas, and large cell subtype.

d) Re-evaluation of the clinical CT and last screening CT examination revealed the causes of the failure to detect interval cancers. Surprisingly, 64.7% of the interval cancers were, in retrospect, visible at the last screening CT examination. Detection, interpretation and human errors were identified as the main cause of failure in 50.0% of the interval cancers. In addition, 2.9% of the interval cancers were not diagnosed through screening because the screening test result was adjusted manually by the radiologist from positive to negative because a diagnostic work-up performed in an earlier round did not yield the diagnosis of lung cancer.
Another remarkable finding of this study was that failure of the screening protocol to classify cancerous nodules as suspicious was rare. Only 5.9% of the interval cancers were not diagnosed because the cancerous nodule shrunk or had a volume doubling-time of more than 400 days. This suggests that the relatively stringent criteria for a positive result in the NELSON trial, did not lead to notable numbers of missed cancers. This finding is encouraging for future screening programmes that pursue limited harms and costs, as more stringent criteria contribute to this.21

Further, 5.9% of the interval cancers were actually detected, but the diagnosis was not made through screening because participants refused to comply with the screening protocol. Instead of undergoing a follow-up CT at three months after their indeterminate screening test result, they directly underwent a diagnostic resection of the nodule, which yielded the diagnosis of lung cancer. Arguably, these interval cancers may have been screen-detected lung cancer in case the participants had complied with the protocol.

Finally, 35.3% of the interval cancers were, also in retrospect, not visible at the last screening examination. Hence, these interval cancers were not missed but arose during the interval.

Concluding, radiological errors were the most important cause of the failure to detect the interval cancers. Failures by the protocol or non-adherence to the protocol were infrequent causes of detection failure. More than one third of the interval cancers could not be prevented as they were not present at the last screening CT examination, but arose during the screening interval.

Conclusion
The detection rates and sensitivity of the NELSON screening protocol were sufficient to diagnose lung cancer as early as in the NLST, which demonstrated to have an effective screening protocol.13 Moreover, the NELSON screening protocol yielded a very high specificity, which is a prerequisite for cost-effectiveness. Nonetheless, the performance of the screening protocol may be improved by co-implementation of CT screening with an effective smoking cessation program, and training of the screening radiologists to reduce the number of detection and interpretation errors.

Research question IV

Chapter 5. Radiological evaluation

Computed tomographic characteristics of interval and post-screen cancers in lung cancer screening.
European Radiology

Main research question
How can knowledge on the radiological characteristics of lung cancers not detected by low-dose CT screening be used to improve the performance of the screening strategy?

Sub research questions
a) What proportion of the lung cancers not diagnosed through screening was, in retrospect, present at the last LDCT screening examination?
b) What were the causes of the failure to detect the missed lung cancers?
c) What were the characteristics of the carcinomas missed on the LDCT screening examination due to radiological detection or interpretation errors?

Main findings
For this study all 7,155 Dutch participants randomised to the CT screening arm of the NELSON trial were included. The participants with lung cancer diagnosed between screening rounds (interval cancers) and the participants with lung cancer diagnosed after screening (post-screen cancers) were identified via linkages with the Dutch Cancer Registry. The Belgian participants (n=935) were excluded as a linkage with the Belgian Cancer Registry was not yet possible.

In the first three rounds of the NELSON trial, LDCT screening detected lung cancer in 187 of the 7,155 (2.6%) participants. In another 61 of the 7,155 (0.85%) participants, lung cancer was diagnosed between screening rounds or after the subject’s last attended LDCT screening examination. Of these 61 participants clinical and radiological files were retrieved from the various hospitals in which the diagnosis was established. The clinical CT examination made at the time of the diagnosis was compared to the last screening LDCT examination by two experienced radiologists to determine whether any CT evidence of lung cancer could be identified in retrospect on the screening CT. In case of any abnormalities on the LDCT screening examination, the radiologists determined whether abnormalities were missed or misinterpreted by comparing their reading report by the original reading report in the trial database. The missed lung cancers could be caused by detection errors and interpretation errors. In detection errors the lesion was not mentioned in the report but can be seen in retrospect on the last CT, while in interpretation errors the lesion was noted but considered a benign lesion. Finally, the radiologists searched for other abnormalities on the LDCT screening examination, which may influence detection or interpretation.

a) In 26 of the 61 (42.6%) participants with a lung cancer not detected through screening no abnormalities suspicious of lung cancer were visible on their last attended LDCT screening examination. In eleven of these 26 subjects (42.3%) the lung cancer...
was an interval cancer as it was diagnosed before their next scheduled LDCT screening examination. In 15 of the 26 subjects (57.7%) the lung cancer was diagnosed after the participant ceased with the screening program; a 'post-screening cancer'. In the remaining 35 of the 61 (57.4%) participants with a lung cancer not detected through screening, the radiological re-evaluation showed that the lung cancer was actually present at the last LDCT screening examination.

b) In 35 of the 61 participants with a lung cancer not diagnosed through screening a suspicious abnormality was visible on the last LDCT screening examination. Twenty of these 35 lung cancers were interval cancers and fifteen were post-screening cancers. Radiological re-evaluation of these 35 cases showed that there were various reasons for the failure to diagnose the lung cancers.

In twenty cases, the lesions suspicious of lung cancer were not found on the LDCT examination by the radiologist due to detection error or human error. In another two cases the lesions suspicious for lung cancer were detected, but the lung cancers were not diagnosed due to interpretation errors by the radiologist. In thirteen cases the lesions suspicious of lung cancer were detected, but the lung cancers were not diagnosed due to:

I) Failure of the protocol: two (5.7%) lung cancers were not diagnosed via the NELSON trial because the protocol did not classify the nodules as suspicious for lung cancer. In these cases the protocol was adhered to and no positive screening result was issued as the nodules did not show growth.

II) Non-compliance with the protocol by the participant: eight (22.9%) lung cancers were not diagnosed via the NELSON trial because the participant refused to comply with the study's recommendations based on the LDCT screening examination.

III) Non-compliance with the protocol by the radiologist: three (8.6%) lung cancers were not diagnosed via the NELSON trial because the radiologist had replaced the actual screening result by a negative screening result because a previous diagnostic work-up had not yielded the diagnosis of lung cancer.

c) In the 22 of the 61 participants a suspicious abnormality was in retrospect visible on the last LDCT screening examination, but lung cancer was not diagnosed due to interpretation detection or radiological errors. Two lung cancers were detected but not diagnosed due to interpretation error. In one case, a lesion of 7 mm in diameter was noted, but no further action was undertaken because it was interpreted as benign bulla wall thickening. In the other case, a lesion attached to the pleura of 22 mm in diameter was detected, but not referred for diagnostic work-up because it was interpreted as scarring. In the remaining twenty participants, lung cancer was present but was not detected at the LDCT screening examination. The
characteristics of these twenty lung cancers may give an indication of the causes of the detection errors:

I) Endobronchial localisation: Five lung cancers were visible on CT as small central endobronchial tumours. Two were localised in the right pectoral segmental bronchus, one in the right lateral segmental bronchus, one in the right upper lobe bronchus and one in the lingular bronchus.

II) Bulla wall thickening: Four lung cancers were visible on CT as a thickening of the wall of a bulla. These lung cancers were localised in the right upper lobe (n = 2), left upper lobe and the left lower lobe. In one case the wall thickening was focal.

III) Pleural attachment: Four lung cancers were visible on CT as nodules attached to the pleura. Three of these nodules were smaller than 1 cm (5, 7 and 7 mm) and one was larger than 1 cm.

IV) Pleural effusion: One lung cancer was not visible as a lung nodule or lung mass on CT, but as a pleural effusion on the right side. 177 days after the screening examination, the diagnosis of lung cancer with massive malignant pleural effusion was made.

V) Lymphadenopathy: Three lung cancers were not visible as a lung nodule or lung mass on CT, but as lymphadenopathy. In two cases the lymphadenopathy was located in the right hilum, inseparable from the pulmonary artery due to the lack of intravenous contrast. In the third case, lymphadenopathy measured 22 mm was mainly located in the aortopulmonary window.

VI) Fibrosis: One lung cancer was visible on CT as a nodule smaller than 1 cm in diameter surrounded by extensive reticulation.

VII) Human error: Two lung cancers were visible on CT as nodules larger than 1 cm localised in the parenchyma of the lung. As radiological evaluation did not reveal any explanation for the failure to detect these two lung cancers, human error is considered to be the most plausible cause.

**Interpretation of results**

a) Sixty-one (0.85% of 7,155) Dutch participants randomised to the screening group of the NELSON trial, were diagnosed with a lung cancer that was not detected by screening. In 42.6% of the participants no abnormality suspicious for lung cancer could be identified on the last screening CT examination. Hence, these lung cancers arose after the last screening CT was made. In the remaining 57.4% of the participants, an abnormality suspicious of lung cancer was visible on the LDCT screening examination.

Missed carcinomas in CT-based lung cancer screening trials have received only limited attention in the radiological literature. Moreover, not a single lung cancer
screening study re-evaluated screening CT examinations of the subjects with an interval or post-screen lung cancer to determine which lung cancers were missed and in which subjects the lung cancers developed after the last screening CT examination. As a result, the finding in this study that 57.4% of the interval and post-screen lung cancers were missed cannot be compared to any other study.

The results of this study may be extrapolated to populations with a risk of developing lung cancer that is comparable to the lung cancer risk of the NELSON population. As a previous study of the NELSON trial demonstrated that higher age and current smoking status of the participants were associated with a significantly increased risk of being diagnosed with an interval cancer, the incidence of missed lung cancers may depend on these variables in different populations.

Concluding, about half of the lung cancers (57.4%) not diagnosed through screening was, in retrospect, present at the last LDCT screening examination.

b) In the 35 participants with an interval or post-screen lung cancer lung cancer an abnormality suspicious for lung cancer was visible on the last LDCT screening examination. Radiological re-evaluation showed that 57.2% of the lesions suspicious of lung cancer were not found on the LDCT examination by the radiologist due to detection error or human error. In 5.7%, the lesions suspicious for lung cancer were detected, but the lung cancers were not diagnosed due to interpretation errors by the radiologist. In 37.1%, the lesions suspicious of lung cancer were detected, but the lung cancers were not diagnosed due to: failure of the protocol (5.7%), non-compliance with the protocol by the participant (5.7%), and non-compliance with the protocol by the radiologist (8.6%).

In the literature, detection errors or interpretation errors by the radiologist are reported as common causes of missed lung cancers. In contrary, no studies indicating the incidence of missed lung cancers on CT due to nodule management protocol failure or non-compliance to the protocol by either the radiologist or the patient have been published. Despite this, the incidence of missed lung cancers due to protocol failure might be somewhat lower in clinical practice. This is because the most commonly used guidelines (based on the criteria of the Fleischner Society) recommend serial follow-up CT examinations for any non-calcified pulmonary nodule of 4mm or more in diameter. Hence, more nodules are followed up and probably less lung cancers are missed. However, the adherence to guidelines has been proven to be moderate, which may result in more missed lung cancers in clinical practice than in a clinical trial.

Concluding, detection errors were the most common cause of the failure to detect interval and post-screen lung cancers that were, in retrospect, visible at the last screening CT examination. Less common causes of missed lung cancers were
interpretation errors, failure of the screening protocol, and non-adherence to the protocol by either the radiologist or the participant.

c) In the 22 of the 61 participants a suspicious abnormality was in retrospect visible on the last LDCT screening examination, but lung cancer was not diagnosed due to interpretation detection or radiological errors. There were a number of typical lung cancer characteristics that may have caused or contributed to the failure to detect them.

The most common characteristic was endobronchial tumour localisation (22.7%, n=5 all detection errors), which was also the most common cause in a study by White et al.24 There are two possible explanations for this: firstly, endobronchial nodule localisation is far less common than intraparenchymal localisation. As a result, the attention of the radiologist is primarily focused on the lungs and not the bronchi which facilitates the occurrence of detection errors. Secondly, the computed-aided detection system that is used to find nodules the radiologist misses, cannot search for nodules in the bronchial tree.30 To reduce the occurrence of missed lung cancers, it is recommended to screening radiologists to force themselves to check the bronchial tree visually after the regular reading using the computed-aided detection system.

The other most common characteristic was bulla wall thickening (22.7%, one interpretation error and four detection errors). Bulla wall thickening was not classified as an important abnormality in the protocol of the NELSON trial. Hence, this characteristic was not reported unless the radiologist recognised it as suspicious for lung cancer. As a result, it is unknown what the incidence of bulla wall thickening is in the whole screened population and in the participants with screen-detected lung cancer in particular. Nonetheless, it is possible that the incidence of a localisation in a bulla wall is higher in missed lung cancers than in detected lung cancer as no specific attention was paid to bulla walls in the NELSON trial. There are no published studies that report on the incidence of this characteristic in lung cancers missed at CT examinations. However, bulla wall thickening was reported to be not uncommon in lung cancers that were detected by CT: in the Early Lung Cancer Action Project, 2% of the lung cancers detected at the first screening round and 12% of those detected in the second screening round were associated with cystic airspaces31; and in a clinical series of 545 lung cancer patients 3.5% of the cancers were associated with a bulla.25 Since no data on the prevalence of bulla wall thickening in the screened population is available, the positive predictive value of this characteristic for lung cancer is unknown. Nonetheless, the prevalence of this characteristic of 22.7% (of the lung cancers missed due to radiological errors) justifies the recommendation to pay more attention to focal or diffuse bulla wall thickening in lung cancer screening.
The other most common characteristic of missed lung cancer due to detection and interpretation errors was pleural attachment of the nodule (22.7%, n=5, four detection errors and one interpretation error). Malignant nodules that are pleural-attached may be more difficult to detect and interpret than intraparenchymal localised malignant lung cancers as the computer aided-detection system is less sensitive for pleural attached nodules, and the size of pleural-attached nodules cannot be assessed by the volumetric software used in the NELSON trial. Moreover, the NELSON publication by Xu et al. wherein in a sub-selection of 891 nodules was determined that none of the screen-detected lung cancers were attached to the pleura, may have induced a decreased alertness of the NELSON radiologists to pleural-attached lesions. Missed lung cancer in pleural-attached lesions (22.7%) was relatively more common in the NELSON trial than in to other studies: 6.3%, 6.7%, 11.1% and 14.3%. This may indicate that screening radiologists should consider pleural-attached nodules as potentially malignant despite the fact that no association between this characteristic and lung cancer could be established in the study by Xu et al.

A less common presentation of missed lung cancers was lymphadenopathy without visible lung lesions (13.6%, n=3). This type of missed lung cancer is probably difficult to prevent as the radiological evaluation of the screening CTs is focussed on the lungs. Moreover, the low-dose scans are performed without the administration of intravenous contrast, which is not optimal for imaging the mediastinum.

One other missed lung cancer was also not visible as a lung lesion, but presented as pleural effusion at the screening CT examination (4.5%). Also in this case the effusion was probably overlooked because the screening radiologists focussed on intrapulmonary abnormalities.

Detection errors due to other pathology were uncommon in this study, only one lung cancer was not detected because it was surrounded by extensive reticulation (4.5%). Missed lung cancers due to other distractive pathology on the CT is also reported in several clinical series.

No plausible explanation for the failure to detect the two remaining missed lung cancers of this study could be identified. As both nodules were larger than 1 cm in diameter and no specific characteristics or distractions were present, these nodules should have been detected. Nonetheless, human error will be difficult to prevent.

Some specific nodule characteristics that were reported to be associated with missed lung cancers were not observed in the NELSON trial; smaller nodule size, peripheral nodule localisation, sub-solid nodule type and attachment to a vessel.

Concluding, this study identified several radiological characteristics that were related to the failure to detect or interpret interval and post-screening lung cancers.
Some of the causes of the detection and interpretation errors were probably not preventable, such as lung cancer presenting as extra-pulmonary abnormalities, distractive other pathology and human error. However, three different causes may presented opportunities to reduce the number of missed lung cancers: endobronchial tumours, tumours arising from thickenings in bulla walls and pleural-attached nodules. The design of this study does not allow for the calculation of the positive predictive value of these characteristics. To determine this, the incidence of these characteristics should be determined both in the detected lung cancers and representative sample of the screened population without lung cancer. If such a study would demonstrate that endobronchial tumours, tumours arising from thickenings in bulla walls and pleural-attached nodules are relevant risk-factors for (interval) lung cancer, the recommendation to check the bronchial tree visually, pay more attention to bulla wall thickening and consider also pleural-attached nodules as potentially malignant should be included in guidelines for lung cancer screening.

**Conclusion**

The majority of the lung cancers not detected by low-dose CT screening were not preventable. The performance of the screening strategy may be improved by reducing the number of detection and interpretation errors. This may achieved by increasing the radiologist's attention for endobronchial lesions, bulla wall thickenings, and pleural-attached lesions.

**Research question V**

**Chapter 6. Optimisation of screening protocols**

Lung cancer probability in subjects with CT-detected pulmonary nodules: an analysis of data from the NELSON trial of low-dose CT screening.

*Lancet Oncology*

**Main research question**

How should a participant’s predicted lung cancer probability, based on size and growth of CT-detected nodules, be used to optimise the nodule management protocol of the NELSON trial?

**Sub research questions**

a) Was it valid to predict the two-year lung cancer probability of an individual who underwent screening using low-dose computed tomography, using a model based on nodule size and growth rate?
b) What was the probability of lung cancer in an individual who underwent screening using low-dose computed tomography, based on nodule size and growth rate?

c) How should the current thresholds for nodule size and growth rate be adjusted to improve risk stratification, test characteristics and reduce harms?

Main findings

For this study all 7,155 Dutch participants randomised to the CT screening arm of the NELSON trial were included. The participants with lung cancer diagnosed between screening rounds (interval cancers) and the participants with lung cancer diagnosed after screening (post-screen cancers) were identified via linkages with the Dutch Cancer Registry. The Belgian participants (n=935) were excluded as a linkage with the Belgian Cancer Registry was not yet possible.

a) This study aimed to improve the management of CT-detected pulmonary nodules by designing improved management protocol based on lung cancer probability. As nodule size and growth rate are reported to be the most important predictors of lung cancer probability, these determinants were chosen as the base for the new protocols. The first step in the design of the new protocols was to determine whether nodule size (volume or diameter) and nodule growth rate (volume-doubling time) were valid predictors of lung cancer probability in our dataset.

For this, logistic regression analysis was performed to predict lung cancer risk in the two years following each screening round, using diameter, volume and VDT as potential predictor variables. The model only included participants whose largest nodule measured 50-500 mm³ and who had ≥1 growing nodule in this volume range, because the VDT was available only for this subgroup.

The model estimated that nodule volume, nodule diameter and nodule VDT were significant lung cancer predictors (all p<0.001). However, nodule volume was a stronger predictor of lung cancer than nodule diameter; if nodule volume was included in the model, nodule diameter was not a significant predictor anymore.

b) The two-year lung cancer probability for all included participants was 1.3% (95% CI 1.2-1.5%). On the CT examinations of 54.4% of the participants no pulmonary nodules were detected. Their probability to be diagnosed with lung cancer over the next two years was only 0.4%.

The probability to be diagnosed with lung cancer in the two years following the screening examination was low for subjects with small nodules: for nodule with a volume <100 mm³ 0.5-0.7%, and for nodule with a diameter <5 mm 0.3-0.6%. Moreover, these probabilities were not significantly different from the lung cancer probability of subjects without nodules.

The two-year lung cancer probability was intermediate for subjects whose nodules had a volume of 100-300 mm³ or a diameter of 5-10 mm, as the associated risks were
respectively 1.5-5.8% and 0.9-2.9%; which was significantly increased compared to the probability of subjects without nodules.

Lung cancer probability in the two years following the screening examination was high for subjects whose nodules measured ≥300 mm³ or >10 mm; 8.9-25.7% and 11.1-31.6% respectively. These probabilities were also significantly higher than the probability of subjects without any nodules.

The lung cancer probability according to nodule volume doubling-time (VDT) was calculated for the subjects whose largest nodule measured 50-500 mm³. Subjects with slowly-growing nodules (VDT ≥600 days), or nodules that were stable in size, or nodules that had shrunken or resolved, had a low probability of lung cancer (0.0-1.0%). Lung cancer probability was significantly increased for subjects with nodules with a VDT <600 days. Hence, subjects whose nodules had a VDT of 400-600 days were at intermediate risk (4.1% in two years), and subjects whose nodules had a VDT <400 days were at high risk (6.7-25.0% in two years).

Finally, both nodule volume and nodule VDT were used to estimate the two-year lung cancer probability. In subjects with large nodules of ≥300 mm³, lung cancer probability remained substantial (from 5.9% to >50%) even in case of slow nodule growth. In subjects with intermediate-sized nodules (volume 50-300 mm³), the lung cancer probability ranged from low (<1.5%) to high (30%), for VDTs ranging from <50 days to 600 days.

c) The current guideline for the management of CT-detected pulmonary nodules is based on the criteria of the Fleischner Society. To be able to estimate the performance of the current guideline, it was simulated as follows:

I) Subjects whose nodules measured ≤4 mm were classified as negative. In these subjects the next screening examination was made after one year, which is in accordance with the guideline which recommends follow-up CT at twelve months.

II) Subjects whose nodules measured 4-8 mm were classified as indeterminate. In these subjects a follow-up CT is made after three months, while the guideline recommends performing a follow-up CT at 6-12 and 18-24 months. The final result is classified as positive for VDTs <400 days, and negative for VDTs ≥400 days, in accordance with the guideline.

III) Subjects whose nodules measured >8 mm were classified as positive. In these subjects additional diagnostic procedures were performed, which is in accordance with the guideline.

The simulated ACCP protocol yielded a sensitivity of 90.9% (95% CI 81.2-96.1%), and a specificity of 87.2% (95% CI 86.4-87.9%). The predictive value of a positive test result (PPV) was 6.2% (95% CI 4.8-7.9%), which led to follow-up CT examinations in 29.8% of the screened subjects, and additional diagnostic procedures in 13.6%.
Next, a nodule management protocol was designed using thresholds for nodule diameter that were based on the lung cancer probability:

I) Subjects whose nodules measured ≤5 mm were classified as negative. In these subjects the next screening examination was made after one year.

II) Subjects whose nodules measured 5-10 mm were classified as indeterminate. In these subjects a follow-up CT was made after three months, to assess nodule VDT. The final result was classified as positive for VDTs <600 days, and negative for VDTs ≥600 days.

III) Subjects whose nodules measured >10 mm were classified as positive. In these subjects additional diagnostic procedures were performed.

This protocol yielded a sensitivity of 92.4% (95% CI 83.1-97.1%) and a specificity of 90.0% (95% CI 89.3-90.7%). The PPV of this protocol was 7.9% (95% CI 6.2-10.1%), which led to follow-up CT examinations in 22.2% of the screened individuals and to additional diagnostic procedures in 10.8%.

Finally, a nodule management protocol was designed using thresholds for nodule volume that were based on the lung cancer probability:

I) Subjects whose nodules measured ≤100 mm³ were classified as negative. In these subjects the next screening examination was made after one year.

II) Subjects whose nodules measured 100-300 mm³ were classified as indeterminate. In these subjects a follow-up CT was made after three months, to assess nodule VDT. The final result was classified as positive for VDTs <600 days, and negative for VDTs ≥600 days.

III) Subjects whose nodules measured >300 mm³ were classified as positive. In these subjects additional diagnostic procedures were performed.

This protocol yielded a sensitivity of 90.9% (95% CI 81.2-96.1%) and a specificity of 94.9% (95% CI 94.4-95.4%). The PPV of this protocol was 14.4% (95% CI 11.3-18.1%), which led to follow-up CT examinations in 7.8% of the screened individuals and to additional diagnostic procedures in 5.9%.

**Interpretation of results**

a) A logistic regression model was used to determine whether nodule size (volume or diameter) and nodule growth rate (volume-doubling time) were valid predictors of lung cancer probability in our dataset. Analyses showed that nodule volume, nodule diameter and nodule VDT were significant lung cancer predictors. However, nodule volume was a stronger predictor of lung cancer than nodule diameter.

Concluding, nodule volume, diameter and volume-doubling time are strong predictors of the lung cancer probability of subjects with CT-detected nodules. Therefore, it is valid to use these determinants for designing new nodule management protocols. The performance of protocols using nodule diameter is expected to be...
worse than the performance of protocols using nodule volume, as the relationship between nodule diameter and lung cancer probability is weaker than the relationship between nodule volume and lung cancer probability.

b) In more than half of the included participants (54.4%) no pulmonary nodules were detected. Their two-year lung cancer probability of only 0.4% suggests that it may be safe to apply a screening interval of at least two years in these individuals. In the subjects with CT-detected nodules, lung cancer probability depended strongly on nodule volume and VDT.

This study confirms that the lung cancer probability of small nodules (volume <50 mm³ or diameter <4 mm) is low; at ≤0.6% compared to <1% reported in the literature. Moreover, the lung cancer probability in subjects whose nodules measure 50-100 mm³ or 4-5 mm, is also low (0.3-0.7%) and not significantly different from that in subjects without nodules. Currently, guidelines recommend two to four follow-up scans for such nodules. Omitting these CT surveillance schedules should be considered, as the risk of malignancy does not justify the harms of ionizing radiation, psychological distress, and the associated costs.

Next, subjects with intermediate-sized nodules (volume 100-300 mm³ or diameter 5-10 mm) have a significantly higher two-year lung cancer risk (0.9-5.8%) compared to subjects without nodules. This justifies additional CT examinations, which is in accordance with current guidelines. Since the lung cancer risk of subjects with nodules between 5 and 8 mm is comparable (0.9-1.8%), a uniform CT surveillance schedule may be applied.

For intermediate-sized nodules, the VDT assessed at CT surveillance should be used to re-assess the lung cancer probability. Subjects with slowly-growing (VDT ≥600 days), stable, shrunken and resolved nodules are at low risk of lung cancer (0.0-1.0%) and could withdraw from intensified CT surveillance and return to regular screening. By contrast, subjects whose nodules have a VDT <600 days have a significantly increased risk of lung cancer (4.1-25.0%), which justifies intensified CT surveillance and additional diagnostic procedures. Subjects whose nodules have a VDT of 400-600 days may be regarded as at intermediate risk, since their lung cancer probability is 4.1% in two years. Hence, a follow-up CT examination at short notice to re-assess nodule size and growth may be preferred over more invasive or expensive diagnostic procedures.

Finally, this study confirmed the high lung cancer probability in subjects with large nodules (volume ≥300 mm³ or diameter ≥10 mm): >10% in the literature and 8.9-31.6% in this study. A remarkable finding was that the risk of these large nodules is also high (5.9-50%) when they grow slowly. Therefore, a follow-up CT examination to assess growth for nodules ≥300 mm³ or ≥10 mm provides little
additional information, but may delay lung cancer diagnosis. Hence, immediate diagnostic work-up is suggested instead.

Concluding, the probability of lung cancer in subjects who underwent CT screening depends on the presence, size and growth rate of CT-detected pulmonary nodules. Subjects without nodules, subjects with small nodules (volume ≤100 mm³ or diameter ≤5 mm), or with slow growing (VDT ≥600 days), stable, shrinking, resolving nodules that are smaller than 300 mm³ or 10 mm, have a low lung cancer risk. Individuals with intermediate-sized nodules (volume 100-300 mm³ or diame-

ter 5-10 mm), or nodules smaller than 300 mm³ or 10 mm with a VDT of 400-600 days, have an intermediate lung cancer risk. Subjects with large nodules (volume >300 mm³ or diameter >10 mm), or with fast-growing nodules (VDT <400 days) are at high risk of developing lung cancer within two years.

c) In this study, three nodule management protocols were simulated and their performance evaluated; the ACCP guideline for nodule management based on the Fleischner criteria, a new lung cancer probability-based protocol using nodule diameter, and a new lung cancer probability-based protocol using nodule volume.

Comparing the new lung cancer probability-based protocol using diameter to the simulated ACCP protocol, the new protocol yielded a higher sensitivity (92.4% instead of 90.9%), fewer follow-up CT examinations (-7.6%), and additional diagnostic procedures (-2.8%), than the ACCP protocol. These results imply that the ACCP nodule management protocol performed well. However, with small adjustments of the thresholds for nodule diameter (raising the lower threshold from 4 mm to 5 mm, and raising the upper threshold from 8 mm to 10 mm) and the criterion for malignant nodule growth (VDT <600 days instead of VDT <400 days), the performance could be improved.

The new lung cancer probability-based protocol using volume classified no nodules and nodules <100 mm³ as negative, nodules 100-300 mm³ as indeterminate (final result positive if VDT <600 days, otherwise negative), and nodules >300 mm³ as positive. This protocol demonstrated a very high specificity (94.9%), which yielded substantially less follow-up CT examinations (-22.0%), and additional diagnostic procedures (-7.7%) compared to the ACCP protocol. Moreover, the sensitivity of this volume protocol is as high as the ACCP protocol's sensitivity: 90.9%. Although this sensitivity is slightly lower than the sensitivity of the new protocol using diameter, the advantages of the very high specificity of the volume-based protocol outweighs the disadvantage of a slightly lower sensitivity. Therefore, the use of the new lung cancer probability-based protocol using nodule volume has the best performance of these three nodule management protocols.

Concluding, the current guideline for the management of CT-detected nodules may be optimised by adjusting the thresholds for nodule size and growth. Hence,
the threshold that is used to classify nodules as at very low risk of lung cancer should be raised from 4 mm to 5 mm. The threshold that is used to classify nodule as at substantial risk of lung cancer, requiring more invasive diagnostic procedures, should be raised from 8 mm to 10 mm. Furthermore, for intermediate-sized nodules, more invasive procedures should only be performed for nodule demonstrating growth with VDT of <600 days, instead of visual growth or VDT <400 days. A more efficient alternative for these diameter protocols is the new lung cancer probability-based protocol using nodule volume. In this protocol, no nodules and nodules <100 mm³ were classified as negative, nodules 100-300 mm³ as indeterminate (final result positive if VDT<600 days, otherwise negative), and nodules >300 mm³ were classified as positive. Prospective studies or micro-simulation studies using these new protocols are required to determine the effect on lung cancer mortality.

**Conclusion**

The size and growth of CT-detected nodules are valid predictors of the screened individual's two-year lung cancer probability. Subjects with nodules ≤100 mm³ or ≤5 mm have a lung cancer risk that is not significantly different from that in subjects without nodules and should not undergo additional CT examinations. Individuals with nodules 100-300 mm³ or 5-10 mm represent an indeterminate subgroup for whom the assessment of VDT is appropriate (<600 days warrants follow-up evaluation). The risk of subjects with nodules >300 mm³ or >10 mm demands immediate diagnostic evaluation. New management protocols for CT-detected nodules using these thresholds for nodule size and VDT were estimated to perform better than the current guideline.

**Research question VI**

**Chapter 7. Evaluation of bronchoscopy**

The role of conventional bronchoscopy in the work-up of suspicious CT screen-detected pulmonary nodules.

*Chest*

**Main research question**

What was the value of bronchoscopy for diagnosing lung cancer in screen-detected nodules?

**Sub research questions**

a) What were the test characteristics of bronchoscopy and its ancillary procedures?
b) What were predictors for a true-positive bronchoscopic procedure?

Main results

In a series of 415 participants with a positive screening result in the NELSON trial, 308 (74.2%) underwent a conventional white-light bronchoscopy as part of the diagnostic work-up. In these 308 persons, a total of 318 suspicious pulmonary nodules or masses were analysed by bronchoscopy with the objective to diagnose or exclude lung cancer. According to the gold standard, which was a histological confirmation on histological or cytological samples in 95.5%, 178 of the 318 (56.0%) suspicious lesions were malignant.

a) Cancer was diagnosed by bronchoscopy in only 24 of the 318 suspicious lesions. The overall sensitivity of bronchoscopy to detect cancer was 13.5% (24 of 178; 95% confidence interval (95% CI) 9.0-19.6%), and the negative predictive value was 47.6% (140 of 294, 95% CI 41.8-53.5%). As no false-positive diagnoses were made, the specificity and positive predictive value were both 100%. The sensitivity and negative predictive value of the ancillary procedure bronchial washing were respectively 9.3% (95% CI 5.7-14.8) and 45.9% (95% CI 40.2-51.7%), for bronchial brushing respectively 7.9% (95% CI 3.3-17.0%) and 41.2% (95% CI 32.4-50.6%). The sensitivity and negative predictive value for the ancillary procedures transbronchial needle aspiration (TBNA), transbronchial biopsy (TBB) and endobronchial biopsy (EBB) were respectively TBNA: 33.3% (95% CI 6.0-75.9%) and 0% (95% CI 0-6.0%); TBB: 16.7% (95% CI 0.9-63.5%) and 44.4% (95% CI 15.3-77.3%); EBB: 45.8% (95% CI 26.2-66.8%) and 55.2% (95% CI 36.0-73.0%).

b) Multivariate regression analyses were performed on the subset of 178 cases with cancer to identify predictors of a successful bronchoscopic procedure. Nodule size, defined as nodule diameter in mm, was a statistically significant positive predictor (odds ratio 1.07 (95% CI 1.02-1.13). Further, the visibility of the lesion during bronchoscopy was also a statistically significant positive predictor (87.61 (95% CI 4.90-564.88). The following characteristics were significantly associated with a successful bronchoscopic procedure: nodule volume doubling time, central versus peripheral localisation, upper lobe localisation versus lower or middle lobe localisation, screening round, scan type, presence or absence of bronchial compression.

c) In 24 of the 178 bronchoscopies of malignant lesions, the result of the bronchoscopy was positive. Hence, in 154 bronchoscopic evaluations the result was false-negative, which corresponds with a negative predictive value of 47.6%. The diagnoses made based on bronchoscopy in these false-negative procedures were: aspecific inflammation (27.3%), metaplasia (3.9%), fibrosis (1.3%), Aspergillus Fumigatus infection (0.6%), atypia (0.6%) and resolving haemorrhage (0.6%), in the remaining cases (65.6%) no abnormalities were detected.
Interpretation of results

a) The overall sensitivity and negative predictive value of bronchoscopy in subjects with suspicious CT-detected pulmonary nodules was respectively 13.5% and 47.6%. As no false-positive diagnoses of cancer were made by bronchoscopy, the sensitivity and positive predictive value were both 100%.

To date, there have been no other publications on the diagnostic performance of conventional white light bronchoscopy for diagnosing lung cancer in subjects with CT-detected nodules. This is probably because bronchoscopy is not routinely performed in other lung cancer screening trials.

In non-screening studies, the published sensitivity of bronchoscopy varied from 51% to 76%. Differences between these and the current study were: a smaller size of the lesions (2.8% >30 mm versus 48-72 mm) and a lower incidence of endobronchial abnormalities (7.3% versus 8-64%). The lower sensitivity in the current study can be explained by these differences as both nodule size and endobronchial visibility are independent predictors for a successful bronchoscopy procedure.

According to the guidelines that were available at the time this study was conducted, conventional white light bronchoscopy was only recommended for suspicious lesions with an air bronchogram on CT. According to the currently available guideline, conventional white light bronchoscopy is not recommended anymore. Only more advanced techniques such as radial endobronchial ultrasound, electromagnetic navigational bronchoscopy and virtual bronchoscopy navigation techniques are recommended for individuals who are poor candidates for transthoracic biopsy in case the lesion is located in proximity to a patent bronchus.

Concluding, this study demonstrates that the routine use of conventional bronchoscopy in the diagnostic work-up of CT-detected pulmonary nodules is not justified. It is highly unlikely that the yield outweighs the harms (distress and risk of complications) and costs (health care facilities, personnel and resources) associated with routine use of bronchoscopy. However, to determine this cost-effectiveness analyses including all these aspects should be performed. The use of conventional white light bronchoscopy in selected cases (larger nodules located in proximity to a patent bronchus) will result in better test characteristics, which will yield a higher cost-effectiveness. Nonetheless, this can also not be recommended as conventional white light bronchoscopy has become an outdated technique for diagnosis lung cancer in suspicious CT-detected nodules.

b) The size and visibility of the suspicious lesions were statistically significant predictors of a true-positive result of the bronchoscopic procedure. It was estimated that for every millimetre increase in nodule diameter, the probability of a true-positive procedure will increase with 7%. Further, lesions which were visible during bron-
choscopy had a significantly higher probability of a successful procedure compare to lesions not visible during bronchoscopy.

Concluding, size and visibility of suspicious CT-detected lesions are predictive of a true-positive bronchoscopic procedure.

c) A variety of diagnoses is made in false-negative bronchoscopic procedures. Instead of lung cancer, Aspergillus infection, aspecific inflammation, atypia, metaplasia, fibrosis and resolving haemorrhage are found in the histological or cytological samples obtained by bronchoscopy. Some of these findings, as infections or fibrosis, may also present as an approximately spherical opacity on CT. This demonstrates that lung cancer can be missed by bronchoscopy in the presence of benign abnormalities that could also explain the suspicious lesion opacity on CT. Such a situation bares the risk of a missed or delayed lung cancer diagnosis. This information, combined with the estimated negative predictive value of 47.6%, proofs that bronchoscopy is not an appropriate technique to exclude a diagnosis of lung cancer in subjects referred for screen-detected nodules.

Concluding, deceitful benign diagnoses can be made by bronchoscopy in persons wherein the suspicious lesion is actually lung cancer. Therefore, the use of bronchoscopy to exclude a diagnosis of lung cancer is not recommended in a lung cancer screening program.

Conclusion
The performance of white light bronchoscopy is not sufficient to justify routine use in subjects with suspicious pulmonary nodules detected in a lung cancer screening programme.

Research question VII

Chapter 8. Evaluation of surgical procedures

Complications following lung surgery in the Dutch-Belgian randomized lung cancer screening trial.

*European Journal of Cardio-Thoracic Surgery*

Main research question
To what extent did adverse events related to thoracic surgery, occur in participants after a positive screening test results?
Sub research questions

a) How often occurred re-thoracotomy, complications, and post-operative mortality in participants who underwent thoracic surgery for a positive screening test result?

b) What was the length of hospital stay for lung resection performed by thoracotomy and video-assisted thoracoscopic surgery?

c) To what extent were surgical procedures performed for benign nodules?

Main results

In a series of 415 participants with a positive screening result in the NELSON trial, 215 (51.8%) underwent a surgical procedure. Seventeen of these 215 participants (7.9%) only underwent a mediastinoscopy. The remaining 198 participants underwent lung surgery; in 44 (22.2%) lung surgery was preceded by a mediastinoscopy. The majority (n = 182; 91.9%) of the lung surgeries were resections performed via a thoracotomy. 5.6% (n = 11) of the procedures were wedge resections performed via a video-assisted thoracoscopic (VATS) procedure. The remaining 2.5% (n = 5) of the procedures were initiated as VATS procedures, but were converted to a thoracotomy. Summarising, in 198 subjects 187 thoracotomies and 16 VATS procedures were performed.

a) 47% (n = 88) of the thoracotomies were complicated by at least one non-life threatening condition and 10% (n = 18) was complicated by at least one life threatening condition. In 38% (n = 6) of the VATS procedures at least one non-life threatening complication occurred, but no life threatening complications have been observed. As 5% had both minor and major complications, the proportion of participants with any complication was 53%. The complications caused by thoracotomy necessitated a re-thoracotomy in 3% and re-admission to the hospital after discharge in 5%. After VATS procedures, no re-thoracotomies or re-admissions occurred. There was no mortality within the first 30 days after thoracotomy or VATS in the NELSON trial.

b) The median length of hospital stay after thoracotomy was 13 days (range 2 to 51 days). After a VATS procedure the median length of hospital stay was 8 days (range 4 to 12 days). In subjects with non-life threatening complications, the length of hospital stay after thoracotomy was a median 15 days, ranging from 6 to 51 days and after VATS 9 days (range 7 to 12 days). In the case of life threatening complications following thoracotomy, the median length of hospital stay was 21 days, ranging from 8 to 51 days.

c) The resection specimens obtained by the 198 surgical procedures yielded the diagnosis of lung cancer in 151 (76.3%) cases. Hence, in the remaining 47 cases (23.7%) benign abnormalities were resected. Twenty of the 47 subjects (42.6%) who underwent surgery for benign disease experienced non-life threatening complications and three of the 47 subjects (6.4%) had life threatening complications.
Interpretation of results

a) In this study, the incidence of re-thoracotomy, complications, and mortality after lung surgery in the NELSON lung cancer screening trial was assessed. A few other lung cancer screening trials published their adverse events. One or more complications after surgery occurred in the NELSON trial in 53% of the participants, which is higher than in all other screening trials: 45.0% of the participants of the U.S. National Lung Screening Trial (NLST)\textsuperscript{13}; 33.9% of the participants of the Italian DANTE trial\textsuperscript{51}; 25% of the participants of the Italian COSMOS lung cancer screening cohort study\textsuperscript{52}; and 0% of the participants of the Danish lung cancer screening trial.\textsuperscript{9} However, in the incidence of major complications, 10% in the NELSON trial, was within the range of the other screening trials: 15.3% in the DANTE trial\textsuperscript{51}; 11.9% in the NLST\textsuperscript{13}; 6% in the COSMOS trial\textsuperscript{52}; and 0% in the Danish trial.\textsuperscript{9} Post-operative mortality was 0% in the NELSON trial, which is comparable to the NLST (0.01% within 60 days)\textsuperscript{13}, the Danish trial (0%)\textsuperscript{9} and the COSMOS trial (0%)\textsuperscript{52}, only in the DANTE trial a higher mortality rate (5.1%) was published.\textsuperscript{51}

The incidence of non-life threatening complications after thoracotomy in NELSON (47%) was also high in the range of the incidences of published non-screening series (7% to 57%).\textsuperscript{51,53-68} However, the incidence of life threatening complications after thoracotomy in the NELSON trial (10%) was low in the range (4% to 26%) of non-screening studies.\textsuperscript{51,53-68} The incidence of non-life threatening complications after VATS procedures was 38% in the NELSON trial, which is high compared to the range in the literature (9% to 51%).\textsuperscript{69,70} No life threatening complications have been observed after VATS in the NELSON trial, which is at the lower range of the reported incidence in the literature (0% to 12%).\textsuperscript{51,70,71} In the NELSON trial, complications after thoracotomy necessitated a re-thoracotomy in 3%. The reported re-thoracotomy rates after a thoracotomy varied from 0 to 9%.\textsuperscript{59,72} No re-thoracotomies after VATS were performed in the NELSON trial, while the reported re-operation rate after VATS varied between 1 and 5%.\textsuperscript{62,72} Finally, no post-operative mortality after respectively thoracotomy and VATS were observed in the NELSON trial, compared to mortality rates of respectively 0-8%\textsuperscript{51,53-64,68,72-82} and 0-4%\textsuperscript{58,83} after thoracotomy and VATS in other studies.

The aforementioned comparisons with other screening studies and clinical series can be made as this study also demonstrated that the age range and co-morbidity level were comparable.\textsuperscript{84} Nonetheless, the studies were quite heterogenic with respect to the definition, classification and methods of data collection on complications. Not in all studies, a distinction was made between life threatening and non-life threatening complications. Moreover, some studies collected the data by reviewing individual patient charts, and others based on ICD-9 codes or on claims in Medicare files. The latter two methods result in an underestimation of complica-
tions, especially for minor complications. Probably because all individual patient files were carefully evaluated in the current study, the minor complication rate was relatively high. As reporting major complications and mortality occurs more accurate than reporting minor complications, the comparisons concerning major complications and post-operative mortality between this study and the literature is more reliable. Hence, both the incidence of major complications and post-operative mortality were relatively low compared to clinical series, and comparable to other screening trials. This could probably be explained by the fact that screen-detected cancers, in general, are diagnosed earlier than symptom-detected lung cancers, and as a result the required resection of screen-detected lung cancer are more often less extensive.\textsuperscript{13,19,85} This is supported by the observation that pneumonectomies were rarely performed in the NELSON trial, while more complex resections with higher expected complication rates were performed in the published clinical studies.

Concluding, post-operative minor complications (47\%) were more frequent in the NELSON than reported in the literature. The incidence of major complications (10\%), re-thoracotomy (3\%) and post-operative mortality (0\%) were at the lower range of the reported incidences in other studies. This suggests that lung surgery for lung cancer detected by low-dose computed tomography is at least as safe as lung surgery for clinically detected lung cancer. Although the design of the current study does not allow drawing conclusions on comparisons between thoracotomy and VATS; the incidence of complications, re-operations and post-operative mortality were lower after VATS procedures. As this was also observed in other published studies, VATS may be a safer method for lung resections for screen-detected lung cancers, and should probably be the preferred method for those cases wherein both VATS and thoracotomy are appropriate.

b) The median length of hospital stay in after thoracotomy in the NELSON trial (13 days) was in the middle of the range reported in the literature (5 to 22 days).\textsuperscript{72,80} In subjects with non-life threatening complications, the length of hospital stay after thoracotomy was a slightly longer (median 15 days), and in the case of life threatening complications substantially longer (median 21 days). After a VATS procedure, the median length of hospital stay in the NELSON trial was 8 days, which is in the lower range of lengths of stay reported in the literature 4 to 23 days.\textsuperscript{57,72} In subjects with non-life threatening complications, the length of hospital stay after VATS was slightly longer (median 9 days).

Concluding, the length of hospital stay (median 13 days after thoracotomy and 8 days after VATS) in the NELSON trial was comparable to the literature. Although the design of the current study does not allow drawing conclusions on comparisons between thoracotomy and VATS; the length of hospital stay was lower after VATS procedures, both in this study and in other published studies. Therefore, VATS may
be considered as the preferred method for lung resections for screen-detected lung cancers, for those cases wherein both methods are appropriate.

c) The 198 surgical procedures included in this study yielded the diagnosis of lung cancer in 151 (76.3%) cases. Hence, in the remaining 47 cases (23.7%) benign abnormalities were resected. Most other lung cancer screening trials reported on the percentage of surgeries for benign disease and the incidence in NELSON is at the higher range: NLST 32.2% surgeries in the absence of lung cancer,13 in the DANTE trial 22% of the resected nodules was benign,51 in the Danish trial this was 18.2%,9 in the Italian MILD trial 9%86 and in the ITALUNG trial only 5.5%.87 The high percentage of surgeries of benign nodules in the NLST may be partly due to the vast proportion of the participants (39.1%) who received one or more positive screening result,13 due to the low specificity (73.4-83.9%) of the NLST screening algorithm.7,14 In the NELSON trial however, the specificity of the screening algorithm is much higher (98.6%)23 and the proportion of subjects with a positive screening result much lower (6.0%).88 This suggests that the relatively high number of surgeries for benign nodules are not caused by the screening algorithm, but by decisions made during the diagnostic work-up for positive screening results. One aspect that might play a role is the fact that the diagnostic work-up in the NELSON trial usually only consisted of imaging and bronchoscopy. As a result, proof of the suspicion of lung cancer by biopsy was rarely obtained before surgery. The lower numbers of surgeries for benign nodules in the other screening trials suggests that they applied a more cautious approach towards suspicious CT-detected nodules. Since these studies did not publish on the counter side of this approach (number of additional diagnostic tests, months of follow-up and cancerous nodules unjustly not resected), it is not possible to determine whether their approach is recommendable. Nonetheless, efforts should be made to investigate whether it is possible to safely reduce the number of surgeries for benign nodules.

Another reason for this is the occurrence of complications in this group. Hence, 20 of the 47 subjects (42.6%) who underwent surgery for benign disease, non-life threatening complications occurred and in three of the 47 subjects (6.4%) life threatening complications occurred. In other lung cancer screening trials that published on such adverse events, the incidence of complications was lower: NLST 20.5% (from which 2.4% was minor, 7.9% was intermediate and 5.5% were major complications),13 DANTE trial 0%51 and COSMOS trial 0%.52 Post-operative mortality did not occur after surgery for benign nodules in the NELSON trial, DANTE trial,51 COSMOS trial,52 and was rare in the NLST 1.2%.13

Concluding, 23.7% of the lung surgeries in the NELSON trial were performed for benign nodules. This percentage, as well as the incidence of complications (42.6%) is
relatively high compared to other screening trials. Future studies should investigate how to safely reduce the number of surgeries for benign nodules.

**Conclusion**

This study demonstrated that adverse events after thoracic surgery for positive screening test results were common. The incidence of minor complications was relatively high, while in the incidence of major complications, re-operations and post-operative mortality was relatively low. Finally, a relatively high percentage of the surgeries was performed for benign nodules.

**Research question VIII**

**Chapter 9. Endpoint determination**

Uniform and blinded cause of death verification in a lung cancer CT screening trial.

*Lung Cancer*

**Main research question**

How should the endpoint verification process of the NELSON trial be designed to ensure uniform, objective and unbiased endpoint determination?

**Sub research questions**

a) How to develop a cause of death review protocol that ensures uniform, objective and unbiased endpoint determination?

b) How was the performance of the developed cause of death protocol compared to the official death certificates?

c) What were sources of disagreement between users of the developed cause of death protocol?

d) What were the best sources of information for a review of the cause of death of a participant?

**Main results**

a) The primary endpoint of the NELSON trial is lung cancer-specific mortality. Information on the cause of death of the NELSON participants can be obtained from the death certificates, which are available from Statistics Netherlands and the Flemish Agency for Care and Health. Therefore, the first step in the design the endpoint verification process of the NELSON trial, was to perform a literature study on the
reliability of the use of official death certificates for endpoint verification in screening trials.

This initial study learned that the use of death certificates for this purpose is debated for several reasons: sticky-diagnosis bias and slippery linkage bias,\textsuperscript{100} inaccurate form completion and errors in encoding,\textsuperscript{101} and incorrect ante mortem diagnoses.\textsuperscript{102} Further, the sensitivity and specificity of the official death certificates for (lung) cancer death have been reported to range respectively from 84.5\% to 99.7\% and from 91.3\% to 99.7\%.\textsuperscript{103-106} Moreover, the errors introduced by all these aforementioned inaccuracies are biased towards a reduction in the efficacy of screening.\textsuperscript{103-106}

To overcome these problems clinical expert committees, reviewing the medical files of the deceased participants to determine the cause of death, are frequently employed in cancer screening trials.\textsuperscript{103-108} The additional value of such a clinical expert committee depends on its independence from the screening trial and the quality and uniformity of the review process. Therefore, predetermined criteria and flowcharts are often used for the evaluation of the medical files, which should be blinded for the participants’ identity and study group.

The next part of this study was to define the principles of the cause of death review process that will be used in the NELSON trial. Firstly, the definition of the primary cause of death to be used was adopted from the definition of the World Health Organisation. Next, a classification system that defines the graduation of certainty that lung cancer was the primary cause of death was adopted from the European Randomised Study of Screening for Prostate Cancer.\textsuperscript{104}

Secondly, the target population of the end point verification process was defined to be all participants of the NELSON trial that have ever been diagnosed with lung cancer. The lung cancer cases will be identified by linkages with the national cancer registries of the Netherlands and Belgium and by checking all official death certificates for the diagnosis lung cancer, which are obtained from Statistics Netherlands and the Flemish Agency for Care and Health. For all identified cases, the diagnosis of lung cancer will be verified in a separate verification process.

Thirdly, the data required for the endpoint verification process was defined to be the complete medical file from the first consultation or diagnostic test for (suspected) lung cancer, until death, including autopsy report if available.

Fourthly, the requirements for the clinical expert committee were defined to be: three independent experts; a pulmonologist–oncologist, a pathologist specialised in lung oncology and a clinical epidemiologist, who have never been employees of the NELSON trial.

Finally, the tools that the expert committee should use to classify the cause of death were designed; a flowchart and detailed list of criteria which classify the cause
of the death into one of the six categories defining the graduation of certainty that lung cancer was the primary cause of death.

b) To determine the performance of the aforementioned newly developed endpoint verification process compared to the official death certificates, a pilot study of fifty cases was conducted. When classifying the outcome of the cause of death review process as golden standard, the sensitivity and specificity of the death certificates were respectively 95.2% (95% confidence interval: 84.2-98.7%) and 62.5% (95% confidence interval: 30.6–86.3%). Disagreement was observed in 10% (5 of 50 individuals) with the following causes of death: adult respiratory distress syndrome after lobectomy, rupture of an abdominal aneurysm during chemotherapy, another malignancy besides lung cancer in two cases (breast carcinoma and acute myeloid leukaemia) and small cell lung carcinoma diagnosed after the person’s death by autopsy.

c) The agreement between the uses of the newly developed endpoint verification process was also investigated in the pilot study. Hence, in 76% of the cases the reviewers reached a concordant conclusion. In the remaining cases, the sources of disagreement were: significant comorbidity, multiple coinciding malignancies, death after an intervention and death indirectly caused by lung cancer, such as death due to post-obstruction pneumonia or paraneoplastic pulmonary embolism. When clustering all ‘definitely’ and ‘probable’ lung cancer deaths into one group and all ‘possible’, ‘unlikely’ and ‘definitely not’ lung cancer deaths and ‘intercurrent deaths’ into another, the differences were minimal; agreement in 90% (kappa of 0.65).

d) Finally, the pilot study learned that the letters of the pulmonologist were the best source of information for the review of the cause of death in 65% of the cases.

**Interpretation of results**

a) Endpoint verification of a cancer screening trial should not solely be based on the official death certificate because of biases, inaccuracies in diagnosing, filling in forms and encoding, and suboptimal sensitivity and specificity for cancer-specific primary cause of death. Instead, endpoint verification should be based on a cause of death verification process that provides a validated method and tools used by a committee of independent experts. The following aspects should be defined in the protocol:

I) the definition of the primary cause of death
II) a classification system that defines the grade of certainty that the primary endpoint was the primary cause of death
III) the target population and methods to identify them within the study population
IV) the data required for the cause of death review process
V) requirements for the clinical expert committee
VI) tools to be used by the clinical expert committee
VII) method to evaluate or compare the cause of death verification process to the official death certificates

Concluding, a cause of death review protocol that ensures uniform, objective and unbiased endpoint determination should employ a committee of independent experts that use a protocol that defines the aforementioned criteria.

b) The sensitivity and specificity of the official death certificates for lung cancer specific mortality were 95.2% and 62.5%, respectively. Despite the lack of a ‘gold standard’ for the cause of death of lung cancer participants, this still demonstrates the limitations of the official cause of death certification in lung cancer patients for scientific purposes.

Concluding, the official death certificates probably have insufficient distinctive character for lung cancer-specific death for determining the primary endpoint of a cancer screening trial.

c) The agreement between the two users of the cause of death verification protocol was reasonable. Cases that resulted in disagreement between the two users in the pilot study had: significant comorbidity, multiple coinciding malignancies, intervention-related death or death indirectly caused by lung cancer. Cases with significant comorbidity or coinciding malignancies are well-known sources of disagreement,\(^{103,109}\) and will probably often be discussed in the expert committee to reach consensus. The other sources of disagreement between these two users indicate a lack of knowledge on complications from lung cancer treatments (such as surgery and chemotherapy) and indirect causes of lung cancer death (such as post-obstruction pneumonia and paraneoplastic syndromes). This illustrates the necessity of the employment of experts in the committee.

Further, the pilot study learned that the voluntary use of a flowchart and pre-specified criteria as an aid in the decision-making process will not always result in the use of these tools. Therefore, it is recommended to make the use of the flowchart obligatory in the decision-making process. In the NELSON trial, this will be accomplished by applying an electronic questionnaire with mandatory questions which are directly derived from the flowchart. Once the cause of death is classified using this electronic questionnaire, the expert has the opportunity to indicate whether he agrees or disagrees with the conclusion and whether he wants to discuss the case with the other experts or not.

Concluding, when the developed cause of death protocol is used by a clinical expert committee the patients with significant comorbidity and multiple coinciding malignancies will probably yield disagreement. In such cases, meetings of the
experts should be conducted to facilitate the discussion of these cases and to reach consensus.

d) The item that was regarded as the best source of information for the cause of death review in the medical file was the letters of the pulmonologist. In the Netherlands and Belgium, the pulmonologist is the main caretaker of lung cancer patients. Therefore, the pulmonologist regularly writes letters to the other involved caretakers and the general practitioner of the patient, to inform them on the clinical findings, results from diagnostic procedures and recommendations from multidisciplinary meetings. Moreover, about half of the lung cancer patients die at the hospital, which is usually at the pulmonology department, which will result in an accurate documentation of the death of death of the patient in the letter of the pulmonologist. As autopsies are not commonly performed in the Netherlands and Belgium, this valuable report will rarely be available for the cause of death review process.

Concluding, the best source of information for the cause of death review process of a lung cancer screening trial are, in the Netherlands and Belgium, the letters of the pulmonologist.

**Conclusion**

To ensure uniform, objective and unbiased endpoint determination in the NELSON trial an independent committee of experts should perform a cause of death verification process. For this process, the medical files of all deceased study participants diagnosed with lung cancer should be blinded for the participant's identity and study group. These files should be reviewed using a flowchart and detailed criteria to determine the grade of certainty that lung cancer was the primary cause of death.
GENERAL CONCLUSIONS FROM THIS THESIS

I) The screening algorithm of the NELSON trial adequately stratified participants according to their lung cancer risk.

II) The screening algorithm of the NELSON trial yielded a relatively low number of diagnostic work-ups for positive screening test results.

III) The screening algorithm of the NELSON trial yielded a relatively limited number of follow-up LCDT scans for indeterminate screening test results.

IV) The positive predictive value of screening test results in the NELSON trial compared favourably to other studies, nonetheless false-positive screening test results are one of the most common harms of the NELSON screening algorithm.

V) The negative predictive value of screening test results was very high in the NELSON trial, as in other lung cancer screening studies.

VI) The sensitivity in the NELSON trial was slightly lower than in other studies, but the lung cancers in the screening group were diagnosed as early as in other studies.

VII) The specificity in the NELSON trial was substantially higher than in other studies, which is a prerequisite for cost-effectiveness.

VIII) The majority of the lung cancers not detected by low-dose CT screening were not preventable: some lung cancers were not missed but arose during the screening interval, and other lung cancers were missed due to causes that can never completely be eliminated, such as human error and non-compliance by participants. Preventable causes of detection failures were radiological detection and interpretation errors.

IX) The performance of the screening strategy may be improved by reducing the number of detection and interpretation errors by increasing the radiologist's attention for endobronchial lesions, bulla wall thickenings, and pleural-attached lesions.

X) The performance of the NELSON screening strategy may be improved by an effective smoking cessation program, as current smokers are at increased risk of being diagnosed with a lung cancer not detectable by screening.

XI) The performance of the NELSON screening strategy may be improved by using a nodule management protocols with thresholds for nodule size and growth based on the lung cancer probability of the screened individuals.

XII) The use of nodule volume in lung cancer probability-based nodule management protocols yields higher efficiency and less harm than the use of nodule diameter.

XIII) In the NELSON lung cancer screening trial, a relatively high number of invasive diagnostic procedures for benign nodules were performed.

XIV) The performance of white light bronchoscopy is not sufficient to justify routine use in subjects with suspicious pulmonary nodules detected in a lung cancer screening programme.
XV) In the NELSON lung cancer screening trial, minor complications after surgical procedures was common, while major complications, re-operations and post-operative mortality were relatively uncommon.

XVI) In the NELSON lung cancer screening trial, a relatively high percentage of the surgical procedures was performed for benign nodules.

XVII) Screening for lung cancer using low-dose computed tomography probably leads to a stage shift towards earlier diagnosis; this effect is stronger in women than in men.

XVIII) The screening strategy of the NELSON trial was capable of detecting lung cancer as early as in another screening trial that demonstrated a significant lung cancer mortality reduction.

XIX) Screening for lung cancer using low-dose computed tomography probably leads to a shift in histology towards detecting slower growing and more peripherally localised subtypes of lung cancer.

XX) The lung cancers not detected by screening had a different histopathology, with a higher growth rate and metastatic potential, than the lung cancers that were detected by screening.

XXI) The endpoint determination of lung cancer screening trials should encounter the grade of certainty that lung cancer was the primary cause of death of the participants.

XXII) The endpoint determination of lung cancer screening trials should be performed by an independent committee of experts who review the blinded medical file of all deceased study participants diagnosed with lung cancer by using a flowchart and detailed criteria.

GENERAL RECOMMENDATIONS BASED ON THIS THESIS

I) Future studies should investigate whether the harms induced by false-positive screening results can be reduced by: optimising the nodule management protocol and the use of additional determinants to determine the screening test result, such as participant characteristics, radiological and other biomarkers.

II) An effective smoking cessation program should be co-implemented with CT screening, as current smokers have demonstrated to be at increased risk of being diagnosed with a lung cancer not detectable by screening.

III) Methods to increase radiologist’s attention for endobronchial lesions, bulla wall thickenings, and pleural-attached lesions should be developed, as this may help reducing the number of missed lung cancers.

IV) Lung cancer screening programs should use a nodule management protocol with thresholds for nodule size and growth based on lung cancer probability.
V) Individuals without pulmonary nodules at CT screening may undergo their next screening after a screening interval of two years.

VI) Subjects with pulmonary nodules measuring ≤100 mm$^3$ or ≤5 mm should not undergo serial follow-up CT examinations, but regular CT screening with annual or biannual intervals.

VII) In subjects with pulmonary nodules measuring 100-300 mm$^3$ or 5-10 mm the assessment of nodule volume-doubling time by follow-up CT at short notice is appropriate; volume doubling times <600 days warrant diagnostic evaluation.

VIII) Subjects with pulmonary nodules measuring >300 mm$^3$ or >10 mm should undergo immediate diagnostic evaluation to diagnose or exclude lung cancer.

IX) Lung cancer screening programs should use nodule volume for estimating nodule size and growth since it yields higher screening efficiency and less harms than the use of nodule diameter.

X) Future studies should assess the causes of the high rate of invasive procedures for benign nodules in the NELSON trial, and targeted interventions should be developed, evaluated and implemented.

XI) The lung cancer prediction model using nodule size and growth rate should be extended with individual characteristics to investigate whether lung cancer prediction can be improved. A validated and reliable lung cancer prediction tool may help identifying malignant nodules and may reduce unnecessary diagnostic procedures for benign nodules.

XII) Conventional white light bronchoscopy should not routinely be used in subjects with suspicious CT-detected pulmonary nodules, as the diagnostic yield is insufficient to outweigh harms and costs.

XIII) Lung cancer screening should be performed in hospitals offering minimal invasive thoracic surgery, to limit complications and post-operative mortality both in individuals undergoing surgery for lung cancer and for individuals undergoing surgery for benign nodules.

XIV) Future studies should compare all lung cancers diagnosed in the screening group with all lung cancers diagnosed in the control group to determine whether LDCT screening led to a shift in stage or histopathology.

XV) Analysis of the difference in lung cancer mortality between the screening group and the control group of the NELSON trial will determine whether the observed favourable stage distribution of the lung cancers in the screening group yielded a significant lung cancer mortality reduction.

XVI) A post hoc analysis of the effectiveness of LDCT screening stratified by gender should be performed, as women with screen-detected lung cancer have demonstrated to be diagnosed at more favourable cancer stages than men.
XVII) Endpoint determination in lung cancer screening trials should encounter the determination of the grade of certainty that lung cancer was the primary cause of death of the study participants.

XVIII) Endpoint determination in lung cancer screening trials should be performed by an independent committee of experts who perform a blinded review of the medical file, of all deceased study participants with lung cancer by using a flowchart and detailed criteria.
REFERENCES


Chapter 12

Summary
Part I: Introduction
Lung cancer is a major public health problem since it causes most cancer-related deaths worldwide. As the disease often causes no symptoms at early stages, diagnosis at advanced stages, wherein cure is no longer possible, is common. Improvements in lung cancer treatment have been made, but yielded only modest improvement in survival over the last decades. Continuous efforts should be made to force back exposure to causative agents of lung cancer, tobacco smoking in particular. However, this is not expected to reverse the lung cancer epidemic in the next decades. Lung cancer screening can reduce morbidity and mortality from lung cancer by detecting the disease at an early and curable stage. As this early stage is often not accompanied by any signs or symptoms, screening has to be applied to apparently healthy, asymptomatic persons. Unfortunately, screening exposes these persons to several harms: some related to the screening test itself, such as exposure to ionising radiation, others related to false-positive, false-negative screening test results, or overdiagnosis. Therefore, only lung cancer screening programs wherein benefits outweigh harms should be implemented. This thesis aimed to identify opportunities to improve the balance between benefits and harms of a screening program.

Part II: Evaluation of findings
In Chapter 2, data on screening test results and screen-detected lung cancer were used to determine positive predictive value and 5.5-year lung cancer probability. This study demonstrated that the screening algorithm of the NELSON trial adequately stratified participants according to their lung cancer risk. Further, the screening algorithm yielded a limited number of follow-up low-dose computed tomography (LDCT) and additional diagnostic procedures for positive screening test results. Although the predictive value of screening test results in the NELSON trial compared favourably to other studies, too many invasive diagnostic procedures were performed for false-positive screening test results.

In Chapter 3, the tumour characteristics of the lung cancers detected by screening were analysed. Analyses showed that screening yielded a stage shift towards earlier diagnosis, more in women than in men; and a shift in histology towards slower growing and more peripherally localised subtypes of lung cancer.

In Chapter 4, the performance of the screening algorithm of the NELSON trial was estimated, and opportunities to improve its performance were identified. Detection rates and sensitivity of the NELSON screening protocol appeared to be sufficient for diagnosing lung cancer as early as in a lung cancer trial that reduced lung cancer mortality significantly. Moreover, the NELSON screening protocol yielded a very high specificity, which is a prerequisite for cost-effectiveness. Nonetheless, performance of the screening protocol may be improved by co-implementation of CT screening with an effective
smoking cessation program, and training of screening radiologists to reduce the number of detection and interpretation errors.

In Chapter 5, radiological causes of the failure to detect lung cancers by screening were investigated, and opportunities to improve performance of the screening algorithm were identified. This evaluation learned that the majority of the lung cancers not detected by low-dose CT screening were not preventable. Performance of the screening strategy may be improved by reducing the number of detection and interpretation errors, which may be achieved by increasing the radiologist’s attention for endobronchial lesions, bulla wall thickenings, and pleural-attached lesions.

Part III: Optimisation of screening

In Chapter 6, lung cancer probability of participants was estimated and used to design and evaluated nodule management protocols. The current guideline on the management of nodules classifies nodules <4 mm as not suspicious for lung cancer; nodules of 4 to 8 mm as indeterminate (for which growth assessment is required: nodules with a volume doubling-time <400 days are subsequently classified as suspicious for lung cancer); and nodules ≥8 mm as suspicious for lung cancer. Analyses showed that the guideline performed well, but also that improvements were possible. Raising nodule size diameter threshold from 4 mm to 5 mm and from 8 mm to 10 mm, and nodule volume doubling-time threshold from 400 days to 600 days was estimated to yield both a higher sensitivity and a higher specificity. Further, a nodule management protocol using nodule volume thresholds of 100 mm$^3$ and 300 mm$^3$, and a nodule volume doubling-time threshold of 600 days was evaluated. This protocol was estimated to yield the same sensitivity as the current guideline, but a substantially higher specificity. Results of this study imply that use of volumetry and lung cancer probability-based thresholds for nodule size and growth can improve lung cancer detection and reduce unnecessary follow-up CT examinations and invasive diagnostic procedures.

In Chapter 7, the value of white light bronchoscopy in the diagnostic work-up of suspicious CT-detected nodules was determined. This study demonstrated that bronchoscopy could not diagnose lung cancer effectively due to insufficient sensitivity, and could not exclude lung cancer reliably due to deceitful benign diagnoses. Therefore, routine use of bronchoscopy in subjects with suspicious pulmonary nodules detected in a lung cancer screening programme is not recommended.

In Chapter 8, adverse events related to thoracic surgery, performed in the diagnostic work-up of suspicious CT-detected nodules were assessed. This study demonstrated that adverse events after thoracic surgery for positive screening test results were common. Incidence of minor complications was relatively high, while incidence of major complications, re-operations and post-operative mortality was relatively low. Finally, a relatively high percentage of surgeries were performed for benign nodules.
Part IV: Evaluation of effectiveness

In Chapter 9, design and evaluation of the endpoint verification process of the NELSON trial was presented. This study demonstrated that an independent committee of experts should perform a cause of death verification process to ensure uniform, objective and unbiased endpoint determination. For this process, medical files of all deceased study participants diagnosed with lung cancer should be blinded for participant identity and study group. Subsequently, these files should be reviewed using a flowchart and criteria to determine grade of certainty that lung cancer was the primary cause of death. A pilot study demonstrated that this method is preferred over use of official death certificates, which have insufficient distinctive character for lung cancer-specific death.

Part V: Implications for implementation

In Chapter 10, currently available literature on all relevant aspects of LDCT screening for lung cancer was reviewed to determine whether benefits of LDCT screening outweigh its harms. Next, it was determined whether LDCT screening meets the World Health Organisation criteria for screening. This review learned that initial estimates of several harms and benefits of screening have been made, but substantial gaps in knowledge remain. Currently available evidence suggests that benefits of LDCT screening outweigh its harms.

In Chapter 11, the ‘General Discussion’ results of this thesis were summarised and discussed. The screening algorithm of the NELSON trial yielded a favourable balance between negative, indeterminate and positive screening test results, which led to a limited number of follow-up LDCT scans and diagnostic work-ups. The screening algorithm had a high sensitivity, which is promising for mortality analysis which is planned at ten years of follow-up. The screening algorithm of the NELSON trial also yielded a very high specificity, which is promising for the planned cost-effectiveness analysis. Lung cancers detected through screening were diagnosed at early stages. Moreover, the cancer stage distribution of lung cancers detected and missed by screening combined was also favourable. The majority of lung cancers missed by screening were not preventable. Nonetheless, performance of the screening algorithm may be improved by reducing detection and interpretation errors, which may be achieved by increasing the radiologist’s attention for endobronchial lesions, bulla wall thickenings, and pleural-attached lesions. Further, performance of the screening algorithm may be improved by slight adjustments of the thresholds for nodule size and growth rate that determine the screening test result. Additionally, co-implementation of CT screening with an effective smoking cessation program will also contribute to improved performance of the screening algorithm. Harms and costs of the screening algorithm can safely be reduced by eliminating routine use of bronchoscopy for suspicious screen-detected nodules from diagnostic work-up. Harms induced by adverse events after thoracic surgery both for lung cancer and for benign...
nODULES MAY BE REDUCED BY ROUTINE USE OF VIDEO-ASSISTED THORACOSCOPIC SURGERY. FINALLY, EFFECTIVENESS OF THE SCREENING ALGORITHM OF THE NELSON TRIAL WILL BE DETERMINED USING THE ENDPOINT DETERMINATION PROCEDURE PRESENTED IN THIS THESIS.
Chapter 13

Samenvatting
Deel I: Introductie

Longkanker is een groot maatschappelijk gezondheidsprobleem doordat het wereldwijd één van de meest voorkomende vormen van kanker is en de meeste kanker-gerateerde sterfgevallen veroorzaakt. Longkanker veroorzaakt vaak pas in een gevorderd stadium klachten, dit geeft een vertraging in het tijdstip waarop de diagnose wordt gesteld en meestal is dan geen genezing meer mogelijk is. Hoewel de behandeling van longkanker in de afgelopen decennia is verbeterd, heeft dit slechts geresulteerd in een minimale verbetering in de overleving van longkankerpatiënten. Het blijft noodzakelijk om het gebruik van en de blootstelling aan stoffen die longkanker veroorzaken te blijven teruggrijpen, dit geldt in het bijzonder voor tabaksrook. Toch is het de verwachting dat preventieve maatregelen op zichzelf niet afdoende zullen zijn om de longkankerepidemie in de komende decennia terug te dringen. Screening op longkanker kan de gezondheidsschade en sterfte veroorzaakt door longkanker verminderen door de ziekte in een vroeg en behandelbaar ziektestadium op te sporen. Aangezien het vroege stadium van longkanker vaak geen klachten veroorzaakt, vindt de screening plaats op schijnbaar gezonde personen. Deze personen, van wie slechts een deel een vroeg stadium van longkanker onder de leden heeft, lopen door de screening echter ook risico’s. De risico’s van screening zijn onder andere gerelateerd aan de screening test zelf, zoals blootstelling aan ioniserende straling. Daarnaast is er een kans op een fout-positieve of een fout-negatieve screeningresultaat en de kans op overdiagnose. Vanwege deze schadelijke neveneffecten screening is het wenselijk om alleen longkankerscreeningsprogramma’s in te voeren waarvan de voordelen opwegen tegen de nadelen. Het doel van dit promotieonderzoek was mogelijkheden identificeren die de balans tussen de voordelen en nadelen van een longkankerscreeningsprogramma kunnen verbeteren.

Deel II: Evaluatie van de bevindingen

In Hoofdstuk 2, wordt beschreven hoe de screeningresultaten en de door screening gedetecteerde longkankers werden gebruikt om de positief voorspellende waarde van de screeningtest te bepalen. Verder werd in dit hoofdstuk de kans op longkanker in de komende 5,5 jaar op basis van de screeningresultaat geschat. Dit onderzoek toonde aan dat het screeningprotocol van de NELSON studie goed in staat was om de studiedeelnamers in te delen naar hun risico op longkanker. Screening in de NELSON studie leidde bovendien tot een beperkt aantal vervolgschecks en aanvullende diagnostische onderzoeken. In vergelijking met andere studies was de voorspellende waarde van een positieve screeningresultaat hoog in de NELSON studie. Echter, er werden wel relatief meer invasieve diagnostische onderzoeken gedaan voor fout-positieve screeningresultaten.

In Hoofdstuk 3 werden de tumorkarakteristieken van de door screening gedetecteerde longkankers gepresenteerd. Analyses toonden aan dat screening heeft geleid tot de diagnose van longkanker in een gunstiger ziektestadium, dit effect was sterker bij vrouwen.
dan bij mannen. Daarnaast werd aangetoond dat screening frequent leidt tot de detectie van traag-groeien lange kanker die zich in de buitenranden van de longen bevinden.

In Hoofdstuk 4 werden de testkarakteristieken van het screeningsprotocol van de NELSON studie geschat en werden mogelijkheden om het screeningsprotocol te verbeteren geïdentificeerd. Het detectievermogen en de sensitiviteit van het screeningsprotocol bleken in staat om longkanker in een net zo'n vroeg stadium op te sporen als gepresenteerd in een ander longkankerscreeningsstudie waarvan de effectiviteit al is aangetoond. Bovendien bleek dat het screeningsprotocol van de NELSON studie een zeer hoge specifiteit heeft, wat een voorwaarde is voor een kosteneffectief screeningsprogramma. Toch kunnen de uitkomsten van het screeningsprotocol mogelijk verbeterd worden door gelijktijdige implementatie met een effectief stoppen-met-roken-programma en een trainingsprogramma voor screeningsradiologen dat het aantal detectie-, en interpretatiefouten verminderd.

In Hoofdstuk 5 werd onderzocht of er radiologische oorzaken ten grondslag lagen aan het missen van longkankers in de studie en of er mogelijkheden om het screeningsprotocol te verbeteren. Dit onderzoek toonde aan dat de meerderheid van de gemiste longkankers niet te voorkomen was. Echter, winst valt te behalen door het verminderen van het aantal detectie-, en interpretatiefouten door radiologen. Deze fouten kunnen mogelijk vermindert worden door de aandacht van de screeningradioloog te verhogen voor endobronchiale laesies, wandverdikkingen in longblazen en laesies die vastzitten aan de longvliezen.

Deel III: Optimalisatie van screening

In Hoofdstuk 6 werd het risico op longkanker van de studiedeelneemers geschat. Deze risico-inschattingen werden gebruikt om protocollen voor management van nodules te ontwerpen en te evalueren. De huidige richtlijn voor het management van longnODULES classificeert nodules kleiner dan 4 mm als niet verdacht voor longkanker; nodules van 4 tot 8 mm als onduidelijk (waarvoor bepaling van de groeisnelheid geïndiceerd is: nodules met een volume-verdubbelingstijd korter dan 400 dagen worden vervolgens als verdacht voor longkanker geclasseerd); en nodules van 8 mm en groter als verdacht voor longkanker. Dit onderzoek toonde aan dat deze richtlijn voldoet, maar ook dat er mogelijkheid tot verbetering is. Zo zullen de sensitiviteit en specificiteit toenemen door het verhogen van de afkapwaarde voor nodulegrootte van 4 naar 5 mm en van 8 naar 10 mm, en de afkapwaarde voor nodulegroei van 400 naar 600 dagen. Daarnaast is een nodulemanagementprotocol ontworpen en geëvalueerd dat gebruik maakt van volumetrie. De afkapwaarden van dit protocol waren; volumes van 100mm³ en 300mm³ voor nodulegrootte, en een volume verdubbelingstijd van 600 dagen. Dit protocol heeft dezelfde sensitiviteit als de huidige richtlijn, maar een substantieel hogere specificiteit. Concluderend, het gebruik van volumetrie en het gebruik van afkapwaarden voor nodulegrootte en nodulegroei die
Samenvatting
gebaseerd zijn op longkankerrisico kunnen longkankerdetectie verbeteren en het aantal onnodige CT scans en invasieve diagnostische onderzoeken verminderen.

In Hoofdstuk 7 is de waarde van bronchoscopie als diagnostisch instrument in de work-up van verdachte longnODULES vastgesteld. Dit onderzoek toonde aan dat longkanker niet effectief vastgesteld kon worden met bronchoscopie door onvoldoende sensitiviteit. Daarnaast kon longkanker niet betrouwbaar uitgesloten worden met bronchoscopie omdat bronchoscopie tot misleidende goedaardige diagnoses kon leiden in patiënten met longkanker. Kortom, het routinematig gebruik van bronchoscopie in een longkanker-screeningsprogramma wordt op basis van dit onderzoek afgeraden.

In Hoofdstuk 8 werden de complicaties in kaart gebracht die kunnen optreden na chirurgie van de long die plaats vond naar aanleiding van verdachte nODULES op de CT-scan. Deze studie toonde aan dat complicaties na longchirurgie vaak voorkwamen. Vergeleken met andere studies kwamen milde complicaties relatief vaak voor in de NELSON studie, maar ernstige complicaties, zoals een her-operatie en postoperatieve sterfte kwamen relatief weinig voor. Daarnaast werd in deze studie gevonden dat er in de NELSON studie relatief vaak geopereerd is voor goedaardige nODULES.

Deel IV: Evaluatie van effectiviteit

In Hoofdstuk 9 werd het eindpuntverificatieproces van de NELSON studie ontworpen en geëvalueerd. Deze studie toonde aan dat een onafhankelijke commissie van experts een geprotocolleerd review proces zouden moeten uitvoeren. Dit leidt tot een eenduidige, objectieve en betrouwbare bepaling van de eindpunten. Om de betrouwbaarheid te verhogen is het belangrijk dat de medische status van alle studiedeelnemers die ooit gediagnosticeerd zijn met longkanker geblinddeerd worden voor de identiteit en studiegroep van de deelnemer. En om vast te stellen of de deelnemer al dan niet overleden is aan longkanker moeten deze medische statussen gereviewd worden aan de hand van een stroomdiagram en vooraf vastgestelde criteria. De pilotstudie toonde aan dat deze methode te verkiezen is boven het gebruik van de officiële overlijdenscertificaten. De laatst genoemde heeft als nadeel dat dit onvoldoende onderscheidend vermogen voor longkanker-specifieke sterfte hebben.

Deel V: Implicaties voor implementatie

In Hoofdstuk 10 werd een studie gepresenteerd waarin gepubliceerde literatuur over alle relevante aspecten van longkankerscreening in ogenschouw werd genomen om te bepalen of de voordelen van longkankerscreening met CT scans opwegen tegen de nadelen. Vervolgens werd bepaald of longkankerscreening met CT voldoet aan de screeningscriteria van de Wereldgezondheidsorganisatie. Dit onderzoek toonde aan dat er voorlopige schattingen zijn gemaakt van de voordelen en nadelen van longkankerscreening, maar dat er ook nog veel onduidelijkheden zijn. Op basis van deze onvolledige informatie kan
slechts geconcludeerd worden dat de literatuur suggereert dat de voordelen van longkankerscreening opwegen tegen de nadelen.

In Hoofdstuk 11, de 'Algemene Discussie' werden de resultaten van dit promotieonderzoek samengevat en besproken. Het screeningsprotocol van de NELSON studie leverde een gunstige balans op tussen het aantal negatieve, twijfelachtige en positieve testuitslagen, waardoor het aantal vervolgonderzoeken beperkt was. Het screeningsprotocol had een hoge sensitiviteit, wat veelbelovend is voor de eindanalyses naar het effect van screening op longkankersterfte. Het screeningsprotocol had ook een zeer hoge specificiteit, wat veelbelovend is voor de analyses naar de kosteneffectiviteit van longkankerscreening. De longkankers gedetecteerd door de screening werden in een vroeg ziektestadium gediagnosticeerd. Bovendien is ook de gecombineerde stadiumverdeling van de longkankers die gedetecteerd en gemist zijn door screening gunstig. De meerderheid van de oorzaken van het missen van longkankers in de screeningsstudie waren niet te voorkomen. Toch zou het screeningsprotocol verbeterd kunnen worden door een vermindering van het aantal detectie- en interpretatiefouten, hetgeen bereikt zou kunnen worden door meer aandacht van de radiologen voor endobronchiale laesies, wandverdikkingen in longblazen en laesies die vastzitten aan de longvliezen. Daarnaast kan het screeningsprotocol mogelijk verbeterd worden door kleine aanpassingen van de afkapwaarden voor nodulegrootte en de snelheid van nodulegroei die het screeningsresultaat bepalen. Implementatie van longkankerscreening gecombineerd met een effectief stoppen-met-roken-programma zal de balans tussen de voordelen en nadelen van longkanker screening verbeteren. Tijdens longkankerscreening lijkt geen plaats te zijn voor het routinematig toepassen van bronchoscopie om longkanker in een nodule uit te sluiten. Door deze vorm van diagnostiek niet op routinebasis toe te passen zullen de kosten en de kans op nadelige effecten van de screening afnemen. Tenslotte zal de effectiviteit van longkankerscreening in de NELSON studie worden vastgesteld met het eindpuntverificatieproces dat gepresenteerd werd in dit proefschrift.
Part VI

Miscellaneous
Chapter 14

Dankwoord
Dankwoord

Er zijn een groot aantal mensen die ik wil bedanken omdat zij direct of indirect hebben bijgedragen aan de totstandkoming van dit proefschrift.

Prof.dr. H.J. de Koning, geachte promotor, beste Harry, je was zowel mijn promotor als mijn directe begeleider en daarmee de belangrijkste persoon tijdens mijn promotieonderzoek. Ik ben blij dat ik bij jou, in mijn ogen dé expert in de wereld op het gebied van screening, mijn onderzoek heb kunnen doen. Je hebt me de vrijheid gegeven om mijn eigen ideeën uit te werken en me vele mogelijkheden geboden om naar interessante workshops, congressen en cursussen te gaan. Bedankt voor het vertrouwen dat je in me hebt gehad en alles wat ik van je heb geleerd.

Prof.dr. H.C. Hoogsteden, geachte promotor, beste professor Hoogsteden, hartelijk dank voor uw steun tijdens mijn promotie en de mogelijkheden die u me geboden heeft.

Prof.dr. M.G.M. Hunink, prof.dr. P.E. Postmus, prof.dr. H. van Swieten, prof. I.D. de Beaufort, geachte leden van de promotiecommissie, hartelijk dank voor uw bereidheid om mijn proefschrift te beoordelen en met mij hierover van gedachten te wisselen op 25 november 2014.

Prof.dr. M. Oudkerk, geacht lid van de promotiecommissie, beste professor Oudkerk, hartelijk dank dat u zitting wilde nemen in de promotiecommissie en mijn proefschrift wilde beoordelen. Daarnaast wil ik u bedanken voor de tijd en energie die u in mijn artikelen heeft gestoken; met uw kritische commentaren heeft u telkens weer geprobeerd om het beste naar boven te halen.

Prof.dr. K. Nackaerts, geacht lid van de promotiecommissie, beste professor Nackaerts, allereerst wil ik u bedanken dat u zitting wilde nemen in de promotiecommissie. Tevens wil ik u bedanken voor de prettige samenwerking, uw waardevolle commentaren op mijn manuscripten, de uitnodiging om deel te nemen aan het Leuvens Longkanker Symposium en de uitnodiging om samen het ‘priority paper evaluation’-artikel te schrijven.

Drs. S. Silva en M.F. Jonker MSc, lieve Sonja en Marcel, ik ben blij dat jullie mij als paranimfen tijdens de verdediging van mijn proefschrift willen bijstaan. Als kamer-(108)-genootjes hebben jullie me al vanaf het begin van mijn onderzoek bijgestaan; met verstandige adviezen, maar vooral ook met humor en een borrel op z’n tijd. Jullie hebben mijn promotietijd onvergetelijk gemaakt, 108 rules! ;)

Dr. E.Th. Scholten, beste Ernst, ik wil je heel erg bedanken voor je enorme bijdrage aan de twee artikelen over de intervalkankers (hoofdstuk 4 en 5), zonder jou waren ze er niet geweest. Ik vond het heel prettig om met je samen te werken en heb veel gehad aan je adviezen en steun.

Dr. J. van Rosmalen, beste Joost, heel erg bedankt voor je langdurige inzet voor het ‘lung cancer probability’-artikel (hoofdstuk 6). Dankzij jouw bewonderenswaardige kennis van de biostatistiek en je flexibiliteit om dit te gebruiken om medische richtlijnen te
optimaliseren is ons artikel ‘Lancet Oncology’-waardig geworden. Ik wens je veel succes met je nu al indrukwekkende loopbaan.

Dr. R.J. van Klaveren, beste Rob, ik wil je heel erg bedanken voor je begeleiding bij het ‘bronchoscopie’-artikel (hoofdstuk 7) en het ‘cause of death’-artikel (hoofdstuk 9). Je hebt me op een gedegen manier geleerd hoe onderzoek opgezet en artikelen geschreven moet worden. Dankzij je vertrouwen dat jij in me had, heb ik de mogelijkheid gekregen om dit promotieonderzoek te gaan doen. Ik vind het erg jammer dat onze samenwerking niet langer heeft mogen duren.

Dr. S.C. van ’t Westeinde, lieve Susan, ten eerste wil ik je bedanken voor je begeleiding en hulp bij mijn allereerste artikel (hoofdstuk 7). Ik heb veel van je geleerd, zowel over het onderzoek als over andere dingen die belangrijk zijn voor een jonge dokter. Ik ben blij dat we als ‘NELSON ladies’ contact zullen houden.

Dr. C.M. van der Aalst, lieve Carlijn, toen ik met mijn promotieonderzoek begon was ik erg blij dat je me op sleeptouw nam en me wegwijs maakte op de afdeling. Bedankt voor je hulp bij mijn artikelen en de zaken er om heen. Ik vond het erg gezellig met je op de kamer, en we zeker zullen als ‘NELSON ladies’ contact houden.

K. ten Haaf MSc, lieve Kevin, je bent een bijzondere collega voor me geweest. Je bent een van de meest oprechte personen die ik ken en ik heb je humor leren waarderen. Je gaf me om me op te vrolijken hebben me door teleurstellingen en frustraties, die bij het promoveren horen, heen geholpen.

Drs. A.U. Yousaf - Khan, beste Uraujh, wat leuk dat je het NELSON team bent komen versterken. Ik vond het gezellig om met je samen te werken en ik heb er alle vertrouwen in dat je een straks een mooi proefschrift zult afleveren. Veel succes met je verdere loopbaan.

M.A. Quak, lieve Marianne, heel erg bedankt voor al je inspanningen voor de NELSON studie en de hulp bij mijn projecten.

R. Faber en F. Santegoeds, beste Roel en Frank, heel erg bedankt voor jullie inspanningen om de datastromen van de NELSON studie in goede banen te leiden en voor jullie adviezen en hulp bij mijn projecten.

A. de Bruijn, lieve Arroy, bedankt voor jouw hulp en ondersteuning die je direct en indirect aan de NELSON studie en mij hebt geboden. Harry boft maar met jou als secretaresse.

Dr. P.A. de Jong, beste Pim, bedankt voor je nuttige commentaren op mijn artikelen en je belangrijke bijdrage aan de twee intervalkanker artikelen (hoofdstuk 4 en 5).


Drs. C. Weenink, Dr. E. Thunnissen, Dr. R. Vliegenthart, veel dank voor jullie bijdragen als co-auteurs aan mijn artikelen.
Dr M.A. den Bakker, Dr. J.A.M. Aerts, prof.dr. J.-W. Coeberg, beste Joachim, Michael en professor Coebergh, hartelijk dank dat jullie wilden plaatsnemen in de expertcommissie van de NELSON studie. Dankzij jullie wordt mijn eindpuntverificatieprotocol (hoofdstuk 9) toegepast en kan het zijn nut bewijzen.

Alle overige coauteurs die nog niet bij naam zijn genoemd, wil ik ook bij deze nogmaals bedanken voor hun bijdrage aan mijn artikelen.

René Vernhout, Emile Gras en Linda van Dongen, heel erg bedankt voor jullie inspanningen voor de NELSON studie en bedankt voor de gastvrijheid op het trialbureau in de Daniel den Hoed.

Ton de Jongh, dank voor het ontwerpen en onderhouden van het NELSON management systeem waar ik veel gebruik van heb gemaakt tijdens mijn onderzoek.

Dames van de ondersteuning en het secretariaat en heren van de ICT van de Afdeling Maatschappelijke Gezondheidszorg, bedankt dat jullie het mede mogelijk hebben gemaakt dat ik mijn werk kon doen.

Saskia van Amelsvoort - van de Vorst, Anneke Hamersma, Henk Pruijsma, Ria Ziengs, Liesbet Peeters, Beatrijs Anrijs, bedankt voor jullie belangrijke bijdrage aan de NELSON studie en jullie hulp bij de dataverzameling voor mijn artikelen.

Daarnaast wil ik alle andere bedankten die heeft bijgedragen aan het opzetten en uitvoeren van de NELSON studie, het beoordelen en behandelen van de patiënten die doorverwezen zijn door de NELSON studie, en iedereen heeft bijgedragen aan de dataverzameling.


Tenslotte wil ik de deelnemers van de NELSON studie hartelijk danken voor hun ongelofelijk belangrijke bijdrage aan het wetenschappelijke onderzoek naar de vroegopsporing van longkanker.

Lieve Astrid, Elise, Kirsten, Nikki, en Jitske, ofwel girls van de koffieclub, jullie hebben mijn tijd bij MGZ zo veel leuker gemaakt door onze koffiebreaks waarin we alles over onze promotietrajecten en ons leven daar buiten met elkaar deelden. Dus speciaal voor jullie mijn twaalfde stelling: “Met een koffieclub overleef je elk promotieonderzoek.” ;)

Ik wil ook mijn andere collega’s van de Afdeling Maatschappelijke Gezondheidszorg bedanken voor de leuke tijd en veel succes wensen met hun promotieonderzoek: Domino, Kerstin, Fenna, Suzette, Britt, David en Katja, en iedereen die ik nog vergeet te noemen.
Katinka, Claudia en Jessica en andere vriendinnen en vrienden bedankt voor jullie interesse in mijn onderzoek en afleiding die jullie me in deze periode gegeven hebben.

Aad en Margot, ik kan me geen betere schoonouders wensen, bedankt voor jullie vertrouwen en steun.

Lieve Mam, Elien, en Tim, bedankt dat jullie er voor me waren en dat jullie vertrouwen in me hebben gehad.

Lieve Ivanca, bedankt voor de prachtige illustratie voor de cover van dit proefschrift en de gezellige afleiding in mijn promotietijd.

Lieve Wouter, ik weet niet beter dan dat je er altijd voor me bent, me steunt, aanmoedigt, en zorgt voor afleiding als ik te veel met werk bezig ben. Met jou kan ik de wereld aan.
Chapter 15

Curriculum vitae
Nanda Horeweg was born on May 14th 1986 in Spijkenisse, the Netherlands. In 2004, she completed secondary school at ‘De Ring van Putten’ in Spijkenisse. Subsequently, she started studying Medicine at the ‘Erasmus University Rotterdam’. She wrote her graduation thesis on the value of bronchoscopy in the diagnostic work-up of suspicious pulmonary nodules detected by CT screening (chapter 8 of this thesis) under supervision of Dr. S.C. van ’t Westeinde and Dr. R.J. van Klaveren. In 2010, she graduated with honours and obtained her medical degree. Thereafter, she started working as resident at the department of Pulmonary Medicine at Erasmus University Medical Center. In 2011, she was appointed as research-physician for the Dutch-Belgian lung cancer screening trial (NELSON trial) at the department of Public Health and the department of Pulmonary Medicine at Erasmus University Medical Center. Henceforth, she evaluated several aspects of lung cancer screening in the NELSON trial, under supervision of prof.dr. H.J. de Koning. Resultant research findings are presented in this thesis.

Chapter 16
PhD portfolio
### PHD PORTFOLIO

**Summary of PhD training and teaching**

**PhD student**
Nanda Horeweg MD

**Erasmus Medical Center Department**
Public Health
Pulmonary Medicine

**PhD period**
01-02-2012 to 01-08-2014

**Promotors**
H.J. de Koning MD PhD
H.C. Hoogsteden MD PhD

#### 1. PhD training

<table>
<thead>
<tr>
<th>General courses</th>
<th>Year</th>
<th>Workload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning and evaluation of screening, NIHES, Rotterdam, Netherlands</td>
<td>2011</td>
<td>1.4 ECTS</td>
</tr>
<tr>
<td>Certificate of English course, Embassy CES, New York, USA</td>
<td>2011</td>
<td>60 hours</td>
</tr>
<tr>
<td>Biostatistical Methods II: classical regression models, NIHES, Rotterdam, Netherlands</td>
<td>2012</td>
<td>4.3 ECTS</td>
</tr>
<tr>
<td>Courses for the quantitative researcher, NIHES, Rotterdam, Netherlands</td>
<td>2012</td>
<td>1.4 ECTS</td>
</tr>
<tr>
<td>Repeated measurements, NIHES, Rotterdam, Netherlands</td>
<td>2012</td>
<td>1.4 ECTS</td>
</tr>
<tr>
<td>Missing values in clinical research, NIHES, Rotterdam, Netherlands</td>
<td>2012</td>
<td>0.7 ECTS</td>
</tr>
<tr>
<td>Analysis of growth data, NIHES, Rotterdam, Netherlands</td>
<td>2012</td>
<td>0.6 ECTS</td>
</tr>
<tr>
<td>Absolute risk prediction, Netherlands Cancer Institute, Amsterdam, Netherlands</td>
<td>2012</td>
<td>0.3 ECTS</td>
</tr>
<tr>
<td>Study design, NIHES, Rotterdam, Netherlands</td>
<td>2013</td>
<td>4.3 ECTS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specific courses</th>
<th>Year</th>
<th>Workload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methodologie van patiëntgebonden-onderzoek en voorbereiding subsidieaanvragen</td>
<td>2012</td>
<td>8 hours</td>
</tr>
<tr>
<td>Teach the teacher: Vaardigheidsonderwijs geven, Desiderius school</td>
<td>2013</td>
<td>12 hours</td>
</tr>
<tr>
<td>Erasmus University, Rotterdam, Netherlands</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BROK course, Erasmus MC, Rotterdam, Netherlands</td>
<td>2013</td>
<td>20 hours</td>
</tr>
<tr>
<td>Scientific integrity, Erasmus MC, Rotterdam, Netherlands</td>
<td>2014</td>
<td>8 hours</td>
</tr>
<tr>
<td>Seminars and workshops</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhD day, Erasmus MC, Rotterdam, Netherlands</td>
<td>2012</td>
<td>6 hours</td>
</tr>
</tbody>
</table>
## Presentations

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
<th>Credits</th>
</tr>
</thead>
<tbody>
<tr>
<td>14th World Conference on Lung Cancer, Amsterdam, Netherlands: poster presentation “The role of conventional bronchoscopy in the work-up of suspicious CT screen detected pulmonary nodules”</td>
<td>2011</td>
<td>1 ECTS</td>
</tr>
<tr>
<td>NELSON lung cancer screening symposium, Rotterdam, Netherlands: oral presentation “Blinded and uniform cause of death verification in a lung cancer CT screening trial”</td>
<td>2011</td>
<td>1 ECTS</td>
</tr>
<tr>
<td>WEON Congres, Rotterdam, Netherlands: oral presentation “Predictive value of scan results” and poster presentation “Blinded and uniform cause of death verification in a lung cancer CT screening trial”</td>
<td>2012</td>
<td>2 ECTS</td>
</tr>
<tr>
<td>European meeting lung cancer screening trials, Rotterdam, Netherlands: oral presentation “Cause of death verification in lung cancer screening trials”</td>
<td>2012</td>
<td>1 ECTS</td>
</tr>
<tr>
<td>Lung cancer screening symposium, Leuven, Belgium: oral presentation “Screening conditions”</td>
<td>2013</td>
<td>1 ECTS</td>
</tr>
<tr>
<td>American Thoracic Society International Conference, Philadelphia, USA: oral presentation “Characteristics of CT-detected lung cancers” and “Outcomes three rounds of the NELSON trial” and poster session facilitator</td>
<td>2013</td>
<td>2 ECTS</td>
</tr>
<tr>
<td>European Lung Cancer Conference, Lugano, Switzerland: oral presentation “Volumetric screening for lung cancer”</td>
<td>2013</td>
<td>1 ECTS</td>
</tr>
<tr>
<td>Meeting design SCAPIS study, Stockholm, Sweden: “Management of CT-detected nodules”</td>
<td>2013</td>
<td>1 ECTS</td>
</tr>
<tr>
<td>World Conference on Lung Cancer, Sydney Australia: oral presentation at plenary presidential symposium “Lung cancer probability of subjects with CT-detected nodules”</td>
<td>2013</td>
<td>1 ECTS</td>
</tr>
<tr>
<td>Research meeting department of Public Health Erasmus University Medical Center, oral presentation “NELSON study”</td>
<td>2013</td>
<td>1 ECTS</td>
</tr>
</tbody>
</table>

## (Inter)national conferences

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>14th World Conference on Lung Cancer, Amsterdam, Netherlands</td>
<td>2011</td>
<td>24 hours</td>
</tr>
<tr>
<td>NELSON lung cancer screening symposium, Rotterdam, Netherlands</td>
<td>2011</td>
<td>8 hours</td>
</tr>
<tr>
<td>WEON Congres, Rotterdam, Netherlands</td>
<td>2012</td>
<td>16 hours</td>
</tr>
<tr>
<td>European meeting lung cancer screening trials</td>
<td>2012</td>
<td>12 hours</td>
</tr>
<tr>
<td>Lung cancer screening symposium, Leuven, Belgium</td>
<td>2013</td>
<td>24 hours</td>
</tr>
<tr>
<td>European Lung Cancer Conference, Lugano, Switzerland</td>
<td>2013</td>
<td>24 hours</td>
</tr>
</tbody>
</table>
American Thoracic Society International Conference, Philadelphia, USA 2013 40 hours  
World Conference on Lung Cancer, Sydney, Australia 2013 40 hours  

**Other**  
Peer reviews for international medical journals  
- International Journal of Cancer 2012 6 hours  
- Lung cancer 2012 6 hours  
- JAMA internal medicine 2013 4 hours  
- Health expectations 2013 2 hours  
- Thorax 2013 2 hours  
- Journal of Thoracic Oncology 2013 14 hours  
- Lung Cancer 2013 4 hours  
- Respiration 2013 6 hours  
- Journal of Thoracic Oncology 2014 8 hours  
- Expert review of Respiratory Medicine 2014 4 hours  
- Lung Cancer Management 2014 2 hours  

**2. Teaching**  
- ‘Medication safety’ 3rd year medical students, Erasmus University, Rotterdam, Netherlands 2012 8 hours  
- Checking bachelor essays, 3rd year medical students, Erasmus University, Rotterdam, Netherlands 2012 60 hours  
- ‘Primary prevention in doctor’s practice’ 3rd year medical students, Erasmus University, Rotterdam, Netherlands 2013 12 hours  
- Checking bachelor essays, 3rd year medical students, Erasmus University, Rotterdam, Netherlands 2013 80 hours  
- Checking bachelor essays, 3rd year medical students, Erasmus University, Rotterdam, Netherlands 2014 80 hours  

**Total**  
2011-2014 46.5 ECTS*  

* 1 ECTS = 28 hours
Chapter 17

List of publications


* equal contribution
<table>
<thead>
<tr>
<th>K152418</th>
<th>K152418 NSE Letter</th>
<th>Agreed Action (Based on Riverain response to 10.23.15 deficiency or through Q152108 Pre-sub meeting)</th>
<th>510(k) Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.23.15 Deficiency</td>
<td>1</td>
<td>Provided Signed Truthful and Accuracy statement</td>
<td>N/A</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Agreed to new IFU with &quot;asymptomatic population&quot; specified</td>
<td>Modified IFU in 510(k) / forms</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Agreed to provide table of Study Data Description including mean and distribution of nodule size in user manual and marketing material.</td>
<td>Added to section 16.3 in 510(k) and modified PTM, marketing slip sheet and study summary materials</td>
</tr>
<tr>
<td>4</td>
<td>N/A</td>
<td>Clarified that although there are several parameters throughout the image processing modules, both within the vessel suppression and CAD algorithms, not a single parameter was explicitly tuned to a database.</td>
<td>N/A</td>
</tr>
<tr>
<td>5</td>
<td>N/A</td>
<td>Clarified thin-slice data from the ANODE09 competition and the VESSEL12 dataset was used in the slice thickness normalization voxel level models.</td>
<td>Already included in section 13.3.3.2</td>
</tr>
<tr>
<td>6</td>
<td>N/A</td>
<td>Agreed to provide acquisition parameters of the LIDC dataset</td>
<td>Added to section 13.3.6 in 510(k)</td>
</tr>
<tr>
<td>7</td>
<td>N/A</td>
<td>Clarified only 31 of the 129 were used in the final classifier.</td>
<td>Added to section 13.3.5 in 510(k)</td>
</tr>
<tr>
<td>8</td>
<td>N/A</td>
<td>Clarified a FROC plot using the LIDC dataset was used to set threshold.</td>
<td>Added to section 13.3.5 in 510(k)</td>
</tr>
<tr>
<td>9</td>
<td>N/A</td>
<td>Clarified the 5 ROI limit is per CT series</td>
<td>Added to section 13.3.3.4 in 510(k)</td>
</tr>
<tr>
<td>10</td>
<td>N/A</td>
<td>Clarified how many LIDC cases used for training the algorithms.</td>
<td>Added to section 13.3.5 in 510(k)</td>
</tr>
<tr>
<td>11</td>
<td>N/A</td>
<td>Addressed by Q21/10 below</td>
<td>N/A</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>Reader Study- Arm 3 Clinical Data updated to include third arm</td>
<td>Updated Section 16 to include Arm 3 data</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>Agreed to provide additional data on solid, sub solid, and GGO in development data and general screening population.</td>
<td>Added table to Section 16.3 of 510(k).</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>Clarified that clinically actionable nodules are defined as cancer and benign. Identified Reference Standard</td>
<td>Added to section 16.2.1 of 510(k).</td>
</tr>
<tr>
<td>14</td>
<td>N/A</td>
<td>Clarified readers were instructed to mark all actionable nodules. No other information was provided.</td>
<td>Added to Section 16.2 of 510(k).</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
<td>No example of large CAD mark with only a few pixels being called a true hit. FDA agreed to accept response given unlikely impact to performance.</td>
<td>N/A</td>
</tr>
<tr>
<td>16</td>
<td>7</td>
<td>Confirmed experts read all cases independently and were asked to mark clinically actionable nodules. More details on truthing tool, explain pathology biopsy for multiple nodules in a case</td>
<td>Added statement to 16.2.2 and 16.3.</td>
</tr>
<tr>
<td>16</td>
<td>8</td>
<td>Agreed for the third ready arm, the original training materials based off of the internal dataset performance will be used to maintain consistency. However, in the final device marketing materials and user manuals, performance will be based on the clinical trial results.</td>
<td>Arm 3 protocol reflects original training materials. Draft Labeling (User manual and marketing materials) report results obtained from clinical study.</td>
</tr>
<tr>
<td>17</td>
<td>N/A</td>
<td>Agreed to provide analysis of area under FROC curve</td>
<td>Added to 16.4 of 510(k)</td>
</tr>
<tr>
<td>18</td>
<td>9b and 9c</td>
<td>Clarified data was provided for cancer and all nodules because benign nodules are also considered actional nodules. Agreed to provide raw data for LROC and FROC analysis</td>
<td>Added to Section 16.2.2 in 510(k)</td>
</tr>
<tr>
<td>19</td>
<td>9a</td>
<td>Agreed to perform traditional a)ROC analysis, b)location based ROC analysis, and e) subregion analysis.</td>
<td>Added to section 16.4 of 510(k)</td>
</tr>
<tr>
<td>20</td>
<td>N/A</td>
<td>Agreed to provide machine test FROC</td>
<td>Added to section 16.4 in 510(k)</td>
</tr>
<tr>
<td>21</td>
<td>10</td>
<td>Agreed to provide characterization of simulated nodules in terms of maximum axial extent, corresponding minimum extent in the same slice, nodule volume, shape in terms of aspect ratios, avg. density within the enclosed volume, and nodule attachment characteristics.</td>
<td>Added to section 13.3.6 of 510(k)</td>
</tr>
<tr>
<td>22</td>
<td>N/A</td>
<td>Agreed to add Software Design Spec and Tracability Matrix to Appendices</td>
<td>Added to sections 13.7 and 13.8 in 510(k)</td>
</tr>
</tbody>
</table>
June 30, 2016

U.S. Food and Drug Administration
Center for Devices and Radiological Heath
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Response to 6/17/16 Deficiency Email
K161201 ClearRead CT™
Riverain Technologies, LLC

Dear Ms. Kang,

This letter is in response to your June 17, 2016 request for additional information regarding the 510(k) submission for Riverain’s ClearRead CT device (K161201). In the enclosed document, Riverain Response to FDA’s 6.17.16 Deficiency Email Regarding K161201, our responses can be found after each of your questions. Please note that we have maintained your own question numbering.

This submission includes one (1) printed version and a DVD-ROM. The eCopy is an exact duplicate of the paper copy. The DVD-ROM also includes data files, Statistical Data.zip, located in the Statistical Data Folder. This data is not included in printed form.

If there are any questions regarding this submission, please contact me at 937-531-5446 or jbutsch@riveraintech.com.

We request that this new response, including commercial information and Riverain Technology’s intent to market the device described in this notification, be maintained by FDA in confidence pursuant to 21 CFR §807.95 for the maximum period allowed by 21 CFR §807.95(b) and (c), and including the maximum post-determination period specified in 21 CFR §807.95(e). Please notify me directly of any request for release of information pertaining to this submission prior to public disclosure of such information.

Sincerely,

[Signature]
Jennifer Vetter Butsch
Director of Regulatory Affairs
Riverain Medical
June 30, 2016

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Response to 6/17/16 Deficiency Email
K161201 ClearRead CT™
Riverain Technologies, LLC

Dear Ms. Kang,

This letter is in response to your June 17, 2016 request for additional information regarding the 510(k) submission for Riverain’s ClearRead CT device (K161201). In the enclosed document, Riverain Response to FDA’s 6.17.16 Deficiency Email Regarding K161201, our responses can be found after each of your questions. Please note that we have maintained your own question numbering.

This submission includes one (1) printed version and a DVD-ROM. The eCopy is an exact duplicate of the paper copy. The DVD-ROM also includes data files, Statistical Data.zip, located in the Statistical Data Folder. This data is not included in printed form.

If there are any questions regarding this submission, please contact me at 937-531-5446 or jbutsch@riveraintech.com.

We request that this new response, including commercial information and Riverain Technology’s intent to market the device described in this notification, be maintained by FDA in confidence pursuant to 21 CFR §807.95 for the maximum period allowed by 21 CFR §807.95(b) and (c), and including the maximum post-determination period specified in 21 CFR §807.95(e). Please notify me directly of any request for release of information pertaining to this submission prior to public disclosure of such information.

Sincerely,

[Signature]

Jennifer Vetter Butsch
Director of Regulatory Affairs
Riverain Medical
4.0 TRUTHFUL AND ACCURATE STATEMENT

As Required per 21 CFR §807.87(k)

I certify that, in my capacity as Director, Regulatory Affairs and Quality Assurance at Riverain Technologies, I believe to the best of my knowledge, that all data and information submitted in the premarket notification are truthful and accurate and that no material fact has been omitted.

Jennifer Butsch
Riverain Technologies
Director of Regulatory Affairs and Quality Assurance

5/16/201
510(k) Number

5.0 CLASS III SUMMARY AND CERTIFICATION

As Required per 21 CFR §807.87(j) and 807.94

This section is not applicable to the current 510(k).

CONFIDENTIAL
CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity interest in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME: Steve Worrell  
TITLE: CEO

FIRM/ORGANIZATION: Riverain Technologies

SIGNATURE: [Signature]  
DATE (mm/dd/yyyy): 6/30/16

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Do NOT send your completed form to the PRA Staff email address below.
Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
PRASstaff@fda.hhs.gov

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.*
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
Food and Drug Administration

**Certification of Compliance**


(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

<table>
<thead>
<tr>
<th>SPONSOR / APPLICANT / SUBMITTER INFORMATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Name of Sponsor/Applicant/Submitter</td>
<td>Riverain Technologies LLC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Address</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Address</td>
<td>3020 South Tech Blvd.</td>
</tr>
</tbody>
</table>

| 4. Telephone and Fax Numbers |  |
| (Include country code if applicable and area code) |  |
| Tel: | 937-425-6811 |
| Fax: | 937-425-6493 |

<table>
<thead>
<tr>
<th>PRODUCT INFORMATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5. For Drugs/Biologics: Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s).</td>
<td></td>
</tr>
<tr>
<td>For Devices: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s)</td>
<td></td>
</tr>
<tr>
<td>Lung computed tomography system, computer-aided detection, Class II, ClearRead CT 11</td>
<td></td>
</tr>
</tbody>
</table>

**APPLICATION / SUBMISSION INFORMATION**

<table>
<thead>
<tr>
<th>6. Type of Application/Submission Which This Certification Accompanies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IND</td>
<td></td>
</tr>
<tr>
<td>NDA</td>
<td></td>
</tr>
<tr>
<td>ANDA</td>
<td></td>
</tr>
<tr>
<td>BLA</td>
<td></td>
</tr>
<tr>
<td>PMA</td>
<td></td>
</tr>
<tr>
<td>HDE</td>
<td></td>
</tr>
<tr>
<td>510(k)</td>
<td></td>
</tr>
<tr>
<td>POP</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

| 7. Include IND/ANDA/BLA/PMA/HDE/510(k)/POP/ Other Number (If number previously assigned) |  |
| If BLA was selected in Item 6, provide Supplement Number |  |

| 8. Serial Number Assigned to Application/Submission Which This Certification Accompanies |  |

<table>
<thead>
<tr>
<th>9. Certification Statement / Information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.</td>
<td></td>
</tr>
</tbody>
</table>

Certification Statement / Information section continued on page 2
CERTIFICATION STATEMENT / INFORMATION (Continued)

10. If you checked box C, in number 6, provide the National Clinical Trial (NCT) Number(s) for any “applicable clinical trial(s),” under 42 U.S.C. § 282(j)(1)(a)(i), section 402(j)(1)(a)(i) of the Public Health Service Act, referenced in the application/submission which this Certification accompanies. (Add continuation page as necessary.)

   NCT Number(s): NCT02440139

The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331; section 301 of the Federal Food, Drug, and Cosmetic Act.

Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. Name and Title of the Person who Signs Number 15

   Name: Jennifer Batsch
   Title: Director, Regulatory Affairs and Quality Assurance

12. Address

   Address 1 (Street address, P.O. box, company name if c/o)
   3020 South Tech Blvd.

   Address 2 (Apartment, suite, unit, building, floor, etc.)

   City: Miamisburg
   State/Province/Region: OH
   Country: US
   ZIP or Postal Code: 45342

13. Telephone and Fax Numbers

   (Include country code if applicable and area code)
   (Tel):
   (Fax):

14. Date of Certification

   06/21/16

15. Signature of Sponsor/Applicant/Submitter or an Authorized Representative (Sign)

   [Signature]

This section applies only to requirements of the Paperwork Reduction Act of 1995.

***DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.***

The burden time for this collection of information is estimated to average 15 minutes and 45 minutes (depending on the type of application/submission) per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."
ClearRead CT Suite

Overview
ClearRead CT was registered and tested under ClinicalTrials.gov, NCT02440139. ClearRead CT is a dedicated post-processing application that generates a secondary, vessel suppressed, lung CT series with marks and associated measurements, designed to aid the clinician. The clinical study assessed the effectiveness of the software to aid radiologists in detecting actionable lung nodules. Twelve board certified radiologists retrospectively interpreted 324 cases, 108 of which were nodule cases and 216 were normal. Of the 108 nodule cases, 93 were cancer cases, with two of the cases having two cancerous nodules.

Readers and Experts
- 12 Board certified radiologists participated in the study
- 3 Expert radiologists performed data selection and consensus ground truth in accordance to the pre-study protocol

Data Sources
- National Lung Screening Trial
- University of Maryland
- University Hospitals, Cleveland

Study Data Characteristics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2 - 3.0mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40 - 357 mA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5 - 20mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt; -800 HU to ≤ 200 HU</td>
</tr>
</tbody>
</table>

The table below summarizes the number of each type of case as well as the number of cases with multiple nodules.

<table>
<thead>
<tr>
<th>Case Type</th>
<th>Number of Cases</th>
<th>Total Nodules</th>
<th>Cancer Nodules</th>
<th>Benign Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>15</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Cancer</td>
<td>93</td>
<td>153</td>
<td>95</td>
<td>58</td>
</tr>
<tr>
<td>Normal</td>
<td>216</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reading Protocol
The observers interpreted the cases in two sessions: initially the cases were interpreted without the assistance of ClearRead CT, then a minimum of one month later the cases were “re-randomized” and reread using ClearRead CT as an aid. A concurrent reading protocol was used in the aided read, whereby the conventional CT was presented alongside the vessel suppressed series, both with the computer identified locations. Computer calculated descriptors of the detected regions of interest were provided alongside the computer detected locations.

Testing Hypotheses
1. ClearRead CT aided radiologists would have a statistically significant improved area under the curve (AUC) of the localization receiver operating characteristic (LROC) response relative to the unaided read.
2. ClearRead CT aided radiologists reading time would not significantly increase relative to the unaided read time.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Summary Results
1. ClearRead CT aided radiologists AUC was superior to that of unaided readers. Aided readers had a pAUC of 0.7469 versus 0.6786 for unaided readers, respectively on actionable nodules. A significant difference.
2. ClearRead CT was found to significantly decrease reading time, estimated to be 29 seconds.

Reader LROC Results
The table below shows the results for the area under the curve of the Localized Receiver Operating Characterization (LROC) curve for both readers aided with ClearRead CT (CRCT) and readers who were unaided (UA). As shown, readers aided with CRCT were superior to their unaided reads, based on the difference in the partial area under the curve (pAUC). The figure immediately below the table shows the LROC response when averaged across the 12 readers. A significant improvement in performance is achieved in terms of the sensitivity/specificity trade off when ClearRead CT is used as an aid.

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>pAUC</th>
<th>Std Error</th>
<th>pAUC CRCT-UA</th>
<th>Std Error</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LROC pAUC</td>
<td>CRCT</td>
<td>0.7469</td>
<td>0.0293</td>
<td>0.0683</td>
<td>0.0326</td>
<td>0.0418</td>
<td>0.0027</td>
<td>0.1339</td>
</tr>
<tr>
<td>LROC pAUC</td>
<td>UA</td>
<td>0.6786</td>
<td>0.0293</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% confidence interval of AUC for UA-CRCT for actionable cases/nodules (n=178) versus normal cases (n=216) (Note: As the interval does not include "0" this is an indication of superiority)

Reading Time Results
The table below shows the least square mean estimates of read time for both modalities (aided and unaided); the difference in these values; the p-value of the test of this difference being equal to zero; and the 95% confidence interval about the difference. The estimates both with and without outliers are provided in the table. All random effects were statistically significant.

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>Std. Error</th>
<th>CRCT-UA</th>
<th>Std. Error</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>11.343</td>
<td>0.073</td>
<td>-0.295</td>
<td>0.0720</td>
<td>0.0002</td>
<td>-0.440</td>
<td>-0.150</td>
</tr>
<tr>
<td>All read times</td>
<td>Unaided</td>
<td>11.639</td>
<td>0.073</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without Outliers</td>
<td>CRCT</td>
<td>11.352</td>
<td>0.073</td>
<td>-0.288</td>
<td>0.0720</td>
<td>0.0001</td>
<td>-0.424</td>
<td>-0.151</td>
</tr>
<tr>
<td>Without Outliers</td>
<td>Unaided</td>
<td>11.639</td>
<td>0.073</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>84.4</td>
<td>72.8</td>
<td>97.8</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.4</td>
<td>97.8</td>
<td>131.4</td>
</tr>
<tr>
<td>Without outliers</td>
<td>CRCT</td>
<td>85.1</td>
<td>73.8</td>
<td>98.1</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.5</td>
<td>98.4</td>
<td>130.9</td>
</tr>
</tbody>
</table>
A Fundamentally Different Approach

Riverain’s ClearRead CT Suite is the solution radiologists have been waiting for. Comprised of two powerful tools, ClearRead CT Vessel Suppress and ClearRead CT Detect, the ClearRead CT Suite is a leap forward. ClearRead CT provides the following capabilities:

• Enterprise wide capability based on patent pending image normalization technology that allows “plug in” capability across all CT manufacturers and diverse imaging protocols
• High throughput, scalable, computation on ‘off the shelf’ hardware and virtual machine deployments
• A patent pending, vessel suppressed, CT data series that aids both machine and humans in the detection and characterization of nodules
• Explicit targeting of all primary nodule types; solid, sub-solid and ground glass
• Precise measurements of detected regions afforded by vessel suppression.

ClearRead CT Performance

26% Reduction in Reading Time\(^1\)
29% Reduction in Missed Actionable Nodules\(^1\)

Key Advantages of the ClearRead CT Suite

• Reduces the burden of visual search and assessment by suppressing vascular structure
• Provides the ability to process scans from a wide range of manufacturers and acquisition protocols
• Provides unprecedented detection and segmentation accuracy of lung nodules
• Provides characterization of detected nodules

ClearRead CT Vessel Suppress

Powered by machine learning and advanced modeling, Riverain’s vessel suppression provides a CT view never before seen by the radiologist. Through the suppression of vascular structures, the radiologist is able to focus on nodular structures rather than competing vascular structures. Furthermore, the vessel suppressed view opens the black box by allowing the radiologist to have an unprecedented level of transparency into the CAD’s decision process.

The figure below shows a slice from a CT volume before and after vessel suppression. As can be seen in the vessel suppressed slice to the right, competing vascular structures have been removed and the nodule is cleanly “detached” from the adjacent vascular structure. The vessel suppression algorithm works seamlessly and operates on slices with section thicknesses up to 3mm.
ClearRead CT Detect

Powered by Riverain’s patent pending ClearRead CT Vessel Suppress, ClearRead CT Detect achieves what was previously unattainable in detection performance and measurement precision. The figure below shows a slice of the native CT series with a computer generated segmentation (nodule boundary definition) on the vessel suppressed slice on the right.

ClearRead CT Detect example with detected region of interest, segmented and characterized on vessel suppressed view (right).

ClearRead CT Host Machine Specifications

Recommended Server Specifications:
- Intel Core 2 or later, at least 2.4 GHz, 4 available cores
- 6+ GB Random Access Memory (RAM)
- 100 GB hard disk (dedicated storage)
- 1 Gbit/sec Ethernet controller
- USB 2.0 or greater

Operating System:
- Windows 7 Professional/Enterprise/Ultimate 64-bit
- Windows 8.1 Professional/Enterprise 64-bit
- Windows 2008 R2 Server 64-bit
- Windows 2012 R2 Server 64-bit

Web Browser:
- Microsoft Internet Explorer 10 or better, with cookies and JavaScript enabled

Software Protection Key:
- One USB Type A port available
- Power consumption 50mA operating/0.5mA standby

Third Party Software:
Riverain recommends against installing Connect CT on a multi-use instance of a VM or having multiple roles for a physical server by adding additional third party software.

References
1. Riverain Technologies. ClearRead CT, FDA Reader Study Results, 2015

About Riverain
Riverain Technologies™ is a medical software innovator that develops solutions to aid radiologists in the early detection of disease. With the use of Riverain’s ClearRead X-ray Suite and ClearRead CT Suite, radiologists are able to optimize the use of existing equipment for enhanced image interpretation. This enables radiologists to better utilize their diagnostic expertise in image interpretation for identification of diseases, such as lung cancer.
ClearRead CT Suite

Physician's Training Manual

The Best Practice Requires the Best Tools™

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Safe Operation Precautions

**GENERAL USE WARNINGS**

**WARNING:** Use of the device on any image projection other than the axial CT chest views is not supported.

**WARNING:** Only the original chest CT series is to be used for diagnostic interpretation by physicians. ClearRead CT output is designed only as an aid to the interpretation process.

**WARNING:** For continued safe use of this equipment, follow the instructions contained in this Physician’s Training Manual. Read this guide carefully before using the equipment, and refer to it as necessary.

**WARNING:** Federal law restricts this device to sale by or on the order of a physician.

**WARNING:** Conditions of image quality that diminish chest radiographic sensitivity, such as under- or over-exposure or artifacts, may also diminish the effectiveness of the device.

**WARNING:** Incorrect DICOM headers or other factors can cause ClearRead CT to reject an input CT series for processing, in which case no result will be returned for viewing. Do not delay your reading of the primary image in order to view the ClearRead CT output.

**WARNING:** ClearRead CT relies on Patient Position and Patient Orientation information from the DICOM header. If the header is incorrect, the system might fail to process the series.

**WARNING:** Users should never be dissuaded from working up an earlier finding even if it is not seen on the ClearRead CT output image. The device will not identify all areas that represent nodules.

**WARNING:** ClearRead CT has an option to send CAD results with an overlay. If your site uses a PACS that can receive and display overlays, and your ClearRead CT has been configured to send overlays, you must establish controls to prevent or record user editing of the CAD results.

**WARNING:** ClearRead CT is a medical device. It should be used only as described in the accompanying Riverain manuals. Other activities (such as web browsing, email, or installation of third-party software without specific authorization from Riverain) are prohibited. Software authorized by Riverain Technologies should be scanned with anti-virus software before use.

**NOTE:** A standard CT series is expected to contain both lungs. Images not containing both lungs might fail to be processed.
REGULATORY REQUIREMENTS

This product complies with the following regulatory requirements:

- FCC (class A)
- UL or CSA
- CE₀₄₁₃
Table of Contents

1 : Introduction ............................................................................. 6
2 : Definitions ............................................................................... 6
3 : Indications for Use ..................................................................... 6
4 : Motivation for Creating ClearRead CT .............................................. 7
5 : Summary of ClearRead CT ............................................................ 7
6 : How ClearRead CT Works ............................................................. 7
7 : Performance Expectations.......................................................... 10
   7.1 : General Performance Characteristics ........................................ 10
   7.2 : ROI Markers ....................................................................... 10
   7.3 : ROI Characteristics .............................................................. 11
   7.4 : True Positive And False Positive Marker Types ....................... 11
8 : Using ClearRead CT ................................................................... 12
   8.1 : Interpreting A Case .............................................................. 12
   8.2 : Detection Errors vs. Interpretation Errors ................................... 12
   8.3 : How to Respond to ClearRead CT Markers ............................... 12
   8.4 : Potential Effects of ClearRead CT False Negatives ................ 12
9 : Configurability: Selective Processing .......................................... 13
10 : Contraindications .................................................................... 13
11 : Adverse Effects ...................................................................... 13
12 : Conformance to Standards ......................................................... 13
13 : Connectivity .......................................................................... 13
14 : Examples of ClearRead CT Detection ............................................ 14
   Example 1: True Positive Detection ......................................... 15
   Example 2: True Positive Detection ......................................... 16
   Example 3: True Positive Detection ......................................... 17
   Example 4: True Positive Detection ......................................... 17
   Example 5: True Positive Detection ......................................... 18
   Example 6: True Positive Detection ......................................... 18
   Example 7: True Positive & False Positives ................................. 19
   Example 8: False Positives ...................................................... 19
   Example 9: False Negative ......................................................... 20
   Example 10: False Negative ........................................................ 21
   Example 11: Nodule Under Segmented ....................................... 21
   Example 12: Nodule Under Segmented ....................................... 22
1: Introduction

Your institution has installed the Riverain ClearRead CT system for chest computed tomography volumes. ClearRead CT consists of Computer-Aided Detection (CAD) markers on a vessel suppressed volume. The CAD component identifies regions of interest associated with solid, sub-solid, and/or ground glass nodules. This manual provides physicians who use the ClearRead CT system with an understanding of how the system works, what to expect when using ClearRead CT, and most importantly, the indications for use.

For any questions or concerns not addressed in this manual, go to:

http://www.riveraintech.com

Or contact Riverain Technologies directly at the address below:

Riverain Technologies
3020 S. Tech Blvd
Miamisburg, Ohio 45342
+1-800-990-3387
info@riveraintech.com

2: Definitions

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAD</td>
<td>Computer-Aided Detection</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
</tr>
<tr>
<td>802.3</td>
<td>IEEE Standard for Wired Ethernet</td>
</tr>
</tbody>
</table>

3: Indications for Use

ClearRead CT is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.
4: Motivation for Creating ClearRead CT

Low dose CT is the preferred method for annual lung cancer screening for at
risk patients. However, interpreting a chest CT is a challenging task, owing to
the large number of images commonly present in a chest CT series and number
of interfering structures that compete with the detection of lung nodules.
Given the clinical importance of detection of lung cancer using CT, it is clear
that a technology that aids in the detection of nodules would be useful to
medical professionals and patients alike.

The American Cancer Society statistics show that if lung cancer is found early
enough, the 5-year survival rates more than triples. A proactive approach to
early lung cancer detection is essential to turning the tide in the fight against
this devastating disease. ClearRead CT is designed to provide assistance in the
detection of nodules which may represent cancer.

5: Summary of ClearRead CT

ClearRead CT is a computer-aided detection (CAD) system intended to identify
and mark regions of interest (ROIs). The ClearRead CT system operates on a
chest CT exam. It identifies nodules, optimized for those between 5mm and
30mm in size. The system is limited to marking 5 ROIs per CT series deemed to
be worthy of review. The use of ClearRead CT leads to a reduction in oversight
errors.

6: How ClearRead CT Works

ClearRead CT is a software solution for automated detection of solid, sub-solid,
and/or ground glass nodules designed to operate on chest CT exams. ClearRead
CT relies on advanced algorithms from the engineering disciplines of image
analysis and machine learning. The algorithms compute measurements to
analyze the tissue in the CT series.

The software performs a series of steps to detect regions of interest containing
features associated with nodules. Figure 1 is a block diagram illustrating the
ClearRead CT nodule detection process.
The system receives, as input, a thoracic CT scan along with its associated acquisition parameters (pixel spacing, slice spacing, and slice thickness) via the DICOM header. The first step, volume preparation, segments the reconstruction circle so that the content outside this region can be excluded from further consideration. The next step is body segmentation. Body segmentation uses a combination of thresholding and morphological post-processing to separate patient tissue from the surrounding air and table content. After body segmentation, air segmentation is performed. Air segmentation detects air regions within the patient’s body using a combination of thresholding and morphological post-processing. After the body and air components have been segmented, volume normalization is performed. In volume normalization we standardize the appearance of CT scans so that they have similar noise, contrast, and voxel dimensions.

Once the CT scan has been normalized, it is passed to airway segmentation. This routine begins by finding the trachea to separate the left and right lungs. Once the airways have been segmented the next step is lung segmentation. The segmentation of the lungs is done using a series of thresholding, airway suppression, and morphological post-processing. As part of lung segmentation
routine, the left and right lungs are defined separately as merging can happen if care is not taken. ClearRead CT is designed to detect nodules only within the lung-field region. Regions outside the lungs are not considered for nodule detection.

Having normalized the CT volume for acquisition effects, and having segmented the lung field from the rest of the body, ClearRead CT then begins the vessel suppression process.

The vessel suppression module takes the normalized CT scan and associated lung segmentation as inputs. As an output, it generates a version of the normalized CT scan where vascular structure is suppressed (it also removes structures such as bronchial walls and fissure lines). It does not, however, remove nodular structures. This includes nodules that may be attached to vascular structure. The normalized image and vessel suppressed volume are fed to the nodule detection process.

Figure 2 provides a high-level diagram of the CAD solution for ClearRead CT. The ROI generation process uses a combination of thresholding and morphological post-processing on the lung regions within the vessel suppressed volume. Post detection, the candidate ROIs are sent to the ROI feature extraction step. The feature extraction module computes a collection of measurements meant to separate true nodules from non-nodules. Example of non-nodules includes residual vessel, bronchial structures, protrusions on the pleural surface that are not nodules, or lung tissue in the ground glass range. Once features have been computed for each ROI, the ROI classification is invoked.

The ROI classification step labels each ROI as nodule or non-nodule. The ROI classification step removes suspected calcified nodules by rejecting ROIs whose average density exceeds 200HU, or 250HU in the case of contrast scans. The ROI classification module limits the number of ROIs to at most five, where the ROIs with the highest classifier scores are selected. Lastly, the CAD engine returns four measurements extracted for the purpose of characterizing an ROI. Each of the four measurements has clinical significance that could aid a clinician in their decision task and although simple for a CAD to measure, are
burdensome for the radiologist at best or in some cases not possible (e.g., volume). The four measurements returned are as follows:

- **Volume**
  - The estimated volume in the segmented region in mm$^3$ units.

- **Maximum Diameter**
  - The largest diameter of the segmented region along the axial direction, in mm units.

- **Minimum Diameter**
  - The length of the diameter perpendicular to the one yielding the maximum, in mm units.

- **Average Density**
  - The median Hounsfield value within the entire segmented region, as measured from the original CT volume.

### 7: Performance Expectations

#### 7.1: General Performance Characteristics

ClearRead CT has been designed to detect nodules greater than or equal to 5mm in size. However, ClearRead CT may detect some nodules smaller than 5mm in diameter.

In a blind, third-party study of pathology-proven cancers, ClearRead CT detected 89.5% of known cancers. Cancers were both comprised of solid, mixed and ground glass. The average false positive rate per normal patient was 0.7469 false positives per CT series. For emphasis, it is noted that ClearRead CT and the radiologist will not necessarily detect the same nodules.

#### 7.2: ROI Markers

ClearRead CT uses the segmented contour on the center slice with ellipses on +/- one slice to indicate a region of interest. The circles are drawn on the image as white circles with a gray outline (if the burned in option is chosen). This provides visibility of the circle in both lucent and dense regions of the image.

The device allows for configuration of the CAD marker display. It is possible to display the CAD markers on both series: the original and the vessel suppressed. Alternatively, the system can be configured to display the CAD markers on the vessel suppressed volume only.
7.3: ROI CHARACTERISTICS

ClearRead CT computes four measurements related to each ROI - volume, maximum diameter, minimum diameter and average density. The ROI characteristics and related information is displayed as an overlay in the bottom left corner of the center slice, and +/- one slice to the center slice of the ROI. This provides visibility of the ROI and its associated characteristic information without obscuring the underlying or surrounding tissues.

The device allows for configuration of the ROI characteristics display. It is possible to display the ROI information either in the bottom left corner or in the top left corner of the image. Alternatively, the user can choose not to display the computed ROI characteristic information.

7.4: TRUE POSITIVE AND FALSE POSITIVE MARKER TYPES

A ClearRead CT true positive is a case in which ClearRead CT correctly detects a nodule. It may direct the radiologist to an area of the CT containing a previously unidentified lesion. True positive detections are the goal of ClearRead CT, while minimizing the number of false positives.

A ClearRead CT false positive is a case where ClearRead CT marks a region and there is no lung nodule. The following are the predominant sources of false positives:

Benign Pathologies:
- Scars
- Mucous plugs
- Pleural plaques

Other Pathologies:
- Tuberculosis (TB)
- Pneumonia
- Presence of other lung diseases such as Emphysema, Pulmonary Embolism, etc.

Normal Anatomy:
- Residual vessel
- Bronchial structures
- Protrusions on the pleural surface
8: Using ClearRead CT

8.1: Interpreting a Case
The radiologist reviews a chest CT concurrently with the vessel suppressed volume. The radiologist reviews the marked regions using the original images and determines whether any action is required. Although the ClearRead CT marker is typically centered on the region of interest, it is possible some markers will not be perfectly centered.

8.2: Detection Errors vs. Interpretation Errors
There are two types of errors in cancer detection:

- In an oversight error, the radiologist fails to see a nodule.
- In an interpretation error, the radiologist sees a nodule but decides it is not actionable.

Computer-aided detection (CAD) helps decrease oversight errors. In this process, the computer aids the radiologist in reducing oversight error.

8.3: How to Respond to ClearRead CT Markers
If upon review of the ROI, a nodule or other abnormality is observed, the radiologist should proceed according to their usual protocol for the type of abnormality observed.

When ClearRead CT has marked a finding that the radiologist can see but determines it is likely benign, the criteria for ordering further evaluation should be the same as if the radiologist noticed the finding without the use of the ClearRead CT system.

If there is no clear explanation for the cause of the marked ROI, the radiologist should dismiss the region as a false positive.

8.4: Potential Effects of ClearRead CT False Negatives
A ClearRead CT false negative is a case in which the computer fails to mark a true lung nodule. As previously indicated, the device will not mark all nodules. Therefore, the clinical action should never be reversed based on the absence of a ClearRead CT marker.
9: Configurability: Selective Processing

ClearRead CT has the ability to filter images using Boolean logic operations on any of the fields in the DICOM header. This filter allows ClearRead CT to distinguish chest CT volumes from other incorrect modalities or anatomy. Thus, it is important that your images contain DICOM headers that are properly populated according to the DICOM standard and that accurately reflect the acquisition and anatomical properties of the image. In addition to selecting only chest CT series, the filter may be extended to control demographic or other characteristics of the images sent to ClearRead CT. For example, the filter can be used to exclude pediatric exams, or to reject images from a particular modality.

10: Contraindications

There are no contraindications for use of the device.

11: Adverse Effects

There are no known direct risks to the health or safety of the patient from the physical use of the ClearRead CT system. This is a post-processing application and does not require additional radiation dose to the patient.

Possible indirect risks are:

- The physician may be dissuaded from working up an earlier finding if the device fails to mark that site, thus missing a possible nodule.
- The physician may be misled into working up a benign finding that would not otherwise have been acted upon.

12: Conformance to Standards

The ClearRead CT system conforms to the DICOM standards for digital communications of medical information.

13: Connectivity

The modality-acquired CT series can be sent to ClearRead CT directly from the modality or from a PACS, where the source of the series is a CT device.
ClearRead CT receives images according to DICOM® protocol\(^2\) (via a standard IEEE 802.3 network connection), processes the chest CT, and outputs the resulting information and/or images through the same 802.3 network connection using the DICOM protocol. Image inputs are limited to Computed Tomography (CT). The output results are sent for physicians to review on one or more devices that conform to the ClearRead CT DICOM Conformance Statement.

The workflow in which ClearRead CT can receive images to process is shown in Figure 3. In one realization of this workflow, ClearRead CT receives the image directly from any of the modalities. In this mode of operation, ClearRead CT receives the input image from the modality, processes the image, and sends the image on to the PACS. ClearRead CT populates the DICOM header of the derived ClearRead CT objects so that it is stored as part of the same study as the original chest CT exam.

In another realization of this workflow, ClearRead CT receives images directly from the PACS. In this mode of operation, ClearRead CT receives the input image from the PACS, processes the image, and sends the ClearRead CT image back to the PACS. ClearRead CT populates the DICOM header of the derived ClearRead CT objects so that it is stored as part of the same study as the original chest CT exam.

![Figure 3 - ClearRead CT Workflow: Receiving Images from Modality or PACS](image)

**14: Examples of ClearRead CT Detection**

The following figures provide typical outputs from ClearRead CT. ROIs are displayed as overlays with computed characteristics - avgdensity (HU), maxdiameter (mm), mindiameter (mm) and volume (mm\(^3\)), shown in the bottom right corner. The ROI contour and its associated computed characteristic information can also be burned in to the image depending on the

---

\(^2\) DICOM is the registered trademark of the National Electrical Manufacturers Association for its standards publications relating to digital communications of medical information.
configuration setting. In the following examples of ClearRead CT detections, note the following:

- Some examples show the full image so as to place the ROI in context, others show a magnified view of the ROIs for clarity.
- In each example, the ROI is indicated by an overlay. Note that if a burn-in option is chosen, the white circle and black outline are both required to clearly see the contour on light and dark portions of the image.
- In some examples, more than one ROI is visible.

The following examples are provided:

- Examples 1 to 6: True positive detections. In these examples, ClearRead CT detected truth confirmed nodules.
- Example 7: True positive and false positive mark on the same image.
- Example 8: Image with the most common false positives explained.
- Examples 9-10: Images with the most common false negatives explained.
- Examples 11-12: Images where the nodules are under segmented.

**EXAMPLE 1: TRUE POSITIVE DETECTION**

Shown here is a CT slice containing large nodule (left), vessel suppressed CT slice with the segmented contour and the associated characteristics as produced by the CAD engine (right). For quick reference, the mark number is indicated along with the ROI contour. Note, the associated ROI mark number and CAD engine computed characteristics are shown in the bottom right corner.
EXAMPLE 2: TRUE POSITIVE DETECTION

Shown above is a small nodule as marked by the CAD engine. Other nodule marked by the CAD engine can also be seen on the same slice. For quick reference, the mark number is indicated along with the ROI contour. When more than one nodule is present on the same slice, the ROI characteristic information is displayed in a tabular format as shown. Note that depending on the configuration setting, the ROI characteristic information can be displayed either in the bottom right corner (default) or in the top right corner of the image. Note, the small pleural nodule above the two indicated was not marked due to the rank limit of five.
**EXAMPLE 3: TRUE POSITIVE DETECTION**

This example shows a cavitated nodule as marked by the CAD engine.

**EXAMPLE 4: TRUE POSITIVE DETECTION**

This example shows a small nodule as marked by the CAD engine. Note that ClearRead CT has been designed to detect nodules greater than or equal to 5mm in size. However, ClearRead CT may detect some nodules smaller than 5mm in diameter.
EXAMPLE 5: TRUE POSITIVE DETECTION

This example shows a ground glass nodule marked by the CAD engine.

EXAMPLE 6: TRUE POSITIVE DETECTION

This example shows a sub-solid nodule marked by the CAD engine. Note the spurious ground glass content that is not marked by the CAD.
**EXAMPLE 7: TRUE POSITIVE & FALSE POSITIVES**

This example shows a sub-solid nodule marked by the CAD engine. Note the false positive residual in the left lung in the vessel suppressed series.

**EXAMPLE 8: FALSE POSITIVES**
This example shows a false positive from vessel branching marked by the CAD engine.

**EXAMPLE 9: FALSE NEGATIVE**

This example shows a nodule not marked by the CAD engine. This CT series has more than 5 nodules. However, ranking leads to loss of TPs as the maximum number of cad marks is limited to 5. Note the clear visibility of the nodule in the vessel suppressed series.
**EXAMPLE 10: FALSE NEGATIVE**

This example shows a false negative due to vessel merger.

**EXAMPLE 11: NODULE UNDER SEGMENTED**

This example shows a peripheral nodule marked by the CAD engine. The segmented contour shows that the nodule is under segmented due to proximity to the lung border and bone structures.
EXAMPLE 12: NODULE UNDER SEGMENTED

This example shows a nodule marked by the CAD engine. Note that the vessel nodule merging leads to inaccurate segmentation.

15: Possible Error Messages

If the ClearRead CT system is unable to process an image, you will see the text “Image processing unsuccessful” displayed on a blank image.

It is important to note that incorrect DICOM headers can cause ClearRead CT to reject an input image for processing, in which case no result will be returned for viewing. Do not delay reading of the primary image in order to view the ClearRead CT result.
16: ClearRead CT Clinical Study

**INTRODUCTION**

The Arlington Innovation Center for Health Research of Virginia Tech, (Virginia) performed a clinical study of ClearRead CT.

**STUDY SUMMARY**

In a multi-reader multi-case (MRMC) reader study, radiologists interpreted images in order to compare the radiologists’ ability to detect pulmonary nodules when they were aided by the ClearRead CT application. The reader study’s primary test metric was the difference in the partial area under the curve (pAUC) derived from the localization receiver operating characteristic (LROC) curve when using ClearRead CT relative to the unaided reads. Additionally, radiologist’s interpretation time when using ClearRead CT relative to unaided interpretations was measured. These results along with other secondary measures are captured below.

**STUDY DATA DESCRIPTION**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2-3.0 mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40 – 357 mA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5-20mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt; -800 HU to ≤ 200 HU</td>
</tr>
</tbody>
</table>
Twelve radiologists participated in each of the three reader arms. The readers had no prior knowledge of the cases, interpreted the lung CT series either with or without the aid of the ClearRead CT aids and were instructed to report actionable nodules along with a degree of suspicion for marked areas. Readers could record up to 5 locations corresponding to actionable nodules greater than or equal to 5mm. In the first reader arm (Reader Arm 1), readers were provided only the original CT series. After a washout period (minimum of 37 days), readers read concurrently with the ClearRead CT application (the vessel suppressed series along with CAD markings and characterizations) using the same CT cases. This is referred to as Reader Arm 2. Case order was re-randomized for each reader in Reader Arm 2. In the third reader arm (Reader Arm 3), actionable cases and normal cases were equally split according to a pre-specified criteria. Once split, readers were randomly assigned to read one of the two blocks with ClearRead CT and the other block without ClearRead CT. Data from all three reader arms was pooled and analyzed based on established test hypotheses.

The results are summarized in the following tables, with lower and upper 95% confidence limits:
The overall ability of ClearRead CT to detect actionable nodule cases is superior (i.e. statistically significantly better than) to unaided reads.

As shown below, the aided reader detected approximate 11.58% more actionable nodules, or equivalently, reduced oversite of actionable nodules by approximately 29%. Using the same two groups of nodules as in the LROC AUC analysis above, sensitivity, specificity, PPV and NPV were estimated by modality and tested for equality using the linear mixed model setting. The table below presents the summary of prediction measures within each modality for actionable nodules versus normal. For sensitivity, there is a statistically significant improvement in reads using CRCT versus unaided for detecting cancer nodules and for detecting any nodules in general. However, specificity is significantly lower in the CRCT reads.
Estimates of sensitivity, specificity, PPV, NPV and the associated 95% CIs, across modality for all actionable nodules and normal cases

Read Times:
As the distribution of read times in seconds within each modality were skewed, a log transformation was applied to the time data in order to generate more symmetric distribution of times (i.e. to meet normality assumption). Given the analysis was performed to obtain the difference in the times on the log scale, the back-transformed values are the estimate and 95% CI on the LS mean for each modality separately were calculated and transformed into seconds from milliseconds. The tables below provide the estimated LS mean reading times by modality on a log scale and then back-transformed to the original scale. The reduction in average read time from UA to CRCT was almost half a minute per case (mean differences of 29.0 and 28.4 seconds, respectively).

### CRCT-UA

<table>
<thead>
<tr>
<th>Predictive Measure</th>
<th>Read</th>
<th>Estimate</th>
<th>Std Error</th>
<th>Difference</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPV</td>
<td>CRCT</td>
<td>0.7900</td>
<td>0.0114</td>
<td>0.0521</td>
<td>0.0003</td>
<td>0.0251</td>
<td>0.0791</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.7379</td>
<td>0.0114</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** As the 95% confidence interval of difference in read time (log(milliseconds)) for CRCT-UA falls completely below “0”, superiority can be concluded.

### LS Mean Times (back-transformed) to seconds

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
<th>CRCT-UA (calculated from back-transformed) (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>84.4</td>
<td>72.8</td>
<td>97.8</td>
<td>-29.0</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.4</td>
<td>97.8</td>
<td>131.4</td>
<td></td>
</tr>
</tbody>
</table>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
### LS Mean Times (back-transformed) to seconds

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
<th>CRCT-UA (calculated from back-transformed) (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without outliers</td>
<td>CRCT</td>
<td>85.1</td>
<td>73.8</td>
<td>98.1</td>
<td>-28.4</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.5</td>
<td>98.4</td>
<td>130.9</td>
<td></td>
</tr>
</tbody>
</table>

**Estimate of reading times and LS Mean differences, back transformed to seconds**

It can be concluded that ClearRead read times are lower than unaided read times and that this difference in read times is statistically significant. This is demonstrated in both all read times and in the subset of read times within 3 standard deviations of the mean read time. This equates to a 26% reduction in read time when using CRCT as compared to the unaided read when using all data.

**MACHINE TEST**

Using the clinical data and machine only results, the free response operating characteristic (FROC) curve was derived. The free-response operating characteristic curve is a plot of the sensitivity (proportion of nodules correctly marked) versus the false positive rate per patient in the normal (non-nodule) cases. At the clinical operating point, the sensitivity is 0.8947 and 0.8202 for cancers and all nodules, respectively. The corresponding false positive rate per patient or per case was 0.7469 as illustrated by the dashed lines, in the following figure.
FROC curve for CRCT on clinical data. This chart displays the CRCT FROC curves of stand-alone machine performance for true positive detection of cancer nodules alone and combined cancers and all combined nodules.

The breakdown of nodule subtypes and results are detailed below:

<table>
<thead>
<tr>
<th>Nodule Type</th>
<th>Solid</th>
<th>Sub-Solid</th>
<th>GGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRCT Machine Detection %</td>
<td>84.17%</td>
<td>85.29%</td>
<td>66.67%</td>
</tr>
<tr>
<td>Average Reader Detection % (Count)</td>
<td>61.11% (120)</td>
<td>58.33% (34)</td>
<td>57.29% (24)</td>
</tr>
</tbody>
</table>

Machine vs. Reader Performance Across Nodule Type
September 6, 2016

U.S. Food and Drug Administration
Center for Devices and Radiological Heath
Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Response to 7/28/16 Deficiency Email
K161201 ClearRead CT™
Riverain Technologies, LLC

Dear Ms. Kang,

This letter is in response to your July 28, 2016 request for additional information regarding the 510(k) submission for Riverain’s ClearRead CT device (K161201). In the enclosed document, Riverain Response to 7/28/16 Deficiencies, our responses can be found after each of your questions. Please note that we have maintained your own question numbering.

This submission includes one (1) printed version and a DVD-ROM. The eCopy is an exact duplicate of the paper copy. The DVD-ROM also includes data files, Statistical_Data.zip, located in the Statistical Data Folder. This data is not included in printed form.

If there are any questions regarding this submission, please contact me at 937-531-5446 or jbutsch@riveraintech.com.

We request that this new response, including commercial information and Riverain Technology’s intent to market the device described in this notification, be maintained by FDA in confidence pursuant to 21 CFR §807.95 for the maximum period allowed by 21 CFR §807.95(b) and (c), and including the maximum post-determination period specified in 21 CFR §807.95(e). Please notify me directly of any request for release of information pertaining to this submission prior to public disclosure of such information.

Sincerely,

Jennifer Vetter Butsch
Director of Regulatory Affairs
Riverain Technologies
September 6, 2016

U.S. Food and Drug Administration  
Center for Devices and Radiological Heath  
Document Mail Center – WO66-0609  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

Re:  Response to 7/28/16 Deficiency Email  
K161201 ClearRead CT™  
Riverain Technologies, LLC

Dear Ms. Kang,

This letter is in response to your July 28, 2016 request for additional information regarding the 510(k) submission for Riverain’s ClearRead CT device (K161201). In the enclosed document, Riverain Response to 7/28/16 Deficiencies, our responses can be found after each of your questions. Please note that we have maintained your own question numbering.

This submission includes one (1) printed version and a DVD-ROM. The eCopy is an exact duplicate of the paper copy. The DVD-ROM also includes data files, Statistical_Data.zip, located in the Statistical Data Folder. This data is not included in printed form.

If there are any questions regarding this submission, please contact me at 937-531-5446 or jbutsch@riveraintech.com.

We request that this new response, including commercial information and Riverain Technology’s intent to market the device described in this notification, be maintained by FDA in confidence pursuant to 21 CFR §807.95 for the maximum period allowed by 21 CFR §807.95(b) and (c), and including the maximum post-determination period specified in 21 CFR §807.95(e). Please notify me directly of any request for release of information pertaining to this submission prior to public disclosure of such information.

Sincerely,

[Signature]

Jennifer Vetter Butsch  
Director of Regulatory Affairs  
Riverain Technologies

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
(b)(4) Response to 7.28.16 Deficiencies
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
ClearRead CT Suite

Overview

ClearRead CT was registered and tested under ClinicalTrials.gov, NCT02440139. ClearRead CT is a dedicated post-processing application that generates a secondary, vessel suppressed, lung CT series with marks and associated measurements, designed to aid the clinician. The clinical study assessed the effectiveness of the software to aid radiologists in detecting actionable lung nodules, or image locations in the CT series with suspicious nodular features for which radiologist(s) recommends further examination. Twelve board certified radiologists retrospectively interpreted 324 cases, 108 of which were nodule cases and 216 were normal. Of the 108 nodule cases, 93 were cancer cases, with two of the cases having two cancerous nodules.

Readers and Experts

- 12 Board certified radiologists participated in the study
- 3 Expert radiologists performed data selection and consensus ground truth in accordance to the pre-study protocol

Data Sources

- National Lung Screening Trial
- University of Maryland
- University Hospitals, Cleveland

Study Data Characteristics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2 - 3.0mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40-357 mA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5 - 20mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt; -800 HU to ≤ 200 HU</td>
</tr>
</tbody>
</table>

The table below summarizes the number of each type of case as well as the number of cases with multiple nodules.

<table>
<thead>
<tr>
<th>Case Type</th>
<th>Number of Cases</th>
<th>Total Nodules</th>
<th>Cancer Nodules</th>
<th>Benign Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>15</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Cancer</td>
<td>93</td>
<td>153</td>
<td>95</td>
<td>58</td>
</tr>
<tr>
<td>Normal</td>
<td>216</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reading Protocol

The observers interpreted the cases in two sessions: initially the cases were interpreted without the assistance of ClearRead CT, then a minimum of one month later the cases were “re-randomized” and reread using ClearRead CT as an aid. A concurrent reading protocol was used in the aided read, whereby the conventional CT was presented alongside the vessel suppressed series, both with the computer identified locations. Computer calculated descriptors of the detected regions of interest were provided alongside the computer detected locations.

Testing Hypotheses

1. ClearRead CT aided radiologists would have a statistically significant improved area under the curve (AUC) of the localization receiver operating characteristic (LROC) response relative to the unaided read.
2. ClearRead CT aided radiologists reading time would not significantly increase relative to the unaided read time.
Summary Results
1. ClearRead CT aided radiologists AUC was superior to that of unaided readers. Aided readers had a pAUC of 0.7469 versus 0.6786 for unaided readers, respectively on actionable nodules. A significant difference.
2. ClearRead CT was found to decrease reading time, estimated to be 29 seconds.

Reader LROC Results
The table below shows the results for the area under the curve of the Localized Receiver Operating Characterization (LROC) curve for both readers aided with ClearRead CT (CRCT) and readers who were unaided (UA). As shown, readers aided with CRCT were superior to their unaided reads, based on the difference in the partial area under the curve (pAUC). The figure immediately below the table shows the LROC response when averaged across the 12 readers. A significant improvement in performance is achieved in terms of the sensitivity/specificity trade off when ClearRead CT is used as an aid.

<table>
<thead>
<tr>
<th>LROC pAUC ClearRead CT - Unaided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td>LROC pAUC</td>
</tr>
<tr>
<td>UA</td>
</tr>
</tbody>
</table>

95% confidence interval of AUC for UA-CRCT for actionable cases/nodules (n=178) versus normal cases (n=216) (Note: As the interval does not include “0” this is an indication of superiority)

Reading Time Results
The reduction in average read time from UA to CRCT was almost half a minute per case (mean differences of 29.0 and 28.4 seconds, respectively).
ClearRead CT Suite

A Fundamentally Different Approach

Riverain’s ClearRead CT Suite is the solution radiologists have been waiting for. Comprised of two powerful tools, ClearRead CT Vessel Suppress and ClearRead CT Detect, the ClearRead CT Suite is a leap forward. ClearRead CT provides the following capabilities:

- Enterprise wide capability based on patent pending image normalization technology that allows “plug in” capability across all CT manufacturers and diverse imaging protocols
- High throughput, scalable, computation on ‘off the shelf’ hardware and virtual machine deployments
- A patent pending, vessel suppressed, CT data series that aids both machine and humans in the detection and characterization of nodules
- Explicit targeting of all primary nodule types; solid, sub-solid and ground glass
- Precise measurements of detected regions afforded by vessel suppression.

ClearRead CT Performance¹

26% Reduction in Reading Time
29% Reduction in Missed Actionable Nodules²

Key Advantages of the ClearRead CT Suite

- Reduces the burden of visual search and assessment by suppressing vascular structure
- Provides the ability to process scans from a wide range of manufacturers and acquisition protocols
- Provides unprecedented detection and segmentation accuracy of lung nodules
- Provides characterization of detected nodules

ClearRead CT Vessel Suppress

Powered by machine learning and advanced modeling, Riverain’s vessel suppression provides a CT view never before seen by the radiologist. Through the suppression of vascular structures, the radiologist is able to focus on nodular structures rather than competing vascular structures. Furthermore, the vessel suppressed view opens the black box by allowing the radiologist to have an unprecedented level of transparency into the CAD’s decision process.

The figure below shows a slice from a CT volume before and after vessel suppression. As can be seen in the vessel suppressed slice to the right, competing vascular structures have been removed and the nodule is cleanly “detached” from the adjacent vascular structure. The vessel suppression algorithm works seamlessly and operates on slices with section thicknesses up to 3mm.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118

---

¹FDA Reader Study Data Description

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2 - 30mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40 - 357 mA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5 - 20mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt; -800 HU to ≤ 200 HU</td>
</tr>
</tbody>
</table>

²Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018
ClearRead CT Detect

Powered by Riverain’s patent pending ClearRead CT Vessel Suppress, ClearRead CT Detect achieves what was previously unattainable in detection performance and measurement precision. The figure below shows a slice of the native CT series with a computer generated segmentation (nodule boundary definition) on the vessel suppressed slice on the right.

ClearRead CT Detect example with detected region of interest, segmented and characterized on vessel suppressed view (right).

ClearRead CT Host Machine Specifications

<table>
<thead>
<tr>
<th>Recommended Server Specifications:</th>
<th>Operating System:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intel Core 2 or later, at least 2.4 GHz, 4 available cores</td>
<td>• Windows 7 Professional/Enterprise/ Ultimate 64-bit</td>
</tr>
<tr>
<td>• 6+ GB Random Access Memory (RAM)</td>
<td>• Windows 8.1 Professional/Enterprise 64-bit</td>
</tr>
<tr>
<td>• 100 GB hard disk (dedicated storage)</td>
<td>• Windows 2008 R2 Server 64-bit</td>
</tr>
<tr>
<td>• 1 Gbit/sec Ethernet controller</td>
<td>• Windows 2012 R2 Server 64-bit</td>
</tr>
<tr>
<td>• USB 2.0 or greater</td>
<td></td>
</tr>
</tbody>
</table>

Web Browser: Microsoft Internet Explorer 10 or better, with cookies and Javascript enabled

Software Protection Key: One USB Type A port available

Power consumption 50mA operating/ <0.5mA standby

Third Party Software: Riverain recommends against installing Connect CT on a multi-use instance of a VM or having multiple roles for a physical server by adding additional third party software

References

1. Riverain Technologies. ClearRead CT, FDA Reader Study Results, 2015
2. Actionable nodules are image locations in the CT series with suspicious nodular features, i.e., characteristics, for which radiologist(s) recommends further examination, typically through analysis of a prior exam and/or additional imaging such as follow-up CT, diagnostic CT, PET-CT, etc.

About Riverain

Riverain Technologies™ is a medical software innovator that develops solutions to aid radiologists in the early detection of disease. With the use of Riverain’s ClearRead X-ray Suite and ClearRead CT Suite, radiologists are able to optimize the use of existing equipment for enhanced image interpretation. This enables radiologists to better utilize their diagnostic expertise in image interpretation for identification of diseases, such as lung cancer.
ClearRead CT Suite

Physician’s Training Manual

The Best Practice Requires the Best Tools™
ClearRead

CT Suite

Overview
ClearRead CT was registered and tested under ClinicalTrials.gov NCT02440188. ClearRead CT is a dedicated post-processing application that generates a secondary, vessel suppressed, lung CT series with marks and associated measurements, designed to aid the clinician. The clinical study assessed the effectiveness of the software to aid radiologists in detecting actionable lung nodules, or image locations in the CT series with suspicious nodular features for which radiologist(s) recommends further examination. Twelve board certified radiologists retrospectively interpreted 324 cases, 108 of which were nodule cases and 216 were normal. Of the 108 nodule cases, 93 were cancer cases, with two of the cases having two cancerous nodules.

Readers and Experts
- 12 Board certified radiologists participated in the study.
- 3 Expert radiologists performed data selection and consensus ground truth in accordance to the pre-study protocol.

Data Sources
- National Lung Screening Trial
- University of Maryland
- University Hospitals, Cleveland

Study Data Characteristics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2 - 30 mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40-357 mA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5 - 20 mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt;800 HU to ≤200 HU</td>
</tr>
</tbody>
</table>

The table below summarizes the number of each type of case as well as the number of cases with multiple nodules:

<table>
<thead>
<tr>
<th>Case Type</th>
<th>Number of Cases</th>
<th>Total Nodules</th>
<th>Cancer Nodules</th>
<th>Benign Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>15</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Cancer</td>
<td>93</td>
<td>153</td>
<td>95</td>
<td>58</td>
</tr>
<tr>
<td>Normal</td>
<td>216</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reading Protocol
The observers interpreted the cases in two sessions; initially the cases were interpreted without the assistance of ClearRead CT, then a minimum of one month later the cases were "re-randomized" and reread using ClearRead CT as an aid. A concurrent reading protocol was used in the unaided read, whereby the conventional CT was presented alongside the vessel suppressed series, both with the computer-identified locations. Computer calculated descriptors of the detected regions of interest were provided alongside the computer-detected locations.

Testing Hypotheses
1. ClearRead CT aided radiologists would have a statistically significant improved area under the curve (AUC) of the localization receiver operating characteristic (LROC) response relative to the unaided read.
2. ClearRead CT aided radiologists reading time would not significantly increase relative to the unaided read time.
Summary Results

1. ClearRead CT aided radiologists 0.7469 versus 0.6766 for unaided readers, respectively on actionable modules. A significant difference.
2. ClearRead CT was found to significantly decrease reading time, estimated to be 29 seconds.

Reader LROC Results

The table below shows the results for the area under the curve of the Localized Receiver Operating Characterization (LROC) Curve for both readers aided with ClearRead CT (CRCT) and readers who were unaided (UA). As shown, readers aided with CRCT were superior to their unaided readers based on the difference in the partial area under the curve (pAUC). The figure immediately below the table shows the LROC response when averaged across the 12 readers. A significant improvement in performance is achieved in terms of the sensitivity/specificity trade off when ClearRead CT is used as an aid.

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>pAUC</th>
<th>Std Error</th>
<th>pAUC CRCT-UA</th>
<th>Std Error</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LROC</td>
<td>CRCT</td>
<td>0.7469</td>
<td>0.0293</td>
<td>0.0683</td>
<td>0.0326</td>
<td>0.0418</td>
<td>0.0027</td>
<td>0.1339</td>
</tr>
<tr>
<td>UA</td>
<td></td>
<td>0.6766</td>
<td>0.0293</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% confidence interval of AUC for UA-CRCT for actionable cases/modules (n=178) versus normal cases (n=216) (Note: As the interval does not include "0" this is an indication of superiority)

Reading Time Results

The table below shows the least square mean estimates of read time for both modalities (aided and unaided), the difference in these values, the p-value of the test of this difference being equal to zero, and the 95% confidence interval about the difference. The estimates both with and without outliers are provided in the table. All random effects were statistically significant.

<table>
<thead>
<tr>
<th>Model</th>
<th>Estimate</th>
<th>Std Error</th>
<th>CRCT-Unaided</th>
<th>Std Error</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>11.343</td>
<td>0.073</td>
<td>-0.295</td>
<td>0.0720</td>
<td>0.0002</td>
<td>-0.440</td>
</tr>
<tr>
<td></td>
<td>Unaided</td>
<td>11.639</td>
<td>0.073</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without outliers</td>
<td>CRCT</td>
<td>11.352</td>
<td>0.073</td>
<td>-0.288</td>
<td>0.0720</td>
<td>0.0001</td>
<td>-0.424</td>
</tr>
<tr>
<td></td>
<td>Unaided</td>
<td>11.639</td>
<td>0.073</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LS Mean Times (back-transformed) in seconds

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
<th>CRCT-UA (calculated from back-transformed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>84.4</td>
<td>72.8</td>
<td>97.8</td>
<td>-29.0</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.4</td>
<td>97.8</td>
<td>131.4</td>
<td>-29.0</td>
</tr>
<tr>
<td>Without outliers</td>
<td>CRCT</td>
<td>85.1</td>
<td>73.8</td>
<td>98.1</td>
<td>-26.4</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.5</td>
<td>98.4</td>
<td>130.9</td>
<td>-26.4</td>
</tr>
</tbody>
</table>

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
ClearRead

CT Suite

Overview
ClearRead CT was registered and tested under ClinicalTrials.gov NCT02440188. ClearRead CT is a dedicated post-processing application that generates a secondary, vessel-suppressed lung CT series with marks and associated measurements, designed to aid the clinician. The clinical study assessed the effectiveness of the software to aid radiologists in detecting actionable lung nodules, or image locations in the CT series with suspicious nodular features for which radiologist(s) recommends further examination. Twelve board certified radiologists retrospectively interpreted 324 cases, 106 of which were nodule cases and 218 were normal. Of the 106 nodule cases, 93 were cancer cases, with two of the cases having two cancerous nodules.

Readers and Experts
- 12 Board certified radiologists participated in the study.
- 3 Expert radiologists performed data selection and consensus ground truth in accordance with the pre-study protocol.

Data Sources
- National Lung Screening Trial
- University of Maryland
- University Hospitals, Cleveland

Study Data Characteristics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2 - 3.0 mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40-357 mgA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5 - 20 mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt; 800 HU to ≤ 200 HU</td>
</tr>
</tbody>
</table>

The table below summarizes the number of each type of case as well as the number of cases with multiple nodules:

<table>
<thead>
<tr>
<th>Study Case Composition</th>
<th>Case Type</th>
<th>Number of Cases</th>
<th>Total Nodules</th>
<th>Cancer Nodules</th>
<th>Benign Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>15</td>
<td>25</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td>93</td>
<td>153</td>
<td>95</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>216</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reading Protocol
The observers interpreted the cases in two sessions. Initially the cases were interpreted without the assistance of ClearRead CT, then a minimum of one month later the cases were "rerandomized" and reread using ClearRead CT as an aid. A concurrent reading protocol was used in the aided read, whereby the conventional CT was presented alongside the vessel suppressed series, both with the computer identified locations. Computer calculated descriptors of the detected regions of interest were provided alongside the computer detected locations.

Testing Hypotheses
1. ClearRead CT aided radiologists would have a statistically significant improved area under the curve (AUC) of the localization receiver operating characteristic (LROC) response relative to the unaided read.
2. ClearRead CT aided radiologists reading time would not significantly increase relative to the unaided read time.
Summary Results

1. ClearRead CT-aided radiologists AUC was superior to that of unaided readers. Aided readers had a pAUC of 0.7469 versus 0.6786 for unaided readers, respectively on actionable nodules. A significant difference.
2. ClearRead CT was found to decrease reading time, estimated to be 28 seconds.

Reader LROC Results

The table below shows the results for the area under the curve of the Localized Receiver Operating Characterization (LROC) curve, for both readers aided with ClearRead CT (CRCT) and readers who were unaided (UA). As shown, readers aided with CRCT were superior to their unaided reads on the basis of the difference in the partial area under the curve (pAUC). The figure immediately below the table shows the LROC response when averaged across the 12 readers. A significant improvement in performance is achieved in terms of the sensitivity/specificity trade off when ClearRead CT is used as an aid.

<table>
<thead>
<tr>
<th>LROC pAUC ClearRead CT – Unaided</th>
<th>Model</th>
<th>Modality</th>
<th>pAUC</th>
<th>Std Error</th>
<th>pAUC CRCT-UA</th>
<th>Std Error</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LROC pAUC</td>
<td>CRCT</td>
<td>0.7469</td>
<td>0.0293</td>
<td>0.0683</td>
<td>0.0326</td>
<td>0.0418</td>
<td>0.0027</td>
<td>0.1339</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.6786</td>
<td>0.0293</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% confidence interval of AUC for UA-CRCT for actionable cases/nodules (n=178) versus normal cases (n=216). (Note: As the interval does not include "0" this is an indication of superiority.)

*LROC pAUC was evaluated per reader and scaled to have a maximum value of 1 according to the formula
\[ pAUC \text{scaled} = \text{pAUCmax}(\text{sensitivity})^m(1-\text{specificity})^m \]
where m denotes a reading modality (unaided or aided with ClearRead CT). The maximum values of sensitivity and 1-specificity across the modalities were used to define the range over which the unscaled pAUC (numerator in formula) was calculated.

Reading Time Results

The reduction in average read time from UA to CRCT was almost half a minute per case (mean differences of 29.0 and 28.4 seconds, respectively)

<table>
<thead>
<tr>
<th>LSTime Mean (back-transformed) to seconds</th>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
<th>CRCT-UA (calculated from back-transformed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All read times</td>
<td>CRCT</td>
<td>84.4</td>
<td>72.8</td>
<td>97.8</td>
<td>-29.0</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.4</td>
<td>97.8</td>
<td>131.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Without outliers</td>
<td>CRCT</td>
<td>85.1</td>
<td>73.8</td>
<td>98.1</td>
<td>-28.4</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.5</td>
<td>98.4</td>
<td>130.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ClearRead CT

ClearRead CT reduces image noise and improves contrast resolution, enabling clearer visualization of fine details and improved diagnostic confidence.

### Key Advantages of the ClearRead CT Suite

- **Improved Contrast Resolution**: ClearRead CT enhances the visibility of fine structures, aiding in the detection of subtle abnormalities.
- **Reduced Noise**: The technology reduces image noise, leading to clearer and more precise images.
- **Enhanced Diagnostic Confidence**: The improved clarity facilitates more accurate and confident diagnoses.

### FDA Reader Study Data Description

- **29% Reduction in Missed Acquirable Modules**: ClearRead CT significantly reduces the number of missed acquirable modules during radiography.
- **26% Reduction in Reading Time**: The time required for radiology readings is decreased, improving efficiency.

### ClearRead CT Performance

- **Vessel suppression**: The suppression of non-vessel structures improves the clarity of vessel images.
- **Radiology efficiency**: Increased efficiency and reduced error rates in radiology processes.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
ClearRead CT Detect

Powered by Riverain's patent pending ClearRead CT Vessel Suppression, ClearRead CT Detect achieves what was previously unattainable in detection performance and measurement precision. The figure below shows a slice of the native CT series with a computer generated segmentation (nodule boundary definition) on the vessel suppressed slice on the right.

ClearRead CT Detect example with detected region of interest, segmented and characterized on vessel suppressed view (right).

ClearRead CT Host Machine Specifications

<table>
<thead>
<tr>
<th>Recommended Server Specifications:</th>
<th>Operating System:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intel Core 2 or later, at least 2.4 GHz, 4 available cores</td>
<td>• Windows 7 Professional/Enterprise/ Ultimate 64-bit</td>
</tr>
<tr>
<td>• 6+ GB Random Access Memory (RAM)</td>
<td>• Windows 8.1 Professional/Enterprise 64-bit</td>
</tr>
<tr>
<td>• 100 GB hard disk (dedicated storage)</td>
<td>• Windows 2008 R2 Server 64-bit</td>
</tr>
<tr>
<td>• 1 Gbps/sec Ethernet controller</td>
<td>• Windows 2012 R2 Server 64-bit</td>
</tr>
<tr>
<td>• USB 2.0 or greater</td>
<td>Software Protection Key:</td>
</tr>
</tbody>
</table>

| Web Browser: | • One USB Type A port available |
|-------------| • Power consumption 50mA operating/ <5 mA standby |

Third Party Software:
Riverain recommends against installing Connect CT on a multi-use instance of a VM or having multiple roles for a physical server by adding additional third party software.

References
1. Riverain Technologies ClearRead CT, FDA Reader Study. Results, 2015.
2. Actionable nodules are image locations in the CT series with suspicious nodular features, i.e., characteristics, for which radiologist(s) recommends further examination, typically through analysis of a prior exam and/or additional imaging such as follow-up CT, diagnostic CT, PET-CT, etc.

About Riverain
Riverain Technologies™ is a medical software innovator that develops solutions to aid radiologists in the early detection of disease. With the use of Riverain's ClearRead X-ray Suite and ClearRead CT Suite, radiologists are able to optimize the use of existing equipment for enhanced image interpretation. This enables radiologists to better utilize their diagnostic expertise in image interpretation for identification of diseases, such as lung cancer.
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Hi Yanna,

Once we reach consensus regarding deficiency number two in the July 28th deficiency list, I will formally submit our written response to the document mail center. Should I capture all of the informal transactions that have occurred or limit the formal response only to the final agreed material?

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

Once we reach consensus regarding deficiency number two in the July 28th deficiency list, I will formally submit our written response to the document mail center. Should I capture all of the informal transactions that have occurred or limit the formal response only to the final agreed material?

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

Once we reach consensus regarding deficiency number two in the July 28th deficiency list, I will formally submit our written response to the document mail center. Should I capture all of the informal transactions that have occurred or limit the formal response only to the final agreed material?

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
\[
\text{number of subtypes modules detected across all readers} = \frac{\text{total number of readers} \times \text{total number of subtype modules}}{1000}
\]
Hi Yanna,

I sent Riverain's formal response overnight via FedEx. You should receive it tomorrow.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

I sent Riverain's formal response overnight via FedEx. You should receive it tomorrow.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
1.0 510(K) SUMMARY

Submission Date: April 25, 2016

Submitter Information:

Company Name: Riverain Technologies, LLC.
Company Address: 3020 South Tech Blvd., Miamisburg, OH 45342-4860
Contact Person: Jennifer Butsch
Director, Regulatory Affairs and Quality Assurance
Riverain Technologies
800.990.3387
937.425.6493
jbutsch@riveraintech.com

Device Information:

Trade Name: ClearRead CT™
Regulation Number: 21 CFR §892.2050
Regulation Name: Picture archiving and communications system
Regulatory Class: Class II
Product Code: OEB/LLZ

Device Description: ClearRead CT is a dedicated post-processing application that generates a secondary vessel suppressed Lung CT series with CADe marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Predicate Devices: syngo.CT Lung CAD
(K143196)
Siemens AG Medical Solutions
Class II

syngo.PET&CT Oncology
(K093621)
Siemens AG Medical Solutions  
Class II  

ClearRead Bone Suppression (SoftView)  
(K092363)  
Riverain Technologies, LLC  
Class II

Comparison to Predicate Device Technical Characteristics:
Riverain is of the opinion that the ClearRead CT is substantially equivalent, both in intended use and technical characteristics to the listed predicate devices. Differences in the design and performance from the cited predicate devices do not affect either the safety or the effectiveness of ClearRead CT for its intended use.

<table>
<thead>
<tr>
<th>Predicate:</th>
<th>Predicate:</th>
<th>Predicate:</th>
<th>Subject Device:</th>
</tr>
</thead>
<tbody>
<tr>
<td>syngo.CT Lung CAD</td>
<td>syngo.PET &amp; CT Oncology</td>
<td>ClearRead Bone Suppression</td>
<td>ClearRead CT (Riverain</td>
</tr>
<tr>
<td>(Siemens AG Medical</td>
<td>(Siemens AG Medical Solutions)</td>
<td>(Riverain Technologies)</td>
<td>Technologies)</td>
</tr>
<tr>
<td>Solutions)</td>
<td>K143196</td>
<td>K093621</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Code</th>
<th>OEB</th>
<th>LLZ</th>
<th>LLZ</th>
<th>OEB/LLZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intended Use</td>
<td>Computer-aided detection tool designed to assist radiologists in the detection of solid pulmonary nodules during review of MDCT examinations of the chest</td>
<td>Viewing, manipulation, 3D-Visualization, and comparison of medical images from multiple imaging modalities.</td>
<td>Generating bone suppressed image from an original PA/AP chest radiograph</td>
<td>Computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest</td>
</tr>
</tbody>
</table>

Testing Summary:
Clinical validation was conducted in a multi-reader multi-case (MRMC) study to validate that the device conformed to the defined user needs and intended uses. The reader study measured the area under the curve (AUC) of the localization receiver operating characteristic (LROC) response when using ClearRead CT relative to the unaided read. The study also measured the radiologists' interpretation time when using ClearRead CT relative to unaided interpretations. ClearRead CT was found to significantly increase the AUC, indicating use of the device is superior to the unaided read for detecting nodules. ClearRead CT was found to decrease read times with and without outliers.
Developmental testing was conducted to verify requirements according to the ClearRead CT device specifications. The Risk Analysis was completed and risk control measures
implemented to mitigate hazards. Documentation required for software with a Moderate Level of Concern is included as part of the submission. Device labeling together with results from verification & validation testing demonstrate the device is safe and effective.

**Conclusion:**

In preparing this 510(k) submission, Riverain has carefully considered the relevant statutory and regulatory requirements, and believes that the information contained within satisfies the requirements for demonstrating substantial equivalence.
Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

(b)(4)

Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don't hesitate to contact me. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704<tel:301-796-6704>
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.
Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don't hesitate to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcusertservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
Hi Jennifer,

We have the following clarification questions regarding your clinical study and would appreciate it if you could provide additional information to address those questions:

Please note that we are still reviewing your file and your clarifications on those questions will help facilitate our statistical review. Please send me your response via email by Thursday, 6/16/2016 or at your earliest convenience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704<tel:301-796-6704>
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustserv?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.
Hi Jennifer,

We have the following clarification questions regarding your clinical study and would appreciate it if you could provide additional information to address those questions:

Please note that we are still reviewing your file and your clarifications on those questions will help facilitate our statistical review. Please send me your response via email by Thursday, 6/16/2016 or at your earliest convenience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhccustomerservice?O=500&D=560&B=565&E=&S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Safe Operation Precautions

**GENERAL USE WARNINGS**

- **WARNING:** Use of the device on any image projection other than the axial CT chest views is not supported.
- **WARNING:** Only the original chest CT series is to be used for diagnostic interpretation by physicians. ClearRead CT output is designed only as an aid to the interpretation process.
- **WARNING:** For continued safe use of this equipment, follow the instructions contained in this Physician's Training Manual. Read this guide carefully before using the equipment, and refer to it as necessary.
- **WARNING:** Federal law restricts this device to sale by or on the order of a physician.
- **WARNING:** Conditions of image quality that diminish chest radiographic sensitivity, such as under- or over-exposure or artifacts, may also diminish the effectiveness of the device.
- **WARNING:** Incorrect DICOM headers or other factors can cause ClearRead CT to reject an input CT series for processing, in which case no result will be returned for viewing. Do not delay your reading of the primary image in order to view the ClearRead CT output.
- **WARNING:** ClearRead CT relies on Patient Position and Patient Orientation information from the DICOM header. If the header is incorrect, the system might fail to process the series.
- **WARNING:** Users should never be dissuaded from working up an earlier finding even if it is not seen on the ClearRead CT output image. The device will not identify all areas that represent nodules.
- **WARNING:** ClearRead CT has an option to send CAD results with an overlay. If your site uses a PACS that can receive and display overlays, and your ClearRead CT has been configured to send overlays, you must establish controls to prevent or record user editing of the CAD results.
- **WARNING:** ClearRead CT is a medical device. It should be used only as described in the accompanying Riverain manuals. Other activities (such as web browsing, email, or installation of third-party software without specific authorization from Riverain) are prohibited. Software authorized by Riverain Technologies should be scanned with anti-virus software before use.
- **NOTE:** A standard CT series is expected to contain both lungs. Images not containing both lungs might fail to be processed.

© 2004-2016 Riverain Technologies
REGULATORY REQUIREMENTS

This product complies with the following regulatory requirements:

- FCC (class A)
- UL or CSA
- CE 0413
Table of Contents

1 : Introduction ......................................................... 6
2 : Definitions .............................................................. 6
3 : Indications for Use ..................................................... 6
4 : Motivation for Creating ClearRead CT ............................ 7
5 : Summary of ClearRead CT ........................................... 7
6 : How ClearRead CT Works ............................................ 7
7 : Performance Expectations .......................................... 10
   7.1 : General Performance Characteristics ....................... 10
   7.2 : ROI Markers ...................................................... 10
   7.3 : ROI Characteristics ............................................ 11
   7.4 : True Positive And False Positive Marker Types ............ 11
8 : Using ClearRead CT ................................................... 12
   8.1 : Interpreting A Case .............................................. 12
   8.2 : Detection Errors vs. Interpretation Errors .................. 12
   8.3 : How to Respond to ClearRead CT Markers .................. 12
   8.4 : Potential Effects of ClearRead CT False Negatives ........ 12
9 : Configurability: Selective Processing ........................... 13
10 : Contraindications ................................................. 13
11 : Adverse Effects .................................................... 13
12 : Conformance to Standards ....................................... 13
13 : Connectivity ....................................................... 13
14 : Examples of ClearRead CT Detection ............................ 14
   Example 1: True Positive Detection ................................ 15
   Example 2: True Positive Detection ................................ 16
   Example 3: True Positive Detection ................................ 17
   Example 4: True Positive Detection ................................ 17
   Example 5: True Positive Detection ................................ 18
   Example 6: True Positive Detection ................................ 18
   Example 7: True Positive & False Positives ...................... 19
   Example 8: False Positives ......................................... 19
   Example 9: False Negative .......................................... 20
   Example 10: False Negative ......................................... 21
   Example 11: Nodule Under Segmented .............................. 21
   Example 12: Nodule Under Segmented .............................. 22
15: Possible Error Messages .......................................................22
16: ClearRead CT Clinical Study ..............................................24
    Introduction .........................................................................24
    Study Summary .....................................................................24
    Study Data Description .......................................................24
    Reader Study .......................................................................25
    Machine Test .......................................................................28
1: Introduction

Your institution has installed the Riverain ClearRead CT system for chest computed tomography volumes. ClearRead CT consists of Computer-Aided Detection (CAD) markers on a vessel suppressed volume. The CAD component identifies regions of interest associated with solid, sub-solid, and/or ground glass nodules. This manual provides physicians who use the ClearRead CT system with an understanding of how the system works, what to expect when using ClearRead CT, and most importantly, the indications for use.

For any questions or concerns not addressed in this manual, go to:

http://www.riveraintech.com

Or contact Riverain Technologies directly at the address below:

Riverain Technologies
3020 S. Tech Blvd
Miamisburg, Ohio 45342
+1-800-990-3387
info@riveraintech.com

2: Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actionable</td>
<td>Image locations in the CT series with suspicious nodular features, i.e.,</td>
</tr>
<tr>
<td>Nodule</td>
<td>characteristics, for which radiologist(s) recommends further examination,</td>
</tr>
<tr>
<td></td>
<td>typically through analysis of a prior exam and/or additional imaging such as</td>
</tr>
<tr>
<td></td>
<td>follow-up CT, diagnostic CT, PET-CT, etc.</td>
</tr>
<tr>
<td>CAD</td>
<td>Computer-Aided Detection</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
</tr>
<tr>
<td>802.3</td>
<td>IEEE Standard for Wired Ethernet</td>
</tr>
</tbody>
</table>

3: Indications for Use

ClearRead CT is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.
4: Motivation for Creating ClearRead CT

Low dose CT is the preferred method for annual lung cancer screening for at-risk patients. However, interpreting a chest CT is a challenging task, owing to the large number of images commonly present in a chest CT series and number of interfering structures that compete with the detection of lung nodules. Given the clinical importance of detection of lung cancer using CT, it is clear that a technology that aids in the detection of nodules would be useful to medical professionals and patients alike.

The American Cancer Society statistics show that if lung cancer is found early enough, the 5-year survival rates more than triples. A proactive approach to early lung cancer detection is essential to turning the tide in the fight against this devastating disease. ClearRead CT is designed to provide assistance in the detection of nodules which may represent cancer.

5: Summary of ClearRead CT

ClearRead CT is a computer-aided detection (CAD) system intended to identify and mark regions of interest (ROIs). The ClearRead CT system operates on a chest CT exam. It identifies nodules, optimized for those between 5mm and 30mm in size. The system is limited to marking 5 ROIs per CT series deemed to be worthy of review. The use of ClearRead CT leads to a reduction in oversight errors.

6: How ClearRead CT Works

ClearRead CT is a software solution for automated detection of solid, sub-solid, and/or ground glass nodules designed to operate on chest CT exams. ClearRead CT relies on advanced algorithms from the engineering disciplines of image analysis and machine learning. The algorithms compute measurements to analyze the tissue in the CT series.

The software performs a series of steps to detect regions of interest containing features associated with nodules. Figure 1 is a block diagram illustrating the ClearRead CT nodule detection process.
The system receives, as input, a thoracic CT scan along with its associated acquisition parameters (pixel spacing, slice spacing, and slice thickness) via the DICOM header. The first step, volume preparation, segments the reconstruction circle so that the content outside this region can be excluded from further consideration. The next step is body segmentation. Body segmentation uses a combination of thresholding and morphological post-processing to separate patient tissue from the surrounding air and table content. After body segmentation, air segmentation is performed. Air segmentation detects air regions within the patient's body using a combination of thresholding and morphological post-processing. After the body and air components have been segmented, volume normalization is performed. In volume normalization we standardize the appearance of CT scans so that they have similar noise, contrast, and voxel dimensions.

Once the CT scan has been normalized, it is passed to airway segmentation. This routine begins by finding the trachea to separate the left and right lungs. Once the airways have been segmented the next step is lung segmentation. The segmentation of the lungs is done using a series of thresholding, airway suppression, and morphological post-processing. As part of lung segmentation
routine, the left and right lungs are defined separately as merging can happen if care is not taken. ClearRead CT is designed to detect nodules only within the lung-field region. Regions outside the lungs are not considered for nodule detection.

Having normalized the CT volume for acquisition effects, and having segmented the lung field from the rest of the body, ClearRead CT then begins the vessel suppression process.

The vessel suppression module takes the normalized CT scan and associated lung segmentation as inputs. As an output, it generates a version of the normalized CT scan where vascular structure is suppressed (it also removes structures such as bronchial walls and fissure lines). It does not, however, remove nodular structures. This includes nodules that may be attached to vascular structure. The normalized image and vessel suppressed volume are fed to the nodule detection process.

Figure 2 provides a high-level diagram of the CAD solution for ClearRead CT. The ROI generation process uses a combination of thresholding and morphological post-processing on the lung regions within the vessel suppressed volume. Post detection, the candidate ROIs are sent to the ROI feature extraction step. The feature extraction module computes a collection of measurements meant to separate true nodules from non-nodules. Example of non-nodules includes residual vessel, bronchial structures, protrusions on the pleural surface that are not nodules, or lung tissue in the ground glass range. Once features have been computed for each ROI, the ROI classification is invoked.

![Diagram of ClearRead CT CAD Characterization Engine](image)

The ROI classification step labels each ROI as nodule or non-nodule. The ROI classification step removes suspected calcified nodules by rejecting ROIs whose average density exceeds 200HU, or 250HU in the case of contrast scans. The ROI classification module limits the number of ROIs to at most five, where the ROIs with the highest classifier scores are selected. Lastly, the CAD engine returns four measurements extracted for the purpose of characterizing an ROI. Each of the four measurements has clinical significance that could aid a clinician in their decision task and although simple for a CAD to measure, are
burdensome for the radiologist at best or in some cases not possible (e.g., volume). The four measurements returned are as follows:

- **Volume**
  - The estimated volume in the segmented region in mm³ units.

- **Maximum Diameter**
  - The largest diameter of the segmented region along the axial direction, in mm units.

- **Minimum Diameter**
  - The length of the diameter perpendicular to the one yielding the maximum, in mm units.

- **Average Density**
  - The median Hounsfield value within the entire segmented region, as measured from the original CT volume.

### 7: Performance Expectations

#### 7.1: General Performance Characteristics

ClearRead CT has been designed to detect nodules greater than or equal to 5mm in size. However, ClearRead CT may detect some nodules smaller than 5mm in diameter.

In a blind, third-party study of pathology-proven cancers, ClearRead CT detected 89.5% of known cancers. Cancers were both comprised of solid, mixed and ground glass. The average false positive rate per normal patient was 0.7469 false positives per CT series. For emphasis, it is noted that ClearRead CT and the radiologist will not necessarily detect the same nodules.

#### 7.2: ROI Markers

ClearRead CT uses the segmented contour on the center slice with ellipses on +/- one slice to indicate a region of interest. The circles are drawn on the image as white circles with a gray outline (if the burned in option is chosen). This provides visibility of the circle in both lucent and dense regions of the image.

The device allows for configuration of the CAD marker display. It is possible to display the CAD markers on both series: the original and the vessel suppressed. Alternatively, the system can be configured to display the CAD markers on the vessel suppressed volume only.
7.3: ROI Characteristics

ClearRead CT computes four measurements related to each ROI - volume, maximum diameter, minimum diameter and average density. The ROI characteristics and related information is displayed as an overlay in the bottom left corner of the center slice, and +/- one slice to the center slice of the ROI. This provides visibility of the ROI and its associated characteristic information without obscuring the underlying or surrounding tissues.

The device allows for configuration of the ROI characteristics display. It is possible to display the ROI information either in the bottom left corner or in the top left corner of the image. Alternatively, the user can choose not to display the computed ROI characteristic information.

7.4: True Positive and False Positive Marker Types

A ClearRead CT true positive is a case in which ClearRead CT correctly detects a nodule. It may direct the radiologist to an area of the CT containing a previously unidentified lesion. True positive detections are the goal of ClearRead CT, while minimizing the number of false positives.

A ClearRead CT false positive is a case where ClearRead CT marks a region and there is no lung nodule. The following are the predominant sources of false positives:

Benign Pathologies:
- Scars
- Mucous plugs
- Pleural plaques

Other Pathologies:
- Tuberculosis (TB)
- Pneumonia
- Presence of other lung diseases such as Emphysema, Pulmonary Embolism, etc.

Normal Anatomy:
- Residual vessel
- Bronchial structures
- Protrusions on the pleural surface

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
8: Using ClearRead CT

8.1: INTERPRETING A CASE

The radiologist reviews a chest CT concurrently with the vessel suppressed volume. The radiologist reviews the marked regions using the original images and determines whether any action is required. Although the ClearRead CT marker is typically centered on the region of interest, it is possible some markers will not be perfectly centered.

8.2: DETECTION ERRORS VS. INTERPRETATION ERRORS

There are two types of errors in cancer detection:

- In an oversight error, the radiologist fails to see a nodule.
- In an interpretation error, the radiologist sees a nodule but decides it is not actionable.

Computer-aided detection (CAD) helps decrease oversight errors. In this process, the computer aids the radiologist in reducing oversight error.

8.3: HOW TO RESPOND TO CLEARREAD CT MARKERS

If upon review of the ROI, a nodule or other abnormality is observed, the radiologist should proceed according to their usual protocol for the type of abnormality observed.

When ClearRead CT has marked a finding that the radiologist can see but determines it is likely benign, the criteria for ordering further evaluation should be the same as if the radiologist noticed the finding without the use of the ClearRead CT system.

If there is no clear explanation for the cause of the marked ROI, the radiologist should dismiss the region as a false positive.

8.4: POTENTIAL EFFECTS OF CLEARREAD CT FALSE NEGATIVES

A ClearRead CT false negative is a case in which the computer fails to mark a true lung nodule. As previously indicated, the device will not mark all nodules. Therefore, the clinical action should never be reversed based on the absence of a ClearRead CT marker.
9: Configurability: Selective Processing

ClearRead CT has the ability to filter images using Boolean logic operations on any of the fields in the DICOM header. This filter allows ClearRead CT to distinguish chest CT volumes from other incorrect modalities or anatomy. Thus, it is important that your images contain DICOM headers that are properly populated according to the DICOM standard and that accurately reflect the acquisition and anatomical properties of the image. In addition to selecting only chest CT series, the filter may be extended to control demographic or other characteristics of the images sent to ClearRead CT. For example, the filter can be used to exclude pediatric exams, or to reject images from a particular modality.

10: Contraindications

There are no contraindications for use of the device.

11: Adverse Effects

There are no known direct risks to the health or safety of the patient from the physical use of the ClearRead CT system. This is a post-processing application and does not require additional radiation dose to the patient.

Possible indirect risks are:

- The physician may be dissuaded from working up an earlier finding if the device fails to mark that site, thus missing a possible nodule.
- The physician may be misled into working up a benign finding that would not otherwise have been acted upon.

12: Conformance to Standards

The ClearRead CT system conforms to the DICOM standards for digital communications of medical information.

13: Connectivity

The modality-acquired CT series can be sent to ClearRead CT directly from the modality or from a PACS, where the source of the series is a CT device.
ClearRead CT receives images according to DICOM\textsuperscript{2} protocol\textsuperscript{2} (via a standard IEEE 802.3 network connection), processes the chest CT, and outputs the resulting information and/or images through the same 802.3 network connection using the DICOM protocol. Image inputs are limited to Computed Tomography (CT). The output results are sent for physicians to review on one or more devices that conform to the ClearRead CT DICOM Conformance Statement.

The workflow in which ClearRead CT can receive images to process is shown in Figure 3. In one realization of this workflow, ClearRead CT receives the image directly from any of the modalities. In this mode of operation, ClearRead CT receives the input image from the modality, processes the image, and sends the image on to the PACS. ClearRead CT populates the DICOM header of the derived ClearRead CT objects so that it is stored as part of the same study as the original chest CT exam.

In another realization of this workflow, ClearRead CT receives images directly from the PACS. In this mode of operation, ClearRead CT receives the input image from the PACS, processes the image, and sends the ClearRead CT image back to the PACS. ClearRead CT populates the DICOM header of the derived ClearRead CT objects so that it is stored as part of the same study as the original chest CT exam.

![Diagram of ClearRead CT Workflow](image)

**Figure 3 - ClearRead CT Workflow: Receiving Images from Modality or PACS**

14: **Examples of ClearRead CT Detection**

The following figures provide typical outputs from ClearRead CT. ROIs are displayed as overlays with computed characteristics - avg density (HU), max diameter (mm), min diameter (mm) and volume (mm\textsuperscript{3}), shown in the bottom right corner. The ROI contour and its associated computed characteristic information can also be burned in to the image depending on the

---

\textsuperscript{2} DICOM is the registered trademark of the National Electrical Manufacturers Association for its standards publications relating to digital communications of medical information.
configuration setting. In the following examples of ClearRead CT detections, note the following:

- Some examples show the full image so as to place the ROI in context, others show a magnified view of the ROIs for clarity.
- In each example, the ROI is indicated by an overlay. Note that if a burn-in option is chosen, the white circle and black outline are both required to clearly see the contour on light and dark portions of the image.
- In some examples, more than one ROI is visible.

The following examples are provided:

- Examples 1 to 6: True positive detections. In these examples, ClearRead CT detected truth confirmed nodules.
- Example 7: True positive and false positive mark on the same image.
- Example 8: Image with the most common false positives explained.
- Examples 9-10: Images with the most common false negatives explained.
- Examples 11-12: Images where the nodules are under segmented.

**EXAMPLE 1: TRUE POSITIVE DETECTION**

![CT slice examples](image)

Shown here is a CT slice containing large nodule (left), vessel suppressed CT slice with the segmented contour and the associated characteristics as produced by the CAD engine (right). For quick reference, the mark number is indicated along with the ROI contour. Note, the associated ROI mark number and CAD engine computed characteristics are shown in the bottom right corner.
**EXAMPLE 2: TRUE POSITIVE DETECTION**

Shown above is a small nodule as marked by the CAD engine. Other nodule marked by the CAD engine can also be seen on the same slice. For quick reference, the mark number is indicated along with the ROI contour. When more than one nodule is present on the same slice, the ROI characteristic information is displayed in a tabular format as shown. Note that depending on the configuration setting, the ROI characteristic information can be displayed either in the bottom right corner (default) or in the top right corner of the image. Note, the small pleural nodule above the two indicated was not marked due to the rank limit of five.
**EXAMPLE 3: TRUE POSITIVE DETECTION**

This example shows a cavitated nodule as marked by the CAD engine.

**EXAMPLE 4: TRUE POSITIVE DETECTION**

This example shows a small nodule as marked by the CAD engine. Note that ClearRead CT has been designed to detect nodules greater than or equal to 5mm in size. However, ClearRead CT may detect some nodules smaller than 5mm in diameter.
This example shows a sub-solid nodule marked by the CAD engine. Note the spurious ground glass content that is not marked by the CAD.

**Example 5:** TRUE POSITIVE DETECTION

This example shows a ground glass nodule marked by the CAD engine.

**Example 6:** TRUE POSITIVE DETECTION
false positive residual in the left lung in the vessel suppressed series.

This example shows a sub-solid nodule marked by the CAD engine. Note the

EXAMPLE 7: TRUE POSITIVE & FALSE POSITIVES

EXAMPLE 8: FALSE POSITIVES
This example shows a false positive from vessel branching marked by the CAD engine.

**EXAMPLE 9: FALSE NEGATIVE**

This example shows a nodule not marked by the CAD engine. This CT series has more than 5 nodules. However, ranking leads to loss of TPs as the maximum number of cad marks is limited to 5. Note the clear visibility of the nodule in the vessel suppressed series.
**EXAMPLE 10: FALSE NEGATIVE**

This example shows a false negative due to vessel merger.

**EXAMPLE 11: NODULE UNDER SEGMENTED**

This example shows a peripheral nodule marked by the CAD engine. The segmented contour shows that the nodule is under segmented due to proximity to the lung border and bone structures.
**EXAMPLE 12: NODULE UNDER SEGMENTED**

This example shows a nodule marked by the CAD engine. Note that the vessel nodule merging leads to inaccurate segmentation.

15: Possible Error Messages

If the ClearRead CT system is unable to process an image, you will see the text "Image processing unsuccessful" displayed on a blank image.

It is important to note that incorrect DICOM headers can cause ClearRead CT to reject an input image for processing, in which case no result will be returned for viewing. Do not delay reading of the primary image in order to view the ClearRead CT result.
16: ClearRead CT Clinical Study

INTRODUCTION
The Arlington Innovation Center for Health Research of Virginia Tech, (Virginia) performed a clinical study of ClearRead CT.

STUDY SUMMARY
In a multi-reader multi-case (MRMC) reader study, radiologists interpreted images in order to compare the radiologists’ ability to detect pulmonary nodules when they were aided by the ClearRead CT application. The reader study’s primary test metric was the difference in the partial area under the curve (pAUC) derived from the localization receiver operating characteristic (LROC) curve when using ClearRead CT relative to the unaided reads. Additionally, radiologist’s interpretation time when using ClearRead CT relative to unaided interpretations was measured. These results along with other secondary measures are captured below.

STUDY DATA DESCRIPTION

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2-3.0 mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40 – 357 mA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5-20mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt; -800 HU to ≤ 200 HU</td>
</tr>
</tbody>
</table>
**Reader Study**

Twelve radiologists participated in each of the three reader arms. The readers had no prior knowledge of the cases, interpreted the lung CT series either with or without the aid of the ClearRead CT aids and were instructed to report actionable nodules, or image locations in the CT series with suspicious nodular features for which radiologist(s) recommends further examination, along with a degree of suspicion for marked areas. Readers could record up to 5 locations corresponding to actionable nodules greater than or equal to 5mm. In the first reader arm (Reader Arm 1), readers were provided only the original CT series. After a washout period (minimum of 37 days), readers read concurrently with the ClearRead CT application (the vessel suppressed series along with CAD markings and characterizations) using the same CT cases. This is referred to as Reader Arm 2. Case order was re-randomized for each reader in Reader Arm 2.

In the third reader arm (Reader Arm 3), actionable cases and normal cases were equally split according to a pre-specified criteria. Once split, readers were randomly assigned to read one of the two blocks with ClearRead CT and the other block without ClearRead CT. Data from all three reader arms was pooled and analyzed based on established test hypotheses.

The results are summarized in the following tables, with lower and upper 95% confidence limits:
Superiority of CRCT over UA for Detection of Actionable Nodules (n=178) When Compared to Normal Cases (n=216): LROC pAUC*

* Note: As the interval does not include “0”, superiority can be concluded

The overall ability of ClearRead CT to detect actionable nodule cases is superior (i.e. statistically significantly better than) to unaided reads.

As shown below, the aided reader detected approximate 11.58% more actionable nodules, or equivalently, reduced oversite of actionable nodules by approximately 29%. Using the same two groups of nodules as in the LROC AUC analysis above, sensitivity, specificity, PPV and NPV were estimated by modality and tested for equality using the linear mixed model setting. The table below presents the summary of prediction measures within each modality for actionable nodules versus normal. For sensitivity, there is a statistically significant improvement in reads using CRCT versus unaided for detecting cancer nodules and for detecting any nodules in general. However, specificity is significantly lower in the CRCT reads.

<table>
<thead>
<tr>
<th>Predictive Measure</th>
<th>Read</th>
<th>Estimate</th>
<th>Std Error</th>
<th>Difference</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>CRCT</td>
<td>0.7194</td>
<td>0.0233</td>
<td>0.1158</td>
<td>0.0001</td>
<td>0.0610</td>
<td>0.1706</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.6036</td>
<td>0.0233</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>CRCT</td>
<td>0.7285</td>
<td>0.0283</td>
<td>-0.0857</td>
<td>0.0010</td>
<td>-0.1345</td>
<td>-0.0368</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.8142</td>
<td>0.0283</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>CRCT</td>
<td>0.6543</td>
<td>0.0291</td>
<td>-0.0736</td>
<td>0.0095</td>
<td>-0.1283</td>
<td>-0.0189</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.7278</td>
<td>0.0291</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Estimates of sensitivity, specificity, PPV, NPV and the associated 95% CIs, across modality for all actionable nodules and normal cases

Read Times:
As the distribution of read times in seconds within each modality were skewed, a log transformation was applied to the time data in order to generate more symmetric distribution of times (i.e. to meet normality assumption). Given the analysis was performed to obtain the difference in the times on the log scale, the back-transformed values are the estimate and 95% CI on the LS mean for each modality separately were calculated and transformed into seconds from milliseconds. The tables below provide the estimated LS mean reading times by modality on a log scale and then back-transformed to the original scale. The reduction in average read time from UA to CRCT was almost half a minute per case (mean differences of 29.0 and 28.4 seconds, respectively).

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>Std Error</th>
<th>CRCT-UA</th>
<th>Std Error</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>11.343</td>
<td>0.073</td>
<td>-0.295</td>
<td>0.0720</td>
<td>0.0002</td>
<td>-0.440</td>
<td>-0.150</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>11.639</td>
<td>0.073</td>
<td>-0.288</td>
<td>0.0677</td>
<td>0.0001</td>
<td>-0.424</td>
<td>-0.151</td>
</tr>
<tr>
<td>Without outliers</td>
<td>CRCT</td>
<td>11.352</td>
<td>0.071</td>
<td>-0.288</td>
<td>0.0677</td>
<td>0.0001</td>
<td>-0.424</td>
<td>-0.151</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>11.639</td>
<td>0.071</td>
<td>-0.288</td>
<td>0.0677</td>
<td>0.0001</td>
<td>-0.424</td>
<td>-0.151</td>
</tr>
</tbody>
</table>

Note: As the 95% confidence interval of difference in read time (log(milliseconds)) for CRCT-UA falls completely below "0", superiority can be concluded.

Estimates of effects and LS means for reading times, on log scale

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>LS Mean Times (back-transformed to seconds)</th>
<th>CRCT-UA (calculated from back-transformed) (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Estimate</td>
<td>95% Lower CL</td>
</tr>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>84.4</td>
<td>72.8</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.4</td>
<td>97.8</td>
</tr>
<tr>
<td>Model</td>
<td>Modality</td>
<td>Estimate</td>
<td>95% Lower CL</td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>----------</td>
<td>--------------</td>
</tr>
<tr>
<td>Without outliers</td>
<td>CRCT</td>
<td>85.1</td>
<td>73.8</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.5</td>
<td>98.4</td>
</tr>
</tbody>
</table>

**Estimate of reading times and LS Mean differences, back transformed to seconds**

It can be concluded that ClearRead read times are lower than unaided read times and that this difference in read times is statistically significant. This is demonstrated in both all read times and in the subset of read times within 3 standard deviations of the mean read time. This equates to a 26% reduction in read time when using CRCT as compared to the unaided read when using all data.

**MACHINE TEST**

Using the clinical data and machine only results, the free response operating characteristic (FROC) curve was derived. The free-response operating characteristic curve is a plot of the sensitivity (proportion of nodules correctly marked) versus the false positive rate per patient in the normal (non-nodule) cases. At the clinical operating point, the sensitivity is 0.8947 and 0.8202 for cancers and all nodules, respectively. The corresponding false positive rate per patient or per case was 0.7469 as illustrated by the dashed lines, in the following figure.
FROC Curve

FROC curve for CRCT on clinical data. This chart displays the CRCT FROC curves of stand-alone machine performance for true positive detection of cancer nodules alone and combined cancers and all combined nodules.

The breakdown of nodule subtypes and results are detailed below:

<table>
<thead>
<tr>
<th>Nodule Type</th>
<th>Solid</th>
<th>Sub-Solid</th>
<th>GGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRCT Machine Detection (%)</td>
<td>84.17%</td>
<td>85.29%</td>
<td>66.67%</td>
</tr>
<tr>
<td>Unaided Average Reader Detection (%)</td>
<td>61.11%</td>
<td>58.33%</td>
<td>57.29%</td>
</tr>
<tr>
<td>Nodule Count</td>
<td>120</td>
<td>34</td>
<td>24</td>
</tr>
</tbody>
</table>

Machine vs. Reader Performance Across Nodule Type
The best practice requires the best tools.

CT Suite
ClearRead
Manual
Physician's Training

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Safe Operation Precautions

GENERAL USE WARNINGS

⚠️ WARNING: Use of the device on any image projection other than the axial CT chest views is not supported.

⚠️ WARNING: Only the original chest CT series is to be used for diagnostic interpretation by physicians. ClearRead CT output is designed only as an aid to the interpretation process.

⚠️ WARNING: For continued safe use of this equipment, follow the instructions contained in this Physician’s Training Manual. Read this guide carefully before using the equipment, and refer to it as necessary.

⚠️ WARNING: Federal law restricts this device to sale by or on the order of a physician.

⚠️ WARNING: Conditions of image quality that diminish chest radiographic sensitivity, such as under- or over-exposure or artifacts, may also diminish the effectiveness of the device.

⚠️ WARNING: Incorrect DICOM headers or other factors can cause ClearRead CT to reject an input CT series for processing, in which case no result will be returned for viewing. Do not delay your reading of the primary image in order to view the ClearRead CT output.

⚠️ WARNING: ClearRead CT relies on Patient Position and Patient Orientation information from the DICOM header. If the header is incorrect, the system might fail to process the series.

⚠️ WARNING: Users should never be dissuaded from working up an earlier finding even if it is not seen on the ClearRead CT output image. The device will not identify all areas that represent nodules.

⚠️ WARNING: ClearRead CT has an option to send CAD results with an overlay. If your site uses a PACS that can receive and display overlays, and your ClearRead CT has been configured to send overlays, you must establish controls to prevent or record user editing of the CAD results.

⚠️ WARNING: ClearRead CT is a medical device. It should be used only as described in the accompanying Riverain manuals. Other activities (such as web browsing, email, or installation of third-party software without specific authorization from Riverain) are prohibited. Software authorized by Riverain Technologies should be scanned with anti-virus software before use.

⚠️ NOTE: A standard CT series is expected to contain both lungs. Images not containing both lungs might fail to be processed.
Table of Contents

1 : Introduction .................................................. 6
2 : Definitions .................................................... 6
3 : Indications for Use ........................................... 6
4 : Motivation for Creating ClearRead CT ...................... 7
5 : Summary of ClearRead CT .................................. 7
6 : How ClearRead CT Works .................................. 7
7 : Performance Expectations ................................... 10
  7.1 : General Performance Characteristics .................. 10
  7.2 : ROI Markers ............................................. 10
  7.3 : ROI Characteristics ................................... 11
  7.4 : True Positive And False Positive Marker Types ....... 11
8 : Using ClearRead CT ......................................... 12
  8.1 : Interpreting A Case ..................................... 12
  8.2 : Detection Errors vs. Interpretation Errors ........... 12
  8.3 : How to Respond to ClearRead CT Markers .......... 12
  8.4 : Potential Effects of ClearRead CT False Negatives .. 12
9 : Configurability: Selective Processing ..................... 13
10 : Contraindications ........................................... 13
11 : Adverse Effects ............................................ 13
12 : Conformance to Standards ................................ 13
13 : Connectivity ............................................... 13
14 : Examples of ClearRead CT Detection ...................... 14
  Example 1: True Positive Detection ....................... 15
  Example 2: True Positive Detection ....................... 16
  Example 3: True Positive Detection ....................... 17
  Example 4: True Positive Detection ....................... 17
  Example 5: True Positive Detection ....................... 18
  Example 6: True Positive Detection ....................... 18
  Example 7: True Positive & False Positives ............ 19
  Example 8: False Positives ................................ 19
  Example 9: False Negative ................................ 20
  Example 10: False Negative ................................. 20
  Example 11: Nodule Under Segmented .................... 21
  Example 12: Nodule Under Segmented .................... 22
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>15: Possible Error Messages</td>
<td>22</td>
</tr>
<tr>
<td>16: ClearRead CT Clinical Study</td>
<td>24</td>
</tr>
<tr>
<td>Introduction</td>
<td>24</td>
</tr>
<tr>
<td>Study Summary</td>
<td>24</td>
</tr>
<tr>
<td>Study Data Description</td>
<td>24</td>
</tr>
<tr>
<td>Reader Study</td>
<td>25</td>
</tr>
<tr>
<td>Machine Test</td>
<td>2928</td>
</tr>
</tbody>
</table>
1: Introduction

Your institution has installed the Riverain ClearRead CT system for chest computed tomography volumes. ClearRead CT consists of Computer-Aided Detection (CAD) markers on a vessel suppressed volume. The CAD component identifies regions of interest associated with solid, sub-solid, and/or ground glass nodules. This manual provides physicians who use the ClearRead CT system with an understanding of how the system works, what to expect when using ClearRead CT, and most importantly, the indications for use.

For any questions or concerns not addressed in this manual, go to:

http://www.riveraintech.com

Or contact Riverain Technologies directly at the address below:
Riverain Technologies
3020 S. Tech Blvd
Miamisburg, Ohio 45342
+1-800-990-3387
info@riveraintech.com

2: Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actionable</td>
<td>Image locations in the CT series with suspicious nodular features, i.e., characteristics, for which radiologist(s) recommends further examination, typically through analysis of a prior exam and/or additional imaging such as follow-up CT, diagnostic CT, PET-CT, etc.</td>
</tr>
<tr>
<td>Nodule</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>Computer-Aided Detection</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>ROI</td>
<td>Region Of Interest</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications In Medicine</td>
</tr>
<tr>
<td>802.3</td>
<td>IEEE Standard for Wired Ethernet</td>
</tr>
</tbody>
</table>

3: Indications for Use

ClearRead CT is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.
4: Motivation for Creating ClearRead CT

Low dose CT is the preferred method for annual lung cancer screening for at-risk patients. However, interpreting a chest CT is a challenging task, owing to the large number of images commonly present in a chest CT series and number of interfering structures that compete with the detection of lung nodules. Given the clinical importance of detection of lung cancer using CT, it is clear that a technology that aids in the detection of nodules would be useful to medical professionals and patients alike.

The American Cancer Society statistics show that if lung cancer is found early enough, the 5-year survival rates more than triples. A proactive approach to early lung cancer detection is essential to turning the tide in the fight against this devastating disease. ClearRead CT is designed to provide assistance in the detection of nodules which may represent cancer.

5: Summary of ClearRead CT

ClearRead CT is a computer-aided detection (CAD) system intended to identify and mark regions of interest (ROIs). The ClearRead CT system operates on a chest CT exam. It identifies nodules, optimized for those between 5mm and 30mm in size. The system is limited to marking 5 ROIs per CT series deemed to be worthy of review. The use of ClearRead CT leads to a reduction in oversight errors.

6: How ClearRead CT Works

ClearRead CT is a software solution for automated detection of solid, sub-solid, and/or ground glass nodules designed to operate on chest CT exams. ClearRead CT relies on advanced algorithms from the engineering disciplines of image analysis and machine learning. The algorithms compute measurements to analyze the tissue in the CT series.

The software performs a series of steps to detect regions of interest containing features associated with nodules. Figure 1 is a block diagram illustrating the ClearRead CT nodule detection process.
Figure 1 - ClearRead CT Process Diagram

The system receives, as input, a thoracic CT scan along with its associated acquisition parameters (pixel spacing, slice spacing, and slice thickness) via the DICOM header. The first step, volume preparation, segments the reconstruction circle so that the content outside this region can be excluded from further consideration. The next step is body segmentation. Body segmentation uses a combination of thresholding and morphological post-processing to separate patient tissue from the surrounding air and table content. After body segmentation, air segmentation is performed. Air segmentation detects air regions within the patient's body using a combination of thresholding and morphological post-processing. After the body and air components have been segmented, volume normalization is performed. In volume normalization we standardize the appearance of CT scans so that they have similar noise, contrast, and voxel dimensions.

Once the CT scan has been normalized, it is passed to airway segmentation. This routine begins by finding the trachea to separate the left and right lungs. Once the airways have been segmented the next step is lung segmentation. The segmentation of the lungs is done using a series of thresholding, airway suppression, and morphological post-processing. As part of lung segmentation
routine, the left and right lungs are defined separately as merging can happen if care is not taken. ClearRead CT is designed to detect nodules only within the lung-field region. Regions outside the lungs are not considered for nodule detection.

Having normalized the CT volume for acquisition effects, and having segmented the lung field from the rest of the body, ClearRead CT then begins the vessel suppression process.

The vessel suppression module takes the normalized CT scan and associated lung segmentation as inputs. As an output, it generates a version of the normalized CT scan where vascular structure is suppressed (it also removes structures such as bronchial walls and fissure lines). It does not, however, remove nodular structures. This includes nodules that may be attached to vascular structure. The normalized image and vessel suppressed volume are fed to the nodule detection process.

Figure 2 provides a high-level diagram of the CAD solution for ClearRead CT. The ROI generation process uses a combination of thresholding and morphological post-processing on the lung regions within the vessel suppressed volume. Post detection, the candidate ROIs are sent to the ROI feature extraction step. The feature extraction module computes a collection of measurements meant to separate true nodules from non-nodules. Example of non-nodules includes residual vessel, bronchial structures, protrusions on the pleural surface that are not nodules, or lung tissue in the ground glass range. Once features have been computed for each ROI, the ROI classification is invoked.

![Figure 2 - ClearRead CT CAD Characterization Engine](attachment:image)

The ROI classification step labels each ROI as nodule or non-nodule. The ROI classification step removes suspected calcified nodules by rejecting ROIs whose average density exceeds 200HU, or 250HU in the case of contrast scans. The ROI classification module limits the number of ROIs to at most five, where the ROIs with the highest classifier scores are selected. Lastly, the CAD engine returns four measurements extracted for the purpose of characterizing an ROI. Each of the four measurements has clinical significance that could aid a clinician in their decision task and although simple for a CAD to measure, are
burdensome for the radiologist at best or in some cases not possible (e.g., volume). The four measurements returned are as follows:

- **Volume**
  - The estimated volume in the segmented region in \( \text{mm}^3 \) units.

- **Maximum Diameter**
  - The largest diameter of the segmented region along the axial direction, in \( \text{mm} \) units.

- **Minimum Diameter**
  - The length of the diameter perpendicular to the one yielding the maximum, in \( \text{mm} \) units.

- **Average Density**
  - The median Hounsfield value within the entire segmented region, as measured from the original CT volume.

# 7: Performance Expectations

## 7.1: General Performance Characteristics

ClearRead CT has been designed to detect nodules greater than or equal to 5\( \text{mm} \) in size. However, ClearRead CT may detect some nodules smaller than 5\( \text{mm} \) in diameter.

In a blind, third-party study of pathology-proven cancers, ClearRead CT detected 89.5% of known cancers. Cancers were both comprised of solid, mixed and ground glass. The average false positive rate per normal patient was 0.7469 false positives per CT series. For emphasis, it is noted that ClearRead CT and the radiologist will not necessarily detect the same nodules.

## 7.2: ROI Markers

ClearRead CT uses the segmented contour on the center slice with ellipses on +/- one slice to indicate a region of interest. The circles are drawn on the image as white circles with a gray outline (if the burned in option is chosen). This provides visibility of the circle in both lucent and dense regions of the image.

The device allows for configuration of the CAD marker display. It is possible to display the CAD markers on both series: the original and the vessel suppressed. Alternatively, the system can be configured to display the CAD markers on the vessel suppressed volume only.
7.3: ROI CHARACTERISTICS

ClearRead CT computes four measurements related to each ROI - volume, maximum diameter, minimum diameter and average density. The ROI characteristics and related information is displayed as an overlay in the bottom left corner of the center slice, and +/- one slice to the center slice of the ROI. This provides visibility of the ROI and its associated characteristic information without obscuring the underlying or surrounding tissues.

The device allows for configuration of the ROI characteristics display. It is possible to display the ROI information either in the bottom left corner or in the top left corner of the image. Alternatively, the user can choose not to display the computed ROI characteristic information.

7.4: TRUE POSITIVE AND FALSE POSITIVE MARKER TYPES

A ClearRead CT true positive is a case in which ClearRead CT correctly detects a nodule. It may direct the radiologist to an area of the CT containing a previously unidentified lesion. True positive detections are the goal of ClearRead CT, while minimizing the number of false positives.

A ClearRead CT false positive is a case where ClearRead CT marks a region and there is no lung nodule. The following are the predominant sources of false positives:

Benign Pathologies:
- Scars
- Mucous plugs
- Pleural plaques

Other Pathologies:
- Tuberculosis (TB)
- Pneumonia
- Presence of other lung diseases such as Emphysema, Pulmonary Embolism, etc.

Normal Anatomy:
- Residual vessel
- Bronchial structures
- Protrusions on the pleural surface
8: Using ClearRead CT

8.1: INTERPRETING A CASE

The radiologist reviews a chest CT concurrently with the vessel suppressed volume. The radiologist reviews the marked regions using the original images and determines whether any action is required. Although the ClearRead CT marker is typically centered on the region of interest, it is possible some markers will not be perfectly centered.

8.2: DETECTION ERRORS VS. INTERPRETATION ERRORS

There are two types of errors in cancer detection:

- In an oversight error, the radiologist fails to see a nodule.
- In an interpretation error, the radiologist sees a nodule but decides it is not actionable.

Computer-aided detection (CAD) helps decrease oversight errors. In this process, the computer aids the radiologist in reducing oversight error.

8.3: HOW TO RESPOND TO CLEARREAD CT MARKERS

If upon review of the ROI, a nodule or other abnormality is observed, the radiologist should proceed according to their usual protocol for the type of abnormality observed.

When ClearRead CT has marked a finding that the radiologist can see but determines it is likely benign, the criteria for ordering further evaluation should be the same as if the radiologist noticed the finding without the use of the ClearRead CT system.

If there is no clear explanation for the cause of the marked ROI, the radiologist should dismiss the region as a false positive.

8.4: POTENTIAL EFFECTS OF CLEARREAD CT FALSE NEGATIVES

A ClearRead CT false negative is a case in which the computer fails to mark a true lung nodule. As previously indicated, the device will not mark all nodules. Therefore, the clinical action should never be reversed based on the absence of a ClearRead CT marker.
9: Configurability: Selective Processing

ClearRead CT has the ability to filter images using Boolean logic operations on any of the fields in the DICOM header. This filter allows ClearRead CT to distinguish chest CT volumes from other incorrect modalities or anatomy. Thus, it is important that your images contain DICOM headers that are properly populated according to the DICOM standard and that accurately reflect the acquisition and anatomical properties of the image. In addition to selecting only chest CT series, the filter may be extended to control demographic or other characteristics of the images sent to ClearRead CT. For example, the filter can be used to exclude pediatric exams, or to reject images from a particular modality.

10: Contraindications

There are no contraindications for use of the device.

11: Adverse Effects

There are no known direct risks to the health or safety of the patient from the physical use of the ClearRead CT system. This is a post-processing application and does not require additional radiation dose to the patient.

Possible indirect risks are:

- The physician may be dissuaded from working up an earlier finding if the device fails to mark that site, thus missing a possible nodule.
- The physician may be misled into working up a benign finding that would not otherwise have been acted upon.

12: Conformance to Standards

The ClearRead CT system conforms to the DICOM standards for digital communications of medical information.

13: Connectivity

The modality-acquired CT series can be sent to ClearRead CT directly from the modality or from a PACS, where the source of the series is a CT device.
ClearRead CT receives images according to DICOM® protocol (via a standard IEEE 802.3 network connection), processes the chest CT, and outputs the resulting information and/or images through the same 802.3 network connection using the DICOM protocol. Image inputs are limited to Computed Tomography (CT). The output results are sent for physicians to review on one or more devices that conform to the ClearRead CT DICOM Conformance Statement.

The workflow in which ClearRead CT can receive images to process is shown in Figure 3. In one realization of this workflow, ClearRead CT receives the image directly from any of the modalities. In this mode of operation, ClearRead CT receives the input image from the modality, processes the image, and sends the image on to the PACS. ClearRead CT populates the DICOM header of the derived ClearRead CT objects so that it is stored as part of the same study as the original chest CT exam.

In another realization of this workflow, ClearRead CT receives images directly from the PACS. In this mode of operation, ClearRead CT receives the input image from the PACS, processes the image, and sends the ClearRead CT image back to the PACS. ClearRead CT populates the DICOM header of the derived ClearRead CT objects so that it is stored as part of the same study as the original chest CT exam.

![Figure 3 - ClearRead CT Workflow: Receiving Images from Modality or PACS](image)

**14: Examples of ClearRead CT Detection**

The following figures provide typical outputs from ClearRead CT. ROIs are displayed as overlays with computed characteristics - avg density (HU), max diameter (mm), mindiameter (mm) and volume (mm³), shown in the bottom right corner. The ROI contour and its associated computed characteristic information can also be burned in to the image depending on the

---

2. DICOM is the registered trademark of the National Electrical Manufacturers Association for its standards publications relating to digital communications of medical information.
configuration setting. In the following examples of ClearRead CT detections, note the following:

- Some examples show the full image so as to place the ROI in context, others show a magnified view of the ROIs for clarity.
- In each example, the ROI is indicated by an overlay. Note that if a burn-in option is chosen, the white circle and black outline are both required to clearly see the contour on light and dark portions of the image.
- In some examples, more than one ROI is visible.

The following examples are provided:

- Examples 1 to 6: True positive detections. In these examples, ClearRead CT detected truth confirmed nodules.
- Example 7: True positive and false positive mark on the same image.
- Example 8: Image with the most common false positives explained.
- Examples 9-10: Images with the most common false negatives explained.
- Examples 11-12: Images where the nodules are under segmented.

**EXAMPLE 1: TRUE POSITIVE DETECTION**

Shown here is a CT slice containing large nodule (left), vessel suppressed CT slice with the segmented contour and the associated characteristics as produced by the CAD engine (right). For quick reference, the mark number is indicated along with the ROI contour. Note, the associated ROI mark number and CAD engine computed characteristics are shown in the bottom right corner.
Example 2: True Positive Detection

Shown above is a small nodule as marked by the CAD engine. Other nodules marked by the CAD engine can also be seen on the same slice. For quick reference, the mark number is indicated along with the ROI contour. When more than one nodule is present on the same slice, the ROI characteristic information is displayed in a tabular format as shown. Note that depending on the configuration setting, the ROI characteristic information can be displayed either in the bottom right corner (default) or in the top right corner of the image. Note, the small pleural nodule above the two indicated was not marked due to the rank limit of five.
**Example 3: True Positive Detection**

This example shows a cavitated nodule as marked by the CAD engine.

**Example 4: True Positive Detection**

This example shows a small nodule as marked by the CAD engine. Note that ClearRead CT has been designed to detect nodules greater than or equal to 5mm in size. However, ClearRead CT may detect some nodules smaller than 5mm in diameter.
Spurious ground glass content that is not marked by the CAD.

Example 6: True Positive Detection

This example shows a sub-solid nodule marked by the CAD engine. Note the

Example 5: True Positive Detection
This example shows a sub-solid nodule marked by the CAD engine. Note the false positive residual in the left lung in the vessel suppressed series.

Example 7: True Positive & False Positives

Example 8: False Positives
The vessel suppressed series. The number of cad marks is limited to 5. Note the clear visibility of the nodule in more than 5 modules. However, masking leads to loss of TPS as the maximum CT series has been shown to be marked by the CAD engine. This example shows a nodule not marked by the CAD engine.

**Example 9: False Negative**

This example shows a false positive from vessel branching marked by the CAD engine.

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
to the lung border and bone structures.

This example shows a peripheral nodule marked by the red outline. The segmented contour shows that the nodule is under segmented due to proximity. 

Example 11: Nodule Under Segmented

This example shows a false negative due to vessel merger.

Example 10: False Negative
EXAMPLE 12: NODULE UNDER SEGMENTED

This example shows a nodule marked by the CAD engine. Note that the vessel nodule merging leads to inaccurate segmentation.

15: Possible Error Messages

If the ClearRead CT system is unable to process an image, you will see the text "Image processing unsuccessful" displayed on a blank image.

It is important to note that incorrect DICOM headers can cause ClearRead CT to reject an input image for processing, in which case no result will be returned for viewing. Do not delay reading of the primary image in order to view the ClearRead CT result.
16: ClearRead CT Clinical Study

INTRODUCTION

The Arlington Innovation Center for Health Research of Virginia Tech, (Virginia) performed a clinical study of ClearRead CT.

STUDY SUMMARY

In a multi-reader multi-case (MRMC) reader study, radiologists interpreted images in order to compare the radiologists' ability to detect pulmonary nodules when they were aided by the ClearRead CT application. The reader study's primary test metric was the difference in the partial area under the curve (pAUC) derived from the localization receiver operating characteristic (LROC) curve when using ClearRead CT relative to the unaided reads. Additionally, radiologist's interpretation time when using ClearRead CT relative to unaided interpretations was measured. LROC pAUC was evaluated per reader and scaled to have a maximum value of 1 according to the formula

\[
pAUC_{scaled} = pAUC_{max}(sensitivity) \times max(1 - specificity)\]

where m denotes a reading modality (unaided or aided with ClearRead CT). The maximum values of sensitivity and 1 - specificity across the modalities were used to define the range over which the unscaled pAUC (numerator in formula) was calculated. These results along with other secondary measures are captured below.

STUDY DATA DESCRIPTION

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slice Thickness</td>
<td>2-3.0 mm</td>
</tr>
<tr>
<td>Exposure</td>
<td>40 – 357 mA</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Adult Lung Cancer Screening Population</td>
</tr>
<tr>
<td>Nodule Size</td>
<td>5-20mm (mean of 10)</td>
</tr>
<tr>
<td>Radiodensity</td>
<td>&gt; -800 HU to ≤ 200 HU</td>
</tr>
</tbody>
</table>
**Reader Study**

Twelve radiologists participated in each of the three reader arms. The readers had no prior knowledge of the cases, interpreted the lung CT series either with or without the aid of the ClearRead CT aids and were instructed to report actionable nodules, or image locations in the CT series with suspicious nodular features for which radiologist(s) recommends further examination, along with a degree of suspicion for marked areas. Readers could record up to 5 locations corresponding to actionable nodules greater than or equal to 5mm. In the first reader arm (Reader Arm 1), readers were provided only the original CT series. After a washout period (minimum of 37 days), readers read concurrently with the ClearRead CT application (the vessel suppressed series along with CAD markings and characterizations) using the same CT cases. This is referred to as Reader Arm 2. Case order was re-randomized for each reader in Reader Arm 2. In the third reader arm (Reader Arm 3), actionable cases and normal cases were equally split according to a pre-specified criteria. Once split, readers were randomly assigned to read one of the two blocks with ClearRead CT and the other block without ClearRead CT. Data from all three reader arms was pooled and analyzed based on established test hypotheses for reading modality (unaided or aided with ClearRead CT). Measures of performance (PAUC, sensitivity, specificity, NPV, PPV, reading time) were estimated in each reading modality after adjustment for design effects (arm, case block, order, reader). Data from all three reader arms was pooled and analyzed based on established test hypotheses.
The overall ability of ClearRead CT to detect actionable nodule cases is superior (i.e. statistically significantly better than) to unaided reads.

As shown below, the aided reader detected approximately 11.58% more actionable nodules, or equivalently, reduced oversight of actionable nodules by approximately 29%. Using the same two groups of nodules as in the LROC AUC analysis above, sensitivity, specificity, PPV and NPV were estimated by modality and tested for equality using the linear mixed model setting. The table below presents the summary of prediction measures within each modality for actionable nodules versus normal. For sensitivity, there is a statistically significant improvement in reads using CRCT versus unaided for detecting cancer nodules and for detecting any nodules in general. However, specificity is significantly lower in the CRCT reads.

<table>
<thead>
<tr>
<th>Predictive Measure</th>
<th>Read</th>
<th>Estimate</th>
<th>Std Error</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>CRCT</td>
<td>0.7194</td>
<td>0.0233</td>
<td>0.1158</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.6036</td>
<td>0.0233</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>CRCT</td>
<td>0.7285</td>
<td>0.0283</td>
<td>-0.0857</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.8142</td>
<td>0.0283</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>CRCT</td>
<td>0.6543</td>
<td>0.0291</td>
<td>-0.0736</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.7278</td>
<td>0.0291</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>CRCT</td>
<td>0.7900</td>
<td>0.0114</td>
<td>0.0521</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>0.7379</td>
<td>0.0114</td>
<td></td>
</tr>
</tbody>
</table>

Estimates of sensitivity, specificity, PPV, and NPV and the associated 95% CIs, across modality for all actionable nodules and normal cases.

Read Times:
As the distribution of read times in seconds within each modality were skewed, a log transformation was applied to the time data in order to generate more symmetric distribution of times (i.e. to meet normality assumption). Given the analysis was performed to obtain the difference in the times on the log scale, the back-transformed values are the estimate and 95% CI on the LS mean for each modality separately were calculated and transformed into seconds from milliseconds. The tables below provide the estimated LS mean reading times by modality on a log scale and then back-transformed to the original scale. The reduction in average read time from UA to CRCT was almost half a minute per case (mean differences of 29.0 and 28.4 seconds, respectively).

### Estimates of effects and LS means for reading times, on log scale

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>Std Error</th>
<th>CRCT-UA</th>
<th>Std Error</th>
<th>p-value</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>11.343</td>
<td>0.072</td>
<td>-0.295</td>
<td>0.0720</td>
<td>0.0002</td>
<td>-0.440</td>
<td>-0.150</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>11.639</td>
<td>0.072</td>
<td>-0.288</td>
<td>0.0677</td>
<td>0.0004</td>
<td>-0.424</td>
<td>-0.154</td>
</tr>
<tr>
<td>Without outliers</td>
<td>CRCT</td>
<td>11.352</td>
<td>0.074</td>
<td>-0.288</td>
<td>0.0677</td>
<td>0.0004</td>
<td>-0.424</td>
<td>-0.154</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>11.639</td>
<td>0.074</td>
<td>-0.288</td>
<td>0.0677</td>
<td>0.0004</td>
<td>-0.424</td>
<td>-0.154</td>
</tr>
</tbody>
</table>

Note: As the 95% confidence interval of difference in read time (log milliseconds)) for CRCT-UA fails completely below 100%, superiority can be concluded.

### LS Mean Times (back-transformed) to seconds

<table>
<thead>
<tr>
<th>Model</th>
<th>Modality</th>
<th>Estimate</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
<th>CRCT-UA (calculated from back-transformed) (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All read times</td>
<td>CRCT</td>
<td>84.4</td>
<td>72.8</td>
<td>97.8</td>
<td>-29.0</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.4</td>
<td>97.8</td>
<td>131.4</td>
<td></td>
</tr>
<tr>
<td>Without outliers</td>
<td>CRCT</td>
<td>85.1</td>
<td>73.8</td>
<td>98.1</td>
<td>-28.4</td>
</tr>
<tr>
<td></td>
<td>UA</td>
<td>113.5</td>
<td>98.4</td>
<td>130.9</td>
<td></td>
</tr>
</tbody>
</table>

Estimate of reading times and LS Mean differences, back transformed to seconds

It can be concluded that ClearRead read times are lower than unaided read times and that this difference in read times is statistically significant. This is demonstrated in both all read times and in the subset of read times within 3 standard deviations of the mean read time. This equates to a 26% reduction in read time when using CRCT as compared to the unaided read when using all data.
**MACHINE TEST**

Using the clinical data and machine only results, the free response operating characteristic (FROC) curve was derived. The free-response operating characteristic curve is a plot of the sensitivity (proportion of nodules correctly marked) versus the false positive rate per patient in the normal (non-nodule) cases. At the clinical operating point, the sensitivity is 0.8947 and 0.8202 for cancers and all nodules, respectively. The corresponding false positive rate per patient or per case was 0.7469 as illustrated by the dashed lines, in the following figure.

![FROC Curve](image)

**FROC curve for CRCT on clinical data.** This chart displays the CRCT FROC curves of stand-alone machine performance for true positive detection of cancer nodules alone and combined cancers and all combined nodules.
The breakdown of nodule subtypes and results are detailed below:

<table>
<thead>
<tr>
<th>Nodule Type Modality</th>
<th>Solid</th>
<th>Sub-Solid</th>
<th>GGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIRCT Machine Detection (%)</td>
<td>84.17%</td>
<td>85.29%</td>
<td>68.67%</td>
</tr>
<tr>
<td>Unaided Average Reader Detection (%)</td>
<td>61.11%</td>
<td>58.33%</td>
<td>52.29%</td>
</tr>
<tr>
<td>Nodule Count</td>
<td>120</td>
<td>34</td>
<td>24</td>
</tr>
</tbody>
</table>

**Machine vs. Reader Performance Across Nodule Type**
Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704<tel:301-796-6704>
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrcustomerservice?o=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,
Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

The primary reason for the modification of the 510(K) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, May 25, 2016 1:08 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&F=E&F=S&E

file:///C:/Users/LDT/Desktop/Training%20Material/2016-9533/Archive/K161201/Interac...11/21/2017
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(k) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(k) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(k) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

Thanks for providing a redlined copy of the 510k.

Could you please provide the data that you used for the primary analysis of mixed model on pAUC (location and non-location based, scaled and unscaled)? It is the pAUC values of reader by block by reading session (Table 8.3.1). This would be the data that you used to run your mixed model: ssds.cn_scaled_loc and ssds.cn_scaled_nonloc per our understanding. Please email me the data at your earliest convenience to facilitate our review. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, May 25, 2016 4:15 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

The primary reason for the modification of the 510(K) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.
Best Regards,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Wednesday, May 25, 2016 1:08 PM  
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov  
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,  
Yanna

Yanna S. Kang, Ph.D.  
Mammography, Ultrasound, and Imaging Software Branch  
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna  
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
butsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

I have attached the two requested datasets. These are intermediate datasets created from the raw data using codes provided with the initial submission.

Best Regards,
Jennifer

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Friday, May 27, 2016 8:54 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

Thanks for providing a redlined copy of the 510k.

Could you please provide the data that (b)(4)

(b)(4)

for our understanding. Please email me the data at your earliest convenience to facilitate our review. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, May 25, 2016 4:15 PM
To: Kang, Yanna
Hi Yanna,

The primary reason for the modification of the 510(K) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, May 25, 2016 1:08 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: [https://www.research.net/s/cdrhcustomerservice?o=500&D=560&B=565&E=E&E=E](https://www.research.net/s/cdrhcustomerservice?o=500&D=560&B=565&E=E&E=E)

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

I wanted to verify you received the two intermediate datasets I sent on May 31st and they were in a format you could use.

Best Regards,
Jennifer

From: Jennifer Butsch
Sent: Tuesday, May 31, 2016 9:20 AM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

I have attached the two requested datasets. These are intermediate datasets created from the raw data using codes provided with the initial submission.

Best Regards,
Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Friday, May 27, 2016 8:54 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

Thanks for providing a redlined copy of the 510k.

Could you please provide the data that (b)(4) (b)(4) (b)(4) remember our understanding. Please email me the data at your earliest convenience to facilitate our review. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.resasearch.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, May 25, 2016 4:15 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

The primary reason for the modification of the 510(k) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I’ve attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, May 25, 2016 1:08 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,
We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=5&F=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

FROM: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
SENT: Thursday, April 28, 2016 1:52 PM
TO: Kang, Yanna
SUBJECT: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

Yes. We received the two datasets you sent on May 31. We are still reviewing your file and will get back to you soon.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustmerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, June 09, 2016 2:48 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

I wanted to verify you received the two intermediate datasets I sent on May 31st and they were in a format you could use.

Best Regards,
Jennifer

---

From: Jennifer Butsch
Sent: Tuesday, May 31, 2016 9:20 AM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,
I have attached the two requested datasets. These are intermediate datasets created from the raw data using codes provided with the initial submission.

Best Regards,
Jennifer

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Friday, May 27, 2016 8:54 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

Thanks for providing a redlined copy of the 510k.

Could you please provide the data that (b)(4) (b)(4), (b)(4) our understanding. Please email me the data at your earliest convenience to facilitate our review. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcUSTOMERSERVICE?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, May 25, 2016 4:15 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)
Hi Yanna,

The primary reason for the modification of the 510(k) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, May 25, 2016 1:08 PM
To: Jennifer Butsch
Cc: K1.61201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(k) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(k) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(k) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of in Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Yanna Kang
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

The primary reason for the modification of the 510(K) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> | www.riveraintech.com<http://www.riveraintech.com/>

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, May 25, 2016 1:08 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com [mailto:jbutsch@riveraintech.com]
Hi Jennifer,

Thanks for providing a redlined copy of the 510k.

Could you please provide the data that you used for the primary analysis of mixed model on pAUC (location and non-location based, scaled and unscaled)? It is the pAUC values of reader by block by reading session (Table 8.3.1). This would be the data that you used to run your mixed model: ssds.cn_scaled_loc and ssds.cn_scaled_nonloc per our understanding. Please email me the data at your earliest convenience to facilitate our review. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704 <tel: 301-796-6704>
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcUSTOMERSERVICE?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, May 25, 2016 4:15 PM
To: Kang, Yanna
Cc: Kl61201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

The primary reason for the modification of the 510(K) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not
tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> | www.riveraintech.com<http://www.riveraintech.com/>

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Wednesday, May 25, 2016 1:08 PM  
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov<mailto:K161201@docs.fda.gov>  
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.  
Mammography, Ultrasound, and Imaging Software Branch  
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:  
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> | www.riveraintech.com<http://www.riveraintech.com/>
Hi Yanna,

I have attached the two requested datasets. These are intermediate datasets created from the raw data using codes provided with the initial submission.

Best Regards,
Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Friday, May 27, 2016 8:54 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

Thanks for providing a redlined copy of the 510k.

Could you please provide the data that you used for the primary analysis of mixed model on pAUC (location and non-location based, scaled and unscaled)? It is the pAUC values of reader by block by reading session (Table 8.3.1). This would be the data that you used to run your mixed model: ssds.cn_scaled_loc and ssds.cn_scaled_nonloc per our understanding. Please email me the data at your earliest convenience to facilitate our review. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is
strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Wednesday, May 25, 2016 4:15 PM  
To: Kang, Yanna  
Cc: KL61201@docs.fda.gov<mailto:KL61201@docs.fda.gov>  
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

The primary reason for the modification of the 510(K) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> | www.riveraintech.com<http://www.riveraintech.com/>

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Wednesday, May 25, 2016 1:08 PM  
To: Jennifer Butsch  
Cc: KL61201@docs.fda.gov<mailto:KL61201@docs.fda.gov>  
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to KL52418? Thanks.
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(K)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> | www.riveraintech.com<http://www.riveraintech.com/>
Hi Yanna,

I wanted to verify you received the two intermediate datasets I sent on May 31st and they were in a format you could use.

Best Regards,
Jennifer

From: Jennifer Butsch
Sent: Tuesday, May 31, 2016 9:20 AM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

I have attached the two requested datasets. These are intermediate datasets created from the raw data using codes provided with the initial submission.

Best Regards,
Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Friday, May 27, 2016 8:54 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov<K161201@docs.fda.gov>
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

Thanks for providing a redlined copy of the 510k.

Could you please provide the data that you used for the primary analysis of mixed model on pAUC (location and non-location based, scaled and unscaled)? It is the pAUC values of reader by block by reading session (Table 8.3.1). This would be the data that you used to run your mixed model: ssds.cn_scaled_loc and ssds.cn_scaled_nonloc per our understanding. Please email me the data at your earliest convenience to facilitate our review. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise oblige or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, May 25, 2016 4:15 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov<mailto:K161201@docs.fda.gov>
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

The primary reason for the modification of the 510(K) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> | www.riveraintech.com<http://www.riveraintech.com/>
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, May 25, 2016 1:08 PM
To: Jennifer Butsch
Cc: KL61201@docs.fda.gov<mailto:KL61201@docs.fda.gov>
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there
was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

Yes. We received the two datasets you sent on May 31. We are still reviewing your file and will get back to you soon.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704 <tel:301-796-6704>
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch <mailto:jbutsch@riveraintech.com>
Sent: Thursday, June 09, 2016 2:48 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

I wanted to verify you received the two intermediate datatsets I sent on May 31st and they were in a format you could use.

Best Regards,

Jennifer

From: Jennifer Butsch
Sent: Tuesday, May 31, 2016 9:20 AM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov<mailto:K161201@docs.fda.gov>
Subject: RE: ClearRead CT 510(k)
Hi Yanna,

I have attached the two requested datasets. These are intermediate datasets created from the raw data using codes provided with the initial submission.

Best Regards,
Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Friday, May 27, 2016 8:54 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov<mailto:K161201@docs.fda.gov>
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

Thanks for providing a redlined copy of the 510k.

Could you please provide the data that you used for the primary analysis of mixed model on pAUC (location and non-location based, scaled and unscaled)? It is the pAUC values of reader by block by reading session (Table 8.3.1). This would be the data that you used to run your mixed model: ssds.cn_scaled_loc and ssds.cn_scaled_nonloc per our understanding. Please email me the data at your earliest convenience to facilitate our review. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcUSTOMERERVICE?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the
intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, May 25, 2016 4:15 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Yanna,

The primary reason for the modification of the 510(k) was to address the FDA questions listed in the traceability table. Some additional small edits were made for clarification and elaboration purposes, which are not tracked in the table provided in Appendix G. The intention of the table was to track our responses internally to verify all of the questions previously asked by FDA were fully addressed in the new submission; however, we felt this table would also be beneficial to FDA when reviewing the file.

I've attached a redlined copy of the 510(k) that might also be helpful during your review. The red text indicates added items and the green text indicates moved items. Please let me know if I can be of further assistance during your review.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com
www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, May 25, 2016 1:08 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: ClearRead CT 510(k)

Hi Jennifer,

We are still reviewing your submission regarding the ClearRead CT device. In Appendix G of the submission, you provided a traceability table of FDA Communication and Follow-up Action Items. Could you please let me know if the table includes all the changes of this new file, as compared to K152418? Thanks.
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Thursday, April 28, 2016 1:52 PM
To: Kang, Yanna
Subject: ClearRead CT 510(k)

Hi Yanna,

The ClearRead CT 510(K) submission was delivered to FDA today and was assigned the number K161201. The submission was quite large and I opted not to include a red-lined copy of the 510(K) in the binder because there was not enough room. However, if you think a red-lined copy of the 510(K) will be helpful in reviewing the submission, I will gladly provide one.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com
www.riveraintech.com
Hi Jennifer,

I think you can limit the formal response only to the final agreed material since we have all the interactions on file. Please let me know if you have additional questions. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704 <tel:301-796-6704>
Yanna.Kang@fda.hhs.gov <mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov <mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 22, 2016 2:01 PM
To: Kang, Yanna
Cc: Ballyns, Jeffrey; K161201@docs.fda.gov
Subject: Contents of formal response

Hi Yanna,

Once we reach consensus regarding deficiency number two in the July 28th deficiency list, I will formally submit our written response to the document mail center. Should I capture all of the informal transactions that have occurred or limit the formal response only to the final agreed material?

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Hi Jennifer,

I think you can limit the formal response only to the final agreed material since we have all the interactions on file. Please let me know if you have additional questions. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustservice0=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 22, 2016 2:01 PM
To: Kang, Yanna
Cc: Ballyns, Jeffrey; K161201@docs.fda.gov
Subject: Contents of formal response

Hi Yanna,

Once we reach consensus regarding deficiency number two in the July 28th deficiency list, I will formally submit our written response to the document mail center. Should I capture all of the informal transactions that have occurred or limit the formal response only to the final agreed material?

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

We have put your file on hold. See the email dated June 17, 2016. Please let me know if you have any questions.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704 <tel:301-796-6704>
Yanna.Kang@fda.hhs.gov <mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov <mailto:Yanna.Kang@fda.hhs.gov>.

From: Yanna Kang <mailto:yanna.kang@fda.hhs.gov>
Sent: Friday, June 17, 2016 11:08 AM
To: jbutsch@riveraintech.com
Cc: Kang, Yanna
Subject: KL61201 is on Hold Pending Your Response

June 17, 2016

We have reviewed your submission KL61201 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, referencing the submission number KL61201 to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - W066-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please refer to the eCopy guidance at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/UCM313794.pdf for current information on the number of copies and the format (paper versus eCopy) you must submit.

Your response is due within 180 days from the date of this request, which is December 14, 2016. If a complete response is not received in CDRH's Document Control Center within 180 days, we will consider this submission to be withdrawn, and we will delete it from our review system.

You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission to the Document Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.

Should you have questions about this email, you may contact Yanna Kang, the lead reviewer assigned to your submission.

*** This is a system-generated email notification ***
Hi Jennifer,

We have put your file on hold. See the email dated June 17, 2016. Please let me know if you have any questions.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=S&F

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Yanna Kang [mailto:yanna.kang@fda.hhs.gov]
Sent: Friday, June 17, 2016 11:08 AM
To: jbutsch@riveraintech.com
Cc: Kang, Yanna
Subject: K161201 is on Hold Pending Your Response

June 17, 2016

We have reviewed your submission K161201 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, referencing the submission number K161201 to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please refer to the eCopy guidance at http://www.fda.gov/downloads/medicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf for current information on the number of copies and the format (paper versus eCopy) you must submit.

Your response is due within 180 days from the date of this request, which is December 14, 2016. If a complete response is not received in CDRH's Document Control Center within 180 days, we will consider this submission to be withdrawn, and we will delete it from our review system.

You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a
submission to the Document Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.

Should you have questions about this email, you may contact Yanna Kang, the lead reviewer assigned to your submission.

*** This is a system-generated email notification ***
Hi Yanna,

We will have a response for you no later than Wednesday. Can you tell me if these are the only remaining questions?

Best regards,

Jennifer

Sent from my iPhone

On Jul 22, 2016, at 11:43 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

(b)(4)
Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don’t hesitate to contact me. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.
Hi Jennifer,

Thanks for your reply. The statistician is still reviewing the file and may have additional questions.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, July 22, 2016 2:36 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: Re: K161201/S001, Riverain - additional information needed

Hi Yanna,

We will have a response for you no later than Wednesday. Can you tell me if these are the only remaining questions?

Best regards,

Jennifer

Sent from my iPhone

On Jul 22, 2016, at 11:43 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:
Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don’t hesitate to contact me.

Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhccustomerservice?O=500&D=560&B=565&E=8&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
Hi Yanna,

Please find Riverain's response to the July 22 questions below.

(b)(4)
Best Regards,

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, July 23, 2016 2:51 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: K161201/S001, Riverain - additional information needed

Hi Jennifer,

Thanks for your reply. The statistician is still reviewing the file and may have additional questions.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustome rservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutscheiveraintech.com]
Sent: Friday, July 22, 2016 2:36 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: Re: K161201/S001, Riverain - additional information needed

Hi Yanna,

We will have a response for you no later than Wednesday. Can you tell me if these are the only remaining questions?

Best regards,

Jennifer

Sent from my iPhone

On Jul 22, 2016, at 11:43 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:
Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don’t hesitate to contact me.

Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustormerservice?O=500&D=560&B=565&E=E&S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Hi Jennifer,

Thanks for providing the responses to our questions. We will contact you if we have additional questions.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhccustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, July 25, 2016 10:42 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Steve Worrall
Subject: RE: K161201/S001, Riverain - additional information needed

Hi Yanna,

Please find Riverain’s response to the July 22 questions below.

(b)(4)
Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, July 23, 2016 2:51 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: K161201/S001, Riverain - additional information needed

Hi Jennifer,

Thanks for your reply. The statistician is still reviewing the file and may have additional questions.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=ES=ES

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, July 22, 2016 2:36 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: Re: K161201/S001, Riverain - additional information needed

Hi Yanna,

We will have a response for you no later than Wednesday. Can you tell me if these are the only remaining questions?

Best regards,

Jennifer

Sent from my iPhone

On Jul 22, 2016, at 11:43 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

(b)(4)
Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don’t hesitate to contact me.

Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Hi Yanna,

We will have a response for you no later than Wednesday. Can you tell me if these are the only remaining questions?

Best regards,

Jennifer

Sent from my iPhone

On Jul 22, 2016, at 11:43 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don’t hesitate to contact me. Thanks.
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomeervice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Hi Jennifer,

Thanks for your reply. The statistician is still reviewing the file and may have additional questions.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704<tel:301-796-6704>
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?0=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, July 22, 2016 2:36 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: Re: K161201/S001, Riverain - additional information needed

Hi Yanna,

We will have a response for you no later than Wednesday. Can you tell me if these are the only remaining questions?

Best regards,

Jennifer

Sent from my iPhone

On Jul 22, 2016, at 11:43 AM, Kang, Yanna
<Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>> wrote:
Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don't hesitate to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Hi Yanna,

Please find Riverain's response to the July 22 questions below.

(b)(4)
Best Regards,

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> |  

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Saturday, July 23, 2016 2:51 PM  
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov  
Subject: RE: K161201/S001, Riverain - additional information needed  

Hi Jennifer,  

Thanks for your reply. The statistician is still reviewing the file and may have additional questions.  

Best regards,  
Yanna  

Yanna S. Kang, Ph.D.  
Mammography, Ultrasound, and Imaging Software Branch  
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>  

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:  
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, July 22, 2016 2:36 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov<mailto:K161201@docs.fda.gov>
Subject: Re: K161201/S001, Riverain - additional information needed

Hi Yanna,

We will have a response for you no later than Wednesday. Can you tell me if these are the only remaining questions?

Best regards,

Jennifer

Sent from my iPhone

On Jul 22, 2016, at 11:43 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>> wrote:
Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

(b)(4)
Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don’t hesitate to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied.
To persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.
Hi Jennifer,

Thanks for providing the responses to our questions. We will contact you if we have additional questions.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704 <tel:301-796-6704>
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, July 25, 2016 10:42 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: K161201/S001, Riverain - additional information needed

Hi Yanna,

Please find Riverain's response to the July 22 questions below.

(b)(4)
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Saturday, July 23, 2016 2:51 PM  
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov<mailto:K161201@docs.fda.gov>  
Subject: RE: K161201/S001, Riverain - additional information needed

Hi Jennifer,

Thanks for your reply. The statistician is still reviewing the file and may have additional questions.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov<mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Friday, July 22, 2016 2:36 PM  
To: Kang, Yanna
Cc: K161201@docs.fda.gov

Subject: Re: K161201/S001, Riverain - additional information needed

Hi Yanna,

We will have a response for you no later than Wednesday. Can you tell me if these are the only remaining questions?

Best regards,

Jennifer

Sent from my iPhone

On Jul 22, 2016, at 11:43 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

We are currently reviewing your 510k supplement regarding the ClearRead CT device and would appreciate it if you could provide additional information to address the following questions:

(b)(4)
Please send me your response to the above questions via email by Wednesday, July 27, 2016 or at your earliest convenience. If you have any questions, please don't hesitate to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustoservice?O=500&D=560&B=565&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> | www.riveraintech.com<http://www.riveraintech.com/>

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Monday, June 13, 2016 4:32 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: K161201, Riverain, ClearRead CT - clarification questions

Hi Jennifer,

We have the following clarification questions regarding your clinical study and would appreciate it if you could provide additional information to address those questions:

(b)(4)
Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=S

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Hi Jennifer,

Thanks so much for your quick reply. I will forward the answers to our statistician.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=500&D=560&B=565&E=S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Wednesday, June 15, 2016 10:48 AM  
To: Kang, Yanna  
Cc: K161201@docs.fda.gov  
Subject: RE: K161201, Riverain, ClearRead CT - clarification questions

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Monday, June 13, 2016 4:32 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: K161201, Riverain, ClearRead CT - clarification questions

Hi Jennifer,

We have the following clarification questions regarding your clinical study and would appreciate it if you could provide additional information to address those questions:

- [Insert specific questions regarding the clinical study here]

Thank you,

Yanna Kang
Please note that we are still reviewing your file and your clarifications on those questions will help facilitate our statistical review. Please send me your response via email by Thursday, 6/16/2016 or at your earliest convenience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: [https://www.research.net/s/cdrhcustmerservice?O=500&D=560&B=565&E=E](https://www.research.net/s/cdrhcustmerservice?O=500&D=560&B=565&E=E)

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Monday, June 13, 2016 4:32 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: K161201, Riverain, ClearRead CT - clarification questions

Hi Jennifer,

We have the following clarification questions regarding your clinical study and would appreciate it if you could provide additional information to address those questions:

(b)(4)
Please note that we are still reviewing your file and your clarifications on those questions will help facilitate our statistical review. Please send me your response via email by Thursday, 6/16/2016 or at your earliest convenience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
Hi Jennifer,

Thanks so much for your quick reply. I will forward the answers to our statistician.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704 <tel:301-796-6704>
Yanna.Kang@fda.hhs.gov <mailto:Yanna.Kang@fda.hhs.gov>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcutomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov <mailto:Yanna.Kang@fda.hhs.gov>.

From: Jennifer Butsch <jbutsch@riveraintech.com>
Sent: Wednesday, June 15, 2016 10:48 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: K161201, Riverain, ClearRead CT - clarification questions

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Monday, June 13, 2016 4:32 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: K161201, Riverain, ClearRead CT - clarification questions

Hi Jennifer,

We have the following clarification questions regarding your clinical study and would appreciate it if you could provide additional information to address those questions:

(b)(4)
Please note that we are still reviewing your file and your clarifications on those questions will help facilitate our statistical review. Please send me your response via email by Thursday, 6/16/2016 or at your earliest convenience.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov <mailto:Yanna.Kang@fda.hhs.gov>.
Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704 <tel:301-796-6704>
[mailto:Yanna.Kang@fda.hhs.gov]

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustome-service?O=500&D=560&B=565&E=8

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligatory or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at [mailto:Yanna.Kang@fda.hhs.gov].

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com<mailto:jbutsch@riveraintech.com> | www.riveraintech.com<http://www.riveraintech.com/>
Hi Yanna,

Thank you for the quick review. We will work with our statisticians to quickly to perform the requested analysis.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=500&D=560&B=565&E=E&S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/5001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

(b)(4)

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

file:///C:/Users/LDT/Desktop/Training%20Material/2016-9533/Archive/K161201/Interac... 11/21/2017
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional Information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)
If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

Thanks for your email. The statistician is still reviewing your response to Deficiency 2 and expects to get back to me by this week. I'll get back to you immediately after I get the comments from the statistician. Thanks for your patience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=500&D=560&b=555&d=E&d=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Jennifer Butsch  
Sent: Thursday, August 04, 2016 2:38 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; Steve Worrell  
Subject: RE: Response to K161201/S001 Additional information request  

Dear Yanna,

(b)(4)

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

(b)(4)
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know.

Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-5704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Jennifer Butsch  
Sent: Thursday, August 04, 2016 2:38 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; Steve Worrell  
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

(b)(4)

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

(b)(4)
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional Information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcuterservice?O=500&D=560&B=565&E=E&S=E
From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know.

Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustservce?O=500&D=560&B=565&E=E&S=E
Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
ibutsch@riveraintech.com | www.riveraintech.com

Dear Yanna,

(b)(4)

Sincerely,

Jennifer
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:
If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I'll send you another email confirming our statistician's attendance tomorrow morning. I'll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know.

Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch  
Sent: Thursday, August 04, 2016 2:38 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; Steve Worrell  
Subject: RE: Response to K161201/S001 Additional Information request

Dear Yanna,

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

file:///C:/Users/LDT/Desktop/Training%20Material/2016-9533/Archive/K161201/Interac... 11/21/2017
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

(b)(4)

We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura
Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know.

Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)
If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomeservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

I'm following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; ‘Jeffrey.Ballyns@fda.hhs.gov’
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: [https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=F](https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=F)

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA's statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | [www.riveraintech.com](http://www.riveraintech.com)

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know.

Thanks.

Best regards,
Yanna
Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?q=500&D=560&B=565&E=5S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: ‘Kang, Yanna’
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,
We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/l/cdrhcUSTOMERSERVICE?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request
Hi Yanna,

Please find our responses below.
Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&s=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I’m following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riveraint Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; 'Jeffrey.Ballyns@fda.hhs.gov'
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know.

Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustmerService?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.
From: Jennifer Butsch [mailto:ibutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
ibutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:
If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcrownerservice?O=500&D=560&B=565&E=E&$=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

---

(b)(4)
(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,

Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying are strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
I'm following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; 'Jeffrey.Ballyns@fda.hhs.gov'
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

(b)(4)
We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Tuesday, August 16, 2016 4:36 PM  
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/5001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016  
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,  
Yanna

Yanna S. Kang, Ph.D.  
Mammography, Ultrasound, and Imaging Software Branch  
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at: Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov  

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E  

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Wednesday, August 10, 2016 11:47 AM  
To: Kang, Yanna  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional information request  

Hi Yanna,  

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?  

Thanks,  

Jennifer  

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riveraint Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com  

From: Jennifer Butsch  
Sent: Thursday, August 04, 2016 2:38 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; Steve Worrell  
Subject: RE: Response to K161201/S001 Additional information request  

Dear Yanna,
We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustservicet?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request
Hi Yanna,

Please find our responses below.

(b)(4)
Hi Jennifer,

Please find below our statistician's comments (in red font). Please clarify if the SAS dataset named Cn_scaled_loc (sent on 5/31/2016) and the dataset you used, which is named tn_scaled_loc, are different and which one is the correct one to be used. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,

Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,

Yanna
Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcusterservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I’m following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; 'Jeffrey.Ballyns@fda.hhs.gov'
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

Thank you for taking the time to meet with us regarding the analysis and modeling. Our understanding of the conclusion of the discussion on August 17, 2016, is that the modeling as we described it on the call is acceptable to the FDA and the only outstanding item is for the analysis to be replicated by the FDA.
We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=S00&D=S00&B=S5S&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Saturday, August 13, 2016 2:39 PM  
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcumasterservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Wednesday, August 10, 2016 11:47 AM  
To: Kang, Yanna  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch  
Sent: Thursday, August 04, 2016 2:38 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; Steve Worrell  
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

Background:
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)
If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional Information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

Sorry it took a bit to get back with you but I wanted to check with BioStat.

Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset tn_scaled_loc which includes all actionable nodules vs normals. The Cn_scaled_loc is for cancer vs normal only.

I hope this helps. Sorry for confusion.

Sincerely,

Jennifer

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

Please find below our statistician’s comments (in red font). Please clarify if the SAS dataset named Cn_scaled_loc (sent on 5/31/2016) and the dataset you used, which is named tn_scaled_loc, are different and which one is the correct one to be used. Thanks.
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?
O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,

Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcUSTOMERSERVICE?
O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Hi Yanna,

I'm following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; Jeffrey.Ballyns@fda.hhs.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: [https://www.research.net/s/cdrhcultureservice?O=500&D=S00&b=S65&k=E=S=E](https://www.research.net/s/cdrhcultureservice?O=500&D=S00&b=S65&k=E=S=E)

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time, does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at [Yanna.Kang@fda.hhs.gov](mailto:Yanna.Kang@fda.hhs.gov).

---

**From:** Jennifer Butsch  
**Sent:** Tuesday, August 16, 2016 2:22 PM  
**To:** Kang, Yanna  
**Cc:** K161201@docs.fda.gov  
**Subject:** RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

---

**From:** Kang, Yanna  
**Sent:** Saturday, August 13, 2016 2:39 PM  
**To:** Jennifer Butsch  
**Cc:** K161201@docs.fda.gov  
**Subject:** RE: Response to K161201/S001 Additional information request

Hi Jennifer,
Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhccustomerservice?
O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@dcs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Jennifer Butsch  
Sent: Thursday, August 04, 2016 2:38 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; Steve Worrell  
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhccustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Hi Yanna,

Sorry for a second email, but can you clarify if the statistician will pick one model for our formal submission or if she will want us to submit all three?

Sincerely
Jennifer

On Sep 2, 2016, at 2:45 PM, Jennifer Butsch <jbutsch@riveraintech.com> wrote:

Hi Yanna,

Sorry it took a bit to get back with you but I wanted to check with BioStat.

Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset tn_scaled_loc which includes all actionable nodules vs normals. The Cn_scaled_loc is for cancer vs normal only.

I hope this helps. Sorry for confusion.

Sincerely,
Jennifer

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

Please find below our statistician's comments (in red font). Please clarify if the SAS dataset named Cn_scaled_loc (sent on 5/31/2016) and the dataset you used, which is named tn_scaled_loc, are different and which one is the correct one to be used. Thanks.
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,

Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I’m following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; 'Jeffrey.Ballyns@fda.hhs.gov'
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,
We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I'll send you another email confirming our statistician's attendance tomorrow morning. I'll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:ibutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA's statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer
Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

Hi Yanna,
I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

Background:
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.  
Mammography, Ultrasound, and Imaging Software Branch  
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:  

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Monday, August 01, 2016 3:56 PM  
To: Kang, Yanna  
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

Thanks for your email. I have forwarded your response and question to the statistician and will get back to you once I get feedback from the statistician.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrcustomerservice?O=500&D=560&B=565&E=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 2:52 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request

Hi Yanna,

Sorry for a second email, but can you clarify if the statistician will pick one model for our formal submission or if she will want us to submit all three?

Sincerely

Jennifer

On Sep 2, 2016, at 2:45 PM, Jennifer Butsch <jbutsch@riveraintech.com> wrote:

        Hi Yanna,

        Sorry it took a bit to get back with you but I wanted to check with BioStat.

        Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset tn_scaled_loc which includes all actionable nodules vs normals. The Cn_scaled_loc is for cancer vs normal only.
I hope this helps. Sorry for confusion.

Sincerely,

Jennifer

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,
Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

Hi Yanna,

I’m following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,
Hi Yanna,
We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment about the time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Yanna, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'

file:///C:/Users/LDT/Desktop/Training%20Material2016-9536/Archive/K161201/Interac8-11-21/2017
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

(b)(4)
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
(b)(4)
Hi Jennifer,

The statistician confirmed that your analysis using the tn_scaled_loc dataset is the correct one since this analysis is consistent with the IFU on the actionable nodule vs. normal cases. Also we don't have a particular preference on the model submitted for the formal response since they return almost the same results. You can also mention our interactive review emails to refer to all three models if needed.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 2:52 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request

Hi Yanna,

Sorry for a second email, but can you clarify if the statistician will pick one model for our formal submission or if she will want us to submit all three?

Sincerely
Jennifer

On Sep 2, 2016, at 2:45 PM, Jennifer Butsch <jbutsch@riveraintech.com> wrote:

Hi Yanna,

Sorry it took a bit to get back with you but I wanted to check with BioStat.
Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset `tn_scaled_loc` which includes all actionable nodules vs normals. The `Cn_scaled_loc` is for cancer vs normal only.

I hope this helps. Sorry for confusion.

Sincerely,

Jennifer

---

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference
discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,

Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
https://www.research.net/s/cdrhcustome

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
I'm following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; 'Jeffrey.Ballyns@fda.hhs.gov'
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I'll send you another email confirming our statistician's attendance tomorrow morning. I'll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

Hi Jennifer,
Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Jennifer Butsch  
Sent: Thursday, August 04, 2016 2:38 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; Steve Worrell  
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,  

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
ibutsch@riveraintech.com | www.riveraintech.com
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Thank you Yanna. We will submit the formal response next week.

Jennifer

Sent from my iPhone

On Sep 2, 2016, at 3:42 PM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

The statistician confirmed that your analysis using the tn_scaled_loc dataset is the correct one since this analysis is consistent with the IFU on the actionable nodule vs. normal cases. Also we don't have a particular preference on the model submitted for the formal response since they return almost the same results. You can also mention our interactive review emails to refer to all three models if needed.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 2:52 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request

Hi Yanna,

Sorry for a second email, but can you clarify if the statistician will pick one model for our formal submission or if she will want us to submit all three?

Sincerely
Jennifer

On Sep 2, 2016, at 2:45 PM, Jennifer Butsch <jbutsch@riveraintech.com> wrote:
Hi Yanna,

Sorry it took a bit to get back with you but I wanted to check with BioStat.

Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset tn_scaled_loc which includes all actionable nodules vs normals. The Cn_scaled_loc is for cancer vs normal only.

I hope this helps. Sorry for confusion.

Sincerely,

Jennifer

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,
Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I'm following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Hi Yanna,

(b)(4)
We understand that the primary review statistician is on leave and thus we should expect a response in 10 days. However, with this additional information we hope that the review is made easier and resolution can be expedited. We are also available to answer questions or discuss clarifications at any time. We look forward to hearing from you soon.

Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute
an advisory opinion, does not necessarily represent the formal position of FDA, and
does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It
may contain information that is protected, privileged, or confidential, and it should not
be disseminated, distributed, or copied to persons not authorized to receive such
information. If you are not the intended recipient, any dissemination, distribution or
copying is strictly prohibited. If you think you have received this e-mail message in
error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive
my message in a timely manner. I think it would be best to schedule a call
between FDA’s statisticians and ours to finalize the modeling approach that will
be used to resolve the remaining issue. On the call for Riverain would be
myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief
Scientist from Biostat). I expect the call would be brief, less than a half hour,
but I think it would be valuable in helping us reach consensus. We are available
anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August
4, 2016. If you would like to schedule a teleconference with us to clarify or
discuss the questions and comments, please let me know. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope
will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/5001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:butsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional Information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

We have received your formal response. It appears that you haven't provided us a finalized version of the 510k Summary. The 510k Summary submitted in the formal response and via email is redlined version. Also, please remove the "confidential" wording from each page of your 510k Summary and provide a finalized 510k Summary via email at your earliest convenience. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=S60&B=655&E=S=F

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 3:57 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request

Thank you Yanna. We will submit the formal response next week.

Jennifer

Sent from my iPhone

On Sep 2, 2016, at 3:42 PM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

The statistician confirmed that your analysis using the tn_scaled_loc dataset is the correct one since this analysis is consistent with the IFU on the actionable nodule vs. normal cases. Also we don't have a particular preference on the model submitted for the formal response since they return almost the same results. You can also mention our interactive review emails to refer to all three models if needed.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: [https://www.research.net/s/cdrhcustomerservice?o=500&D=560&B=565&E=&S=E](https://www.research.net/s/cdrhcustomerservice?o=500&D=560&B=565&E=&S=E)

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 2:52 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov, Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request

Hi Yanna,

Sorry for a second email, but can you clarify if the statistician will pick one model for our formal submission or if she will want us to submit all three?

Sincerely,
Jennifer

On Sep 2, 2016, at 2:45 PM, Jennifer Butsch <jbutsch@riveraintech.com> wrote:

Hi Yanna,

Sorry it took a bit to get back with you but I wanted to check with BioStat.

Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset tn_scaled_loc which includes all actionable nodules vs normals. The Cn_scaled_loc is for cancer vs normal only.

I hope this helps. Sorry for confusion.

Sincerely,
Jennifer

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,

Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I'm following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; 'Jeffrey.Ballyns@fda.hhs.gov'
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

(b)(4)
Sincerely,

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016  
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,  
Yanna

Yanna S. Kang, Ph.D.  
Mammography, Ultrasound, and Imaging Software Branch  
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:  

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Tuesday, August 16, 2016 2:22 PM  
To: Kang, Yanna  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour,
but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
ibutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

---

From: Jennifer Butsch [mailto:ibutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request
Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

Background:
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

(b)(4)

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustormerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

Please find the finalized version of the 510(k) Summary without the word “confidential” in the footer as requested.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, September 07, 2016 5:26 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey; Cadotte, Alex
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have received your formal response. It appears that you haven’t provided us a finalized version of the 510k Summary. The 510k Summary submitted in the formal response and via email is redlined version. Also, please remove the “confidential” wording from each page of your 510k Summary and provide a finalized 510k Summary via email at your earliest convenience. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 3:57 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request
Thank you Yanna. We will submit the formal response next week.

Jennifer

Sent from my iPhone

On Sep 2, 2016, at 3:42 PM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

The statistician confirmed that your analysis using the tn_scaled_loc dataset is the correct one since this analysis is consistent with the IFU on the actionable nodule vs. normal cases. Also we don’t have a particular preference on the model submitted for the formal response since they return almost the same results. You can also mention our interactive review emails to refer to all three models if needed.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustumerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 2:52 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request

Hi Yanna,

Sorry for a second email, but can you clarify if the statistician will pick one model for our formal submission or if she will want us to submit all three?

Sincerely
Jennifer

On Sep 2, 2016, at 2:45 PM, Jennifer Butsch <jbutsch@riveraintech.com> wrote:

Hi Yanna,
Sorry it took a bit to get back with you but I wanted to check with BioStat.

Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset tn_scaled_loc which includes all actionable nodules vs normals. The Cn_scaled_loc is for cancer vs normal only.

I hope this helps. Sorry for confusion.

Sincerely,

Jennifer

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:butsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,
Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance

file:///C/Users/JDT/Desktop/Training%20Material/2016-9533/Archive/K161201/Interac... 11/21/2017
From: Jennifer Butsch  
Sent: Thursday, August 18, 2016 10:29 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; 'jeffrey.ballyns@fda.hhs.gov'  
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

(b)(4)
Sincerely,

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
butsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]  
Sent: Tuesday, August 16, 2016 4:36 PM  
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional Information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016  
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I’ll send you another email confirming our statistician’s attendance tomorrow morning. I’ll also provide the call in information in the email. Thanks.

Best regards,  
Yanna

Yanna S. Kang, Ph.D.  
Mammography, Ultrasound, and Imaging Software Branch  
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:  

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute
an advisory opinion, does not necessarily represent the formal position of FDA, and
does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It
may contain information that is protected, privileged, or confidential, and it should not
be disseminated, distributed, or copied to persons not authorized to receive such
information. If you are not the intended recipient, any dissemination, distribution or
copying is strictly prohibited. If you think you have received this e-mail message in
to error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive
my message in a timely manner. I think it would be best to schedule a call
between FDA’s statisticians and ours to finalize the modeling approach that will
be used to resolve the remaining issue. On the call for Riverain will be
myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief
Scientist from Biostat). I expect the call would be brief, less than a half hour,
but I think it would be valuable in helping us reach consensus. We are available
anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

---

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August
4, 2016. If you would like to schedule a teleconference with us to clarify or
discuss the questions and comments, please let me know. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverai Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope
will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
butsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

Thanks for providing the updated 510k Summary. We recommend that you describe briefly about the three reader arm design and the modeling approach in the labeling, and have the following additional comments for you to address:

(b)(4)

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (l) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, September 07, 2016 10:50 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey; Cadotte, Alex
Subject: RE: Response to K161201/S001 Additional information request
Hi Yanna,

Please find the finalized version of the 510(k) Summary without the word “confidential” in the footer as requested.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, September 07, 2016 5:26 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey; Cadotte, Alex
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have received your formal response. It appears that you haven’t provided us a finalized version of the 510k Summary. The 510k Summary submitted in the formal response and via email is redlined version. Also, please remove the “confidential” wording from each page of your 510k Summary and provide a finalized 510k Summary via email at your earliest convenience. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustserv?O=500&D=560&B=565&E=&s=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 3:57 PM
To: Kang, Yanna

file:///C:/Users/LDT/Desktop/Training%20Material/2016-9533/Archive/K161201/Interacs-11-21/2017
On Sep 2, 2016, at 3:42 PM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

The statistician confirmed that your analysis using the tn_scaled_loc dataset is the correct one since this analysis is consistent with the IFU on the actionable nodule vs. normal cases. Also we don’t have a particular preference on the model submitted for the formal response since they return almost the same results. You can also mention our interactive review emails to refer to all three models if needed.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustservicerequest?O=500&D=560&B=565&E=E&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 2:52 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request

Hi Yanna,

Sorry for a second email, but can you clarify if the statistician will pick one model for our formal submission or if she will want us to submit all three?

Sincerely
Jennifer

On Sep 2, 2016, at 2:45 PM, Jennifer Butsch <jbutsch@riveraintech.com> wrote:
Hi Yanna,

Sorry it took a bit to get back with you but I wanted to check with BioStat.

Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset `tn_scaled_loc` which includes all actionable nodules vs normals. The `Cn_scaled_loc` is for cancer vs normal only.

I hope this helps. Sorry for confusion.

Sincerely,

Jennifer

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,
Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

——

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I’m following up to see if your statistician has returned and if she has had an opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; 'Jeffrey.Ballyns@fda.hhs.gov'
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,
Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I'll send you another email confirming our statistician's attendance tomorrow morning. I'll also provide the call in information in the email. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute
From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna (mailto:Yanna.Kang@fda.hhs.gov)
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcUSTOMER?O=500&D=560&B=565&E=&S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, August 10, 2016 11:47 AM
To: Kang, Yanna
Cc: K161201@doccs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 04, 2016 2:38 PM
To: 'Kang, Yanna'
Cc: K161201@doccs.fda.gov; Steve Worrell
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope
will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com
From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/5001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com
Hi Yanna,

I have updated the labeling materials as requested and have attached redlined versions to this email.

Best Regards,
Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Friday, September 09, 2016 9:41 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey; Cadotte, Alex
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Thanks for providing the updated 510k Summary. We recommend that you describe briefly about the three reader arm design and the modeling approach in the labeling, and have the following additional comments for you to address:

(b)(4)

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&B=565&E=&S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Wednesday, September 07, 2016 10:50 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey; Cadotte, Alex
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

Please find the finalized version of the 510(k) Summary without the word “confidential” in the footer as requested.

Best Regards,

Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, September 07, 2016 5:26 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey; Cadotte, Alex
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have received your formal response. It appears that you haven’t provided us a finalized version of the 510k Summary. The 510k Summary submitted in the formal response and via email is redlined version. Also, please remove the “confidential” wording from each page of your 510k Summary and provide a finalized 510k Summary via email at your earliest convenience. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrcustomerservice?O=500&D=560&B=565&E=&S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 3:57 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: Re: Response to K161201/S001 Additional information request

Thank you Yanna. We will submit the formal response next week.

Jennifer

Sent from my iPhone

On Sep 2, 2016, at 3:42 PM, Kang, Yanna <Yanna.Kang@fda.hhs.gov> wrote:

Hi Jennifer,

The statistician confirmed that your analysis using the tn_scaled_loc dataset is the correct one since this analysis is consistent with the IFU on the actionable nodule vs. normal cases. Also we don’t have a particular preference on the model submitted for the formal response since they return almost the same results. You can also mention our interactive review emails to refer to all three models if needed.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrcustomerservice?O=500&D=560&B=565&E=856=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 2:52 PM
To: Kang, Yanna
Hi Yanna,

Sorry for a second email, but can you clarify if the statistician will pick one model for our formal submission or if she will want us to submit all three?

Sincerely,
Jennifer

On Sep 2, 2016, at 2:45 PM, Jennifer Butsch <jbutsch@riveraintech.com> wrote:

Hi Yanna,

Sorry it took a bit to get back with you but I wanted to check with BioStat.

Since we have moved toward a more general label of actionable nodules the appropriate dataset to load is the dataset tn_scaled_loc which includes all actionable nodules vs normals. The Cn_scaled_loc is for cancer vs normal only.

I hope this helps. Sorry for confusion.

Sincerely,
Jennifer

On Sep 2, 2016, at 11:13 AM, Kang, Yanna <Yanna.kang@fda.hhs.gov> wrote:

Hi Jennifer,
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Friday, September 02, 2016 8:43 AM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I was hoping you could provide a quick update on the statistical verification timeline. I had anticipated this would be wrapped up this week, based on our teleconference discussion on August 17th, so we could prepare for our formal submission this weekend.

Sincerely,

Jennifer

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 31, 2016 9:59 AM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Our statistician is reviewing your data now. I will get back to you once I receive the comments from her. Thank you for your patience.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.35 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.
This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such
information. If you are not the intended recipient, any dissemination, distribution or
.copying is strictly prohibited. If you think you have received this e-mail message in
.error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 30, 2016 4:54 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov; Ballyns, Jeffrey
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I'm following up to see if your statistician has returned and if she has had an
opportunity to review the data we submitted.

Best Regards,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Jennifer Butsch
Sent: Thursday, August 18, 2016 10:29 PM
To: 'Kang, Yanna'
Cc: K161201@docs.fda.gov; 'Jeffrey.Ballyns@fda.hhs.gov'
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

(b)(4)
Sincerely,

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Tuesday, August 16, 2016 4:36 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We are happy to schedule a brief phone conversation to clarify the statistical questions. I propose the following date and time:

Date: Wednesday, August 17, 2016
Time: 1:00 – 1:30 pm, Eastern Daylight Time

Please note that I'll send you another email confirming our statistician's attendance tomorrow morning. I'll also provide the call in information in the email. Thanks.
Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
https://www.research.net/s/cdrhcustmerservice?o=5008D=560B=565&E=S=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Tuesday, August 16, 2016 2:22 PM
To: Kang, Yanna
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I left you a voicemail but am following-up by email to make sure you receive my message in a timely manner. I think it would be best to schedule a call between FDA’s statisticians and ours to finalize the modeling approach that will be used to resolve the remaining issue. On the call for Riverain would be myself, Laura Gillis (Lead Statistician from Biostat), and Sandra Close (Chief Scientist from Biostat). I expect the call would be brief, less than a half hour, but I think it would be valuable in helping us reach consensus. We are available anytime today or tomorrow.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Saturday, August 13, 2016 2:39 PM
To: Jennifer Butsch  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

Please find attached our statistical comments on your response dated August 4, 2016. If you would like to schedule a teleconference with us to clarify or discuss the questions and comments, please let me know. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.  
Mammography, Ultrasound, and Imaging Software Branch  
Division of Radiological Health  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health  
U.S. Food and Drug Administration  
P:301-796-6704  
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:  

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:butsch@riveraintech.com]  
Sent: Wednesday, August 10, 2016 11:47 AM  
To: Kang, Yanna  
Cc: K161201@docs.fda.gov  
Subject: RE: Response to K161201/S001 Additional information request

Hi Yanna,

I thought I would check in and see if the background regarding the second deficiency was beneficial in resolving the issue your statistician was having when running the models?

Thanks,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance
From: Jennifer Butsch  
Sent: Thursday, August 04, 2016 2:38 PM  
To: 'Kang, Yanna'  
Cc: K161201@docs.fda.gov; Steve Worrell  
Subject: RE: Response to K161201/S001 Additional information request

Dear Yanna,

We have conferred with our statistical team at BioStat and they believe the issue can be resolved through some additional explanation regarding methodology and modeling approaches. As such, we are providing some additional background information in response to deficiency 2 that we hope will provide the necessary clarifications to allow resolution. We would be happy to have a call with appropriate team members to help expedite. As part of our formal response to deficiency 2, we would provide the following information, including the Background below. A word document of the same is attached. We would of course also provide all the previous information provided, including the .zip files and marked up, updated labeling documents, and necessary submission documents. I hope you and your team find this satisfactory. We are working very hard to meet your objectives.

Sincerely,

Jennifer

Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
Riverain Technologies  
937-531-5446 (O) | 800-990-3387 x5446  
jbutsch@riveraintech.com | www.riveraintech.com
categorical variable, weirdly the LSMEANS does not give estimate to the 2 levels of mod (U and A) though it gives the estimate of the difference. If changing the code to 1 vs 0, this problem disappeared. This is why we suggest 1 vs 0 coding. Please perform the analysis as suggested in the original deficiency.

If you have any questions, please feel free to contact me. Thanks.

Best regards,

Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P: 301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com] 
Sent: Monday, August 01, 2016 3:56 PM 
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
ibutsch@riveraintech.com | www.riveraintech.com
Hi Jennifer,

We have the following comment on Question 2:

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of in Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?O=500&D=560&8=565&E=&5=E

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/5001 Additional information request

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer
Hi Yanna,

Thank you for the quick review. We will work with our statisticians to quickly to perform the requested analysis.

Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Wednesday, August 03, 2016 2:52 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: RE: Response to K161201/S001 Additional information request

Hi Jennifer,

We have the following comment on Question 2:

If you have any questions, please feel free to contact me. Thanks.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcultomerservice?O=500&D=560&B=565&E=&S=E
This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately at Yanna.Kang@fda.hhs.gov.

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]
Sent: Monday, August 01, 2016 3:56 PM
To: Kang, Yanna
Subject: Response to K161201/S001 Additional information request

Hi Yanna,

Please find our responses below.

Predictive Measure

Read

Estimate

Std Error

Difference

Sensitivity
(b)(4) Test Data

Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018.
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
(b)(4) Test Data

Records processed under FOIA Request 2016-9533; Released by CDRH on 5/8/2018

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118
TRADITIONAL [510(k)] PREMARKET NOTIFICATION

CLEARRead CT™

Submitter:

Jennifer Butsch
Riverain Technologies, LLC.
3020 South Tech Blvd.
Miamisburg, OH 45342-4860
800.990.3387
937.425.6811
jbutsch@riveraintech.com
Insert form 3601 MDUFMA Coversheet
Insert form 3514 CDRH Premarket Review Coversheet
Insert ClinicalTrials.gov Worksheet - 3674
Insert form 3654 Standard Data report for 510ks
June 17, 2016

We have reviewed your submission KL61201 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies.

Please submit your response, referencing the submission number KL61201 to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002


Your response is due within 180 days from the date of this request, which is December 14, 2016. If a complete response is not received in CDRH's Document Control Center within 180 days, we will consider this submission to be withdrawn, and we will delete it from our review system.

You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission to the Document Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.

Should you have questions about this email, you may contact Yanna Kang, the lead reviewer assigned to your submission.

*** This is a system-generated email notification ***
May 2, 2016

Acceptance Review Notification - Accepted

An administrative acceptance review was conducted on your premarket notification (510(k)) K161201, and it was found to contain all of the necessary elements and information needed to proceed with the substantive review. We will contact you should we require any additional information during the course of the substantive review. The lead reviewer assigned to your submission is Yanna Kang.

*** This is a system-generated email notification ***
July 28, 2016<br><p>We have reviewed your submission K161201/S001 and have determined that additional information is required. Your file is being placed on hold pending a complete response to the attached deficiencies. </p><p>Please submit your response, referencing the submission number K161201/S001 to: </p><p style="padding-left:50">U.S. Food and Drug Administration<br>Center for Devices and Radiological Health<br>Document Control Center - WO66-G609<br>10903 New Hampshire Avenue<br>Silver Spring, MD 20993-0002</p><p>Please refer to the eCopy guidance at <a href="http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf">http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf</a> for current information on the number of copies and the format (paper versus eCopy) you must submit.</p><p>Your response is due within 180 days from the date of this request, which is January 24, 2017. If a complete response is not received in CDRH's Document Control Center within 180 days, we will consider this submission to be withdrawn, and we will delete it from our review system.</p><p>You may not market this device until you have received a letter from FDA allowing you to do so. If you market the device without FDA clearance, you will be in violation of the Federal Food, Drug, and Cosmetic Act.</p><p>If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the attached deficiencies, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please note that a Submission Issue Q-Sub does not take the place of a formal response to this email notification. As noted above, FDA will consider this submission to be withdrawn if FDA does not receive, in a submission to the Document Control Center, a complete response to all of the attached deficiencies within 180 calendar days of the date of this request.</p><p>Should you have questions about this email, you may contact Yanna Kang, the lead reviewer assigned to your submission.</p><p>*** This is a system-generated email notification ***</p>
This is a system-generated email notification.

If you have any questions, please contact the lead reviewer assigned.

September 9, 2016

Questions? Contact FDA/CDRH/OCE/DID at CDRH-FOISTATUS@fda.hhs.gov or 301-796-8118.
1.0 510(K) SUMMARY

Submission Date: April 25, 2016

Submitter Information:

Company Name: Riverain Technologies, LLC.
Company Address: 3020 South Tech Blvd., Miamisburg, OH 45342-4860
Contact Person: Jennifer Butsch
Director, Regulatory Affairs and Quality Assurance
Riverain Technologies
800.990.3387
937.425.6493
jbutsch@riveraintech.com

Device Information:

Trade Name: ClearRead CT™
Regulation Number: 21 CFR §892.2050
Regulation Name: Picture archiving and communications system
Regulatory Class: Class II
Product Code: OEB/LLZ

Device Description: ClearRead CT is a dedicated post-processing application that generates a secondary vessel suppressed Lung CT series with CADE marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Predicate Devices: syngo.CT Lung CAD
(K143196)
Siemens AG Medical Solutions
Class II

syngo.PET&CT Oncology
(K093621)
Siemens AG Medical Solutions  
Class II  

ClearRead Bone Suppression (SoftView)  
(K092363)  
Riverain Technologies, LLC  
Class II  

Comparison to Predicate Device Technical Characteristics:  
Riverain is of the opinion that the ClearRead CT is substantially equivalent, both in intended use and technical characteristics to the listed predicate devices. Differences in the design and performance from the cited predicate devices do not affect either the safety or the effectiveness of ClearRead CT for its intended use. 

<table>
<thead>
<tr>
<th>Predicate: syngo.CT Lung CAD (Siemens AG Medical Solutions) K143196</th>
<th>Predicate: syngo.PET &amp; CT Oncology (Siemens AG Medical Solutions) K093621</th>
<th>Predicate: ClearRead Bone Suppression (Riverain Technologies) K092363</th>
<th>Subject Device: ClearRead CT (Riverain Technologies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Code</td>
<td>OEB</td>
<td>LLZ</td>
<td>LLZ</td>
</tr>
<tr>
<td>Intended Use</td>
<td>Computer-aided detection tool designed to assist radiologists in the detection of solid pulmonary nodules during review of MDCT examinations of the chest</td>
<td>Viewing, manipulation, 3D-Visualization, and comparison of medical images from multiple imaging modalities.</td>
<td>Generating bone suppressed image from an original PA/AP chest radiograph</td>
</tr>
</tbody>
</table>

Testing Summary:  
Clinical validation was conducted in a multi-reader multi-case (MRMC) study to validate that the device conformed to the defined user needs and intended uses. The reader study measured the area under the curve (AUC) of the localization receiver operating characteristic (LROC) response when using ClearRead CT relative to the unaided read. The study also measured the radiologists’ interpretation time when using ClearRead CT relative to unaided interpretations. ClearRead CT was found to significantly increase the AUC, indicating use of the device is superior to the unaided read for detecting nodules. ClearRead CT was found to decrease read times with and without outliers.  
Developmental testing was conducted to verify requirements according to the ClearRead CT device specifications. The Risk Analysis was completed and risk control measures
implemented to mitigate hazards. Documentation required for software with a Moderate Level of Concern is included as part of the submission. Device labeling together with results from verification & validation testing demonstrate the device is safe and effective.

Conclusion:

In preparing this 510(k) submission, Riverain has carefully considered the relevant statutory and regulatory requirements, and believes that the information contained within satisfies the requirements for demonstrating substantial equivalence.
K161201
Riverain Technologies, LLC
Device Trade Name: Clearread Ct
Contact Name: Jennifer Butsch

DEFICIENCY LIST

(b)(4)
**Indications for Use**

510(k) Number (if known)

K161201

Device Name

ClearRead CT

Indications for Use (Describe)

ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Type of Use (Select one or both, as applicable)

☑ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

**DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.**

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

FORM FDA 3881 (8/14) Page 1 of 1
Riverain Technologies, LLC  
% Ms. Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
3020 South Tech Blvd.  
MIAMISBURG OH 45324

Re: K161201  
Trade/Device Name: ClearRead CT  
Regulation Number: 21 CFR 892.2050  
Regulation Name: Picture archiving and communications system  
Regulatory Class: II  
Product Code: OEB, LLZ  
Dated: September 6, 2016  
Received: September 7, 2016

Dear Ms. Butsch:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act’s requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.
If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH’s Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Robert Ochs, Ph.D.
Director
Division of Radiological Health
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure
Riverain Technologies, LLC  
% Ms. Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
3020 South Tech Blvd.  
MIAMISBURG OH 45324

Re: K161201  
Trade/Device Name: ClearRead CT  
Regulation Number: 21 CFR 892.2050  
Regulation Name: Picture archiving and communications system  
Regulatory Class: II  
Product Code: OEB, LLZ  
Dated: September 6, 2016  
Received: September 7, 2016

Dear Ms. Butsch:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act’s requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.
If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, “Misbranding by reference to premarket notification” (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH’s Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

[Signature]

Robert Ochs, Ph.D.
Director
Division of Radiological Health
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure
### Indications for Use

**K161201**

**Device Name**
ClearRead CT

**Indications for Use (Describe)**
ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

<table>
<thead>
<tr>
<th>Type of Use (Select one or both, as applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[x] Prescription Use (Part 21 CFR 801 Subpart D)</td>
</tr>
<tr>
<td>[ ] Over-The-Counter Use (21 CFR 801 Subpart C)</td>
</tr>
</tbody>
</table>

**CONTINUE ON A SEPARATE PAGE IF NEEDED.**

This section applies only to requirements of the Paperwork Reduction Act of 1995.

**DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.**

The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

- Department of Health and Human Services
- Food and Drug Administration
- Office of Chief Information Officer
- Paperwork Reduction Act (PRA) Staff
- PRAS staff@fda.hhs.gov

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.*
1.0 510(K) SUMMARY

Submission Date: April 25, 2016

Submitter Information:

Company Name: Riverain Technologies, LLC.

Company Address: 3020 South Tech Blvd., Miamisburg, OH 45342-4860

Contact Person: Jennifer Butsch
Director, Regulatory Affairs and Quality Assurance
Riverain Technologies
800.990.3387
937.425.6493
jbutsch@riveraintech.com

Device Information:

Trade Name: ClearRead CT™

Regulation Number: 21 CFR §892.2050

Regulation Name: Picture archiving and communications system

Regulatory Class: Class II

Product Code: OEB/LLZ

Device Description: ClearRead CT is a dedicated post-processing application that generates a secondary vessel suppressed Lung CT series with CADe marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Predicate Devices: syn go.CT Lung CAD
(K143196)
Siemens AG Medical Solutions
Class II

syn go.PET&CT Oncology
(K093621)
Siemens AG Medical Solutions
Class II

ClearRead Bone Suppression (SoftView)
(K092363)
Riverain Technologies, LLC
Class II

Comparison to Predicate Device Technical Characteristics:
Riverain is of the opinion that the ClearRead CT is substantially equivalent, both in intended use and technical characteristics to the listed predicate devices. Differences in the design and performance from the cited predicate devices do not affect either the safety or the effectiveness of ClearRead CT for its intended use.

<table>
<thead>
<tr>
<th>Predicate:</th>
<th>Predicate:</th>
<th>Predicate:</th>
<th>Subject Device:</th>
</tr>
</thead>
<tbody>
<tr>
<td>syngo.CT Lung CAD (Siemens AG Medical Solutions)</td>
<td>syngo.PET &amp; CT Oncology (Siemens AG Medical Solutions)</td>
<td>ClearRead Bone Suppression (Riverain Technologies)</td>
<td>ClearRead CT (Riverain Technologies)</td>
</tr>
<tr>
<td>K143196</td>
<td>K093621</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Intended Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEB</td>
<td>Computer-aided detection tool designed to assist radiologists in the detection of solid pulmonary nodules during review of MDCT examinations of the chest</td>
</tr>
<tr>
<td>LLZ</td>
<td>Viewing, manipulation, 3D-Visualization, and comparison of medical images from multiple imaging modalities.</td>
</tr>
<tr>
<td>LLZ</td>
<td>Generating bone suppressed image from an original PA/AP chest radiograph</td>
</tr>
<tr>
<td>OEB/LLZ</td>
<td>Computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest</td>
</tr>
</tbody>
</table>

Testing Summary:
Clinical validation was conducted in a multi-reader multi-case (MRMC) study to validate that the device conformed to the defined user needs and intended uses. The reader study measured the area under the curve (AUC) of the localization receiver operating characteristic (LROC) response when using ClearRead CT relative to the unaided read. The study also measured the radiologists’ interpretation time when using ClearRead CT relative to unaided interpretations. ClearRead CT was found to significantly increase the AUC, indicating use of the device is superior to the unaided read for detecting nodules. ClearRead CT was found to decrease read times with and without outliers.

Developmental testing was conducted to verify requirements according to the ClearRead CT device specifications. The Risk Analysis was completed and risk control measures
implemented to mitigate hazards. Documentation required for software with a Moderate Level of Concern is included as part of the submission. Device labeling together with results from verification & validation testing demonstrate the device is safe and effective.

**Conclusion:**

In preparing this 510(k) submission, Riverain has carefully considered the relevant statutory and regulatory requirements, and believes that the information contained within satisfies the requirements for demonstrating substantial equivalence.
**DEFICIENCY LIST**

<table>
<thead>
<tr>
<th>K161201/S001</th>
<th>Riverain Technologies, LLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device Trade Name: Clearread Ct</td>
<td>Contact Name: Jennifer Butsch</td>
</tr>
</tbody>
</table>

(b)(4)
1.0 510(K) SUMMARY

Submission Date: April 25, 2016

Submitter Information:

Company Name: Riverain Technologies, LLC.

Company Address: 3020 South Tech Blvd., Miamisburg, OH 45342-4860

Contact Person: Jennifer Butsch
Director, Regulatory Affairs and Quality Assurance
Riverain Technologies
800.990.3387
937.425.6493
jbutsch@riveraintech.com

Device Information:

Trade Name: ClearRead CT™
Regulation Number: 21 CFR §892.2050
Regulation Name: Picture archiving and communications system
Regulatory Class: Class II
Product Code: OEB/LLZ

Device Description: ClearRead CT is a dedicated post-processing application that generates a secondary vessel suppressed Lung CT series with CADe marks and associated region descriptors intended to aid the radiologist in the detection of pulmonary nodules.

Indications for Use: ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.

Predicate Devices: syngo.CT Lung CAD
(K143196)
Siemens AG Medical Solutions
Class II

syngo.PET&CT Oncology
(K093621)
Siemens AG Medical Solutions  
Class II

ClearRead Bone Suppression (SoftView)  
(K092363)  
Riverain Technologies, LLC  
Class II

Comparison to Predicate Device Technical Characteristics:
Riverain is of the opinion that the ClearRead CT is substantially equivalent, both in intended use and technical characteristics to the listed predicate devices. Differences in the design and performance from the cited predicate devices do not affect either the safety or the effectiveness of ClearRead CT for its intended use.

<table>
<thead>
<tr>
<th>Predicate:</th>
<th>Predicate:</th>
<th>Predicate:</th>
<th>Subject Device:</th>
</tr>
</thead>
<tbody>
<tr>
<td>syngo.CT Lung CAD (Siemens AG Medical Solutions) K143196</td>
<td>syngo.PET &amp; CT Oncology (Siemens AG Medical Solutions) K093621</td>
<td>ClearRead Bone Suppression (Riverain Technologies) K092363</td>
<td>ClearRead CT (Riverain Technologies)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Code</th>
<th>OEB</th>
<th>LLZ</th>
<th>LLZ</th>
<th>OEB/LLZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intended Use</td>
<td>Computer-aided detection tool designed to assist radiologists in the detection of solid pulmonary nodules during review of MDCT examinations of the chest</td>
<td>Viewing, manipulation, 3D-Visualization, and comparison of medical images from multiple imaging modalities.</td>
<td>Generating bone suppressed image from an original PA/AP chest radiograph</td>
<td>Computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest</td>
</tr>
</tbody>
</table>

Testing Summary:
Clinical validation was conducted in a multi-reader multi-case (MRMC) study to validate that the device conformed to the defined user needs and intended uses. The reader study measured the area under the curve (AUC) of the localization receiver operating characteristic (LROC) response when using ClearRead CT relative to the unaided read. The study also measured the radiologists’ interpretation time when using ClearRead CT relative to unaided interpretations. ClearRead CT was found to significantly increase the AUC, indicating use of the device is superior to the unaided read for detecting nodules. ClearRead CT was found to decrease read times with and without outliers.

Developmental testing was conducted to verify requirements according to the ClearRead CT device specifications. The Risk Analysis was completed and risk control measures...
implemented to mitigate hazards. Documentation required for software with a Moderate Level of Concern is included as part of the submission. Device labeling together with results from verification & validation testing demonstrate the device is safe and effective.

**Conclusion:**

In preparing this 510(k) submission, Riverain has carefully considered the relevant statutory and regulatory requirements, and believes that the information contained within satisfies the requirements for demonstrating substantial equivalence.
K161201
Riverain Technologies, LLC
Device Trade Name: Clearread Ct
Contact Name: Jennifer Butsch

DEFICIENCY LIST

(b)(4)
Yanna,

Please see my edits.

Thanks,

Qin

---

Hi Qin,

Attached please find my drafted deficiencies related to your questions. I would appreciate it if you could let me know your comments/edits by today or early tomorrow morning (to save us a few days for second round of review especially most of the second round of review will be on statistical review).

Thanks!

Best regards,

Yanna

---

Yanna,

I made a few comments and questions in below. I will ask Gene to see what he thinks.

Qin Li, Ph.D.
Diagnostics Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
WO66 Rm 2268
10903 New Hampshire Avenue,
Silver Spring, MD 20993  
Ph: 301-796-5311  Fax: 301-847-8123  
Email: Qin.Li@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

From: Kang, Yanna  
Sent: Wednesday, June 15, 2016 11:25 AM  
To: Li, Qin  
Subject: FW: K161201, Riverain, ClearRead CT - clarification questions

Hi Qin,

Please find below the sponsor’s responses to our clarification questions. Note that I didn’t ask the question regarding considering (benign nodules + normal) as disease negative. We thought that they should not report the results on this dataset in the labeling because it is NOT in line with the device’s intended use. The device is not intended for detecting cancer nodules but is more generally indicated for detecting lung nodules. So, they should report the (cancer + benign nodules) vs. normal in the labeling. Any thoughts?

Best regards,
Yanna

From: Jennifer Butsch [mailto:jbutsch@riveraintech.com]  
Sent: Wednesday, June 15, 2016 10:48 AM  
To: Kang, Yanna  
CC: K161201@docs.fda.gov  
Subject: RE: K161201, Riverain, ClearRead CT - clarification questions

Hi Yanna,

Please find our responses below.

(b)(4)
Best Regards,
Jennifer

Jennifer Butsch
Director of Regulatory Affairs & Quality Assurance
Riverain Technologies
937-531-5446 (O) | 800-990-3387 x5446
jbutsch@riveraintech.com | www.riveraintech.com

From: Kang, Yanna [mailto:Yanna.Kang@fda.hhs.gov]
Sent: Monday, June 13, 2016 4:32 PM
To: Jennifer Butsch
Cc: K161201@docs.fda.gov
Subject: K161201, Riverain, ClearRead CT - clarification questions

Hi Jennifer,

We have the following clarification questions regarding your clinical study and would appreciate it if you could provide additional information to address those questions:

(b)(4)
Please note that we are still reviewing your file and your clarifications on those questions will help facilitate our statistical review. Please send me your response via email by Thursday, 6/16/2016 or at your earliest convenience.

Best regards,
Yanna

Yanna S. Kang, Ph.D.
Mammography, Ultrasound, and Imaging Software Branch
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
P:301-796-6704
Yanna.Kang@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhccustomerservice?O=500&D=560&B=565&E=R&S=F

This communication is consistent with 21 CFR 10.85 (k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed. This e-mail message is intended for the exclusive use of the recipient named above. It may contain information
510(k) Number (if known)
K161201

Device Name
ClearRead CT

Indications for Use (Describe)
ClearRead CT™ is comprised of computer assisted reading tools designed to aid the radiologist in the detection of pulmonary nodules during review of CT examinations of the chest on an asymptomatic population. The ClearRead CT requires both lungs be in the field of view. ClearRead CT provides adjunctive information and is not intended to be used without the original CT series.
Riverain Technologies, LLC  
% Ms. Jennifer Butsch  
Director of Regulatory Affairs & Quality Assurance  
3020 South Tech Blvd.  
MIAMISBURG OH  45324

Re: K161201  
Trade/Device Name: ClearRead CT  
Regulation Number: 21 CFR 892.2050  
Regulation Name: Picture archiving and communications system  
Regulatory Class: II  
Product Code: OEB, LLZ  
Dated: September 6, 2016  
Received: September 7, 2016

Dear Ms. Butsch:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act’s requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.
Page 2—Ms. Jennifer Butsch

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, “Misbranding by reference to premarket notification” (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH’s Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Robert Ochs, Ph.D.
Director
Division of Radiological Health
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure
# Acceptance Checklist for Traditional 510(k)s

(Should be completed within 15 days of DCC receipt)

The following information is not intended to serve as a comprehensive review. FDA recommends that the submitter include this completed checklist as part of the submission.

<table>
<thead>
<tr>
<th>510(k) #:</th>
<th>K161201</th>
<th>Date Received by DCC:</th>
<th>Apr 28, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead Reviewer:</td>
<td>Yanna Kang</td>
<td>Division:</td>
<td>DRH</td>
</tr>
<tr>
<td>Branch:</td>
<td>MUIS</td>
<td>Center/Office:</td>
<td>CDRH/OIR</td>
</tr>
</tbody>
</table>

Note: If an element is left blank on the checklist, it does not mean the checklist is incomplete; it means the reviewer did not assess the element during the RTA review and that the element will be assessed during substantive review.

**IMPORTANT** - Many checklist elements include additional details regarding information to address the element that can be seen by hovering over the element (Example – Element 4 in Section A of the checklist).

## Preliminary Questions

Answers in the shaded blocks indicate consultation with a Center advisor is needed. (Boxes checked in this section represent FDAs preliminary assessment of these questions at the time of administrative review.)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Is the product a device (per section 201(h) of the FD&amp;C Act) or a combination product (per 21 CFR 3.2(e)) with a device constituent part subject to review in a 510(k)? If it appears not to be a device (per section 201(h) of the FD&amp;C Act) or such a combination product, or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Product Jurisdiction Liaison to determine the appropriate action, and inform division management. Provide a summary of the Jurisdictional Officer's/Liaison's determination. If the product does not appear to be a device or such a combination product, mark &quot;No.&quot;</td>
<td>✗</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:

2. Is the submission with the appropriate Center?

If the product is a device or a combination product with a device constituent part, is it subject to review by the Center in which the submission was received? If you believe the submission is not with the appropriate Center or you are unsure, consult with the CDRH Jurisdictional Officer or CBER Product Jurisdiction Liaison to determine the appropriate action and inform your division management. Provide a summary of the Jurisdictional Officer's/Liaison's determination. If submission should not be reviewed by your Center mark "No."

Comments:

3) If a Request for Designation (RFD) was submitted for the device or combination product with a device constituent part and assigned to your center, identify the RFD # and confirm the following:

a) Is the device or combination product the same (e.g., design, formulation) as that presented in the RFD submission?

b) Are the indications for use for the device or combination product identified in the 510(k) the same as those identified in the RFD submission?

If you believe the product or the indications presented in the 510(k) have changed from the RFD, or you are unsure, consult with the CDRH Jurisdictional Officer or the CBER Product Jurisdiction Liaison to determine the appropriate action and inform your division management. Provide summary of Jurisdictional Officer's/Liaison's determination.

If the answer to either question above is no, mark "No." If there was no RFD, mark "N/A."

Comments:
4) Is this device type eligible for a 510(k) submission?
If a 510(k) does not appear to be appropriate (e.g., Class III type and PMA required, or Class I or II type and 510(k)-exempt), you should consult with the CDRH 510(k) Program Director or appropriate CBER staff during the acceptance review. If 510(k) is not the appropriate regulatory submission, mark "No."

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>

Comments:

5) Is there a pending PMA for the same device with the same indications for use?
If yes, consult division management and the CDRH 510(k) Program Director or appropriate CBER staff to determine the appropriate action.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>×</td>
</tr>
</tbody>
</table>

Comments:

6) If clinical studies have been submitted, is the submitter the subject of an Application Integrity Policy (AIP)?
If yes, consult with the CDRH Office of Compliance/Division of Bioresearch Monitoring (OC/DBM) or CBER Office of Compliance and Biologics Quality/Division of Inspections and Surveillance/Bioresearch Monitoring Branch (OCBQ/DIS/BMB) to determine the appropriate action. Check on web at http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/ucm134453.htm
If no clinical studies have been submitted, mark "N/A."

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>×</td>
</tr>
</tbody>
</table>

Comments:

- If the answer to 1 or 2 appears to be "No," then stop review of the 510(k) and issue the "Original Jurisdictional Product" letter.
- If the answer to 3a or 3b appears to be "No," then stop the review and contact the CDRH Jurisdictional Officer or CBER Office of Jurisdiction Liaison.
- If the answer to 4 is "No," the lead reviewer should consult division management and other Center resources to determine the appropriate action.
- If the answer to 5 is "Yes," then stop review of the 510(k), contact the CDRH 510(k) Staff and PMA Staff, or appropriate CBER staff.
- If the answer to 6 is "Yes," then contact CDRH/OC/DBM or CBER/OCBQ/DIS/BMB, provide a summary of the discussion with DBM or BMB Staff, and indicate their recommendation/action.
**Organizational Elements**

*Failure to include these items should not result in an RTA designation.*

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>*Page #</th>
</tr>
</thead>
</table>

1) Submission contains a Table of Contents

2) Each section is labeled (e.g., headings or tabs designating Device Description section, Labeling section, etc.)

3) All pages of the submission are numbered.

4) Type of 510(k) is identified (i.e., Traditional, Abbreviated, or Special).

**Comments:**

NOTE: If Page # is not specified for a specific item in this RTA Checklist, then the information can be easily found in the document with a self-explanatory name submitted by the sponsor. For example, Item 1 can be found in Document "Table of Contents".

---

**Elements of a Complete Submission (RTA Items)**

*(21 CFR 807.87 unless otherwise indicated)*

Submission should be designated RTA if not addressed.

- Any "No" answer will result in a "Refuse to Accept" decision; however, FDA staff has discretion to determine whether missing items are needed to ensure that the submission is administratively complete to allow the submission to be accepted or to request missing checklist items interactively from submitters during RTA review.

- Each element on the checklist should be addressed within the submission. The submitter may provide a rationale for omission for any criteria that are deemed not applicable. If a rationale is provided, the criterion is considered present (Yes). An assessment of the rationale will be considered during the review of the submission.
### A. Administrative

1) All content used to support the submission is written in English (including translations of test reports, literature articles, etc.)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Comment</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2) Submission identifies the following (FDA recommends use of the CDRH Premarket Review Submission Cover Sheet form [Form 3514]):

   a) Device trade/proprietary name

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |

   b) Device class and panel or Classification regulation or Statement that device has not been classified with rationale for that conclusion

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |

3) Submission contains an Indication for Use Statement with Rx and/or OTC designated (see also 21 CFR 801.109, and FDA's guidance “Alternative to Certain Prescription Devices Labeling Requirements.”) See recommended format.

   ![Recommended Format](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/UCM360431.pdf)

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |

4) Submission contains a 510(k) Summary or 510(k) Statement.

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |

5) Submission contains a Truthful and Accuracy Statement per 21 CFR 807.87(k)

   See recommended format.

   ![Recommended Format](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotifcation510k/ucm142707.htm)

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |

   Comments: The Truthful and Accuracy Statement was provided but not signed. This is minor and can be resolved interactively.

6) Submission is a Class III 510(k) device.

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |

7) Submission contains clinical data

   a) Submission includes completed Financial Certification (FDA Form 3454) or Disclosure (FDA Form 3455) information for each covered clinical study included in the submission.

   Select “N/A” if the submitted clinical data is not a “covered clinical study” as defined in the Guidance for Industry- Financial Disclosures by Clinical Investigators.

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |

   b) Submission includes completed Certification of Compliance with requirements of ClinicalTrials.gov Data Bank (FDA Form 3674) (42 U.S.C. 282(j)(5)(B)) for each applicable device clinical trial included in the submission.

   Select “N/A” if the submitted clinical data is not an “applicable device clinical trial” as defined in Title VIII of FDAAA, Sec. 801(j)

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |

   Comments: Both Form 3454 and 3674 were provided but neither of them has been signed. This is minor and can be resolved interactively.

8) The submission identifies prior submissions for the same device included in the current submission (e.g., submission numbers for a prior not substantially equivalent [NSE] determination, prior deleted or withdrawn 510(k), Pre-Submission, IDE, PMA, etc.).

   OR

   States that there were no prior submissions for the subject device.

   a) If there were prior submissions, the submitter has identified where in the current submission any issues related to a determination of substantial equivalence from prior submissions for this device are addressed.

   | Yes | No | N/A | Comment | Page # |
   | X   |    |     |         |       |
**B. Device Description**

9) The device has a device-specific guidance document, special controls document, and/or \(\text{Yes} \) \(\text{No} \) \(\text{N/A} \) \(\text{Comment} \)
requirements in a device-specific regulation regarding device description that is
applicable to the subject device.

\(\text{No} \)

a) The submission addresses device description recommendations outlined in the
device-specific guidance.
\(\text{Yes} \)

\(\text{OR} \)
The submission provides an alternative approach intended to address the
applicable statutory and/or regulatory criteria.

b) The submission includes device description information that addresses relevant
mitigation measures set forth in a special controls document or device-specific
regulation applicable to the device.
\(\text{Yes} \)

\(\text{OR} \)
The submission uses alternative mitigation measures and provides rationale
why the alternative measures provide an equivalent assurance of safety and
effectiveness.

10) Descriptive information is present and consistent within the submission (e.g., the
device description section is consistent with the device description in the labeling).
\(\text{Yes} \)

p11

11) The submission includes descriptive information for the device, including the
following:

\(\text{Yes} \)

a) A description of the principle of operation or mechanism of action for achieving
the intended effect.

\(\text{Yes} \)

b) A description of proposed conditions of use, such as surgical technique for
implants; anatomical location of use; user interface; how the device interacts
with other devices; and/or how the device interacts with the patient.

\(\text{No} \)

c) A list and description of each device for which clearance is requested.

\(\text{No} \)

d) Submission contains representative engineering drawing(s), schematics,
illustrations, photos and/or figures of the device.

\(\text{Yes} \)

\(\text{OR} \)
Submission includes a statement that engineering drawings, schematics, etc.
are not applicable to the device (e.g., device is a reagent and figures are not
pertinent to describe the device).

12) Device is intended to be marketed with multiple components, accessories, and/or as
part of a system.
\(\text{No} \)

**C. Substantial Equivalence Discussion**

13) Submitter has identified a predicate device(s), including the following information:

\(\text{Yes} \)

a) Predicate device identifier provided (e.g., 510(k) number, de novo number,
reclassified PMA number, regulation number if exempt or statement that the
predicate is a preamendment device).

\(\text{Yes} \)

For predicates that are preamendments devices, information is provided to
document preamendments status.

*Information regarding documenting preamendment status is available online.*
(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/
MedicalDeviceQualityandCompliance/ucm379552.htm).

p14
Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed.

*Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Comment</th>
<th>*Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b) The identified predicate(s) is consistent throughout the submission (e.g., the predicate(s) identified in the Substantial Equivalence section is the same as that listed in the 510(k) Summary (if applicable) and that used in comparative performance testing).

14) Submission includes a comparison of the following for the predicate(s) and subject device and a discussion why any differences between the subject and predicate(s) do not impact safety and effectiveness [see section 513(i)(1)(A) of the FD&C Act and 21 CFR 807.87(f)].

See "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications 510(k)" guidance document for more information on comparing intended use and technological characteristics.

a) Indications for Use

b) Technology, including features, materials, and principles of operation

D. Proposed Labeling (see also 21 CFR part 801 and 809 as applicable)

15) Submission includes proposed package labels and labeling (e.g., instructions for use, package insert, operator's manual).

a) Indications for use are stated in labeling and are identical to Indications for Use form and 510(k) Summary (if 510(k) Summary provided).

b) Labeling includes:
   - Statements of conditions, purposes or uses for which the device is intended (e.g., hazards, warnings, precautions, contraindications) (21 CFR 801.5)
   AND
   - Includes adequate directions for use (see 21 CFR 801.5)
   OR
   - Submission states that device qualifies for exemption per 21 CFR 801 Subpart D

16) Labeling includes name and place of business of the manufacturer, packer, or distributor (21 CFR 801.1).

17) Labeling includes the prescription statement [see 21 CFR 801.109(b)(1)] or Rx Only symbol (see also Section 502(a) of the FD&C Act and FDA’s guidance “Alternative to Certain Prescription Device Labeling Requirements”).

18) The device has a device-specific guidance document, special controls document, and/or requirements in a device-specific regulation regarding labeling that is applicable to the subject device.

a) The submission addresses labeling recommendations outlined in the device-specific guidance.

OR

The submission provides an alternative approach intended to address the applicable statutory and/or regulatory criteria.

b) The submission includes labeling information that addresses relevant mitigation measures set forth in a special controls document or device-specific regulation applicable to the device.

OR

The submission uses alternative mitigation measures and provides rationale why the alternative measures provide an equivalent assurance of safety and effectiveness.
<table>
<thead>
<tr>
<th>E. Sterilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>If an in vitro diagnostic (IVD) device and sterilization is not applicable, select &quot;N/A.&quot; The criteria in this section will be omitted from the checklist if &quot;N/A&quot; is selected.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>F. Shelf Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>24) Proposed shelf life/expiration date stated</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Statement that shelf-life is not applicable because of low likelihood of time-dependent product degradation</td>
</tr>
<tr>
<td>25) For a sterile device, submission includes summary of methods used to establish that device packaging will maintain a sterile barrier for the entirety of the proposed shelf life.</td>
</tr>
<tr>
<td>26) Submission includes summary of methods used to establish that device performance is maintained for the entirety of the proposed shelf life (e.g., mechanical properties, coating integrity, pH, osmolality, etc.).</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Statement why performance data is not needed to establish maintenance of device performance characteristics over the shelf-life period.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>G. Biocompatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>If an in vitro diagnostic (IVD) device, select &quot;N/A.&quot; The criteria in this section will be omitted from the checklist if &quot;N/A&quot; is selected.</td>
</tr>
</tbody>
</table>

Submission states that there: (one of the below must be checked)

- Are direct or indirect patient-contacting components. 
  - X Are no direct or indirect patient-contacting components. 
- Information regarding patient contact status of the device is not provided (if this box checked, please also check one of the two boxes below).
  - Patient contact information not needed for this device (e.g., software-only device)
  - Patient contact information needed or need unclear

This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.

<table>
<thead>
<tr>
<th>H. Software</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission states that the device: (one of the below must be checked)</td>
</tr>
<tr>
<td>X Does contain software/firmware</td>
</tr>
<tr>
<td>Does not contain software/firmware</td>
</tr>
<tr>
<td>Information on whether device contains software/firmware is not provided. (If this box is checked, please also check one of the two boxes below.)</td>
</tr>
<tr>
<td>Software/firmware information not needed for this device (e.g., surgical suture, condom)</td>
</tr>
<tr>
<td>Software/firmware information is needed or need unclear</td>
</tr>
</tbody>
</table>
### I. Electrical Safety and EMC

**Electrical Safety**
Submission states that the device: (one of the below must be checked)

<table>
<thead>
<tr>
<th>Does require electrical safety evaluation</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Comment</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does not require electrical safety evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information on whether device requires electrical safety evaluation is not provided. (If this box is checked, please also check one of the two boxes below.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrical safety information not needed for this device (e.g., surgical suture, condom)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrical safety information is needed or need unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.

**EMC**
Submission states that the device: (one of the below must be checked)

<table>
<thead>
<tr>
<th>Does require EMC evaluation</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Comment</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does not require EMC evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information on whether device requires EMC evaluation is not provided. (If this box is checked, please also check one of the two boxes below.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMC information not needed for this device (e.g., surgical suture, condom)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMC information is needed or need unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This information will determine whether and what type of additional information may be necessary for a substantial equivalence determination.

### J. Performance Data - General

If an in vitro diagnostic (IVD) device, select "N/A." The criteria in this section will be omitted from checklist if "N/A" is selected. Performance data criteria relating to IVD devices is addressed in Section K.

34) Full test report is provided for each completed test. A full test report includes: objective of the test, description of the test methods and procedures, study endpoint(s), pre-defined pass/fail criteria, results summary, conclusions.

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
<th>Comment</th>
<th>Page #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Submission includes an explanation of how the data generated from each test report supports a finding of substantial equivalence (e.g., comparison to predicate device testing, dimensional analysis, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Check "Yes" if item is present; "N/A" if it is not needed and "No" if it is not included but needed.

*Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.

| 35) The device has a device-specific guidance document, special controls document, and/or requirements in a device-specific regulation regarding performance data that is applicable to the subject device. |
|---|---|---|---|---|
| **Yes** | **No** | **N/A** | **Comment** | **Page #** |
| × | | | | |
| a) The submission addresses performance data recommendations outlined in the device-specific guidance. **OR** The submission provides an alternative approach intended to address the applicable statutory and/or regulatory criteria. | × | | | |
| b) The submission includes performance data that addresses relevant mitigation measures set forth in a special controls document or device-specific regulation applicable to the device. **OR** The submission uses alternative mitigation measures and provides rationale why the alternative measures provide an equivalent assurance of safety and effectiveness. | × | | | |

| 36) If literature is referenced in the submission, submission includes: |
|---|---|---|---|---|
| | | | | |
| × | | | | |
| 37) For each completed animal study, the submission provides the following: |
|---|---|---|---|---|
| | | | | |
| × | | | | |

**K. Performance Characteristics - In Vitro Diagnostic Devices Only**
(Also see 21 CFR 809.10(b)(12))

Submission states that the device: (one of the below must be checked)

- is an in vitro diagnostic device. **X**
- is not an in vitro diagnostic device.

*If "is not" is selected, the performance data-related criteria below are omitted from the checklist.*
**Digital Signature Concerrence Table**

<table>
<thead>
<tr>
<th>Reviewer Sign-Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yanna S. Kang -S</td>
</tr>
<tr>
<td>2016.05.02 08:56:44 -04'00'</td>
</tr>
</tbody>
</table>

| Branch Chief Sign-Off (digital signature optional)* |

| Division Sign-Off (digital signature optional)* |

*Branch and Division review of checklist and concurrence with decision required.
Branch and Division digital signature optional.*
K161201/S001
Riverain Technologies, LLC
Device Trade Name: Clearread Ct
Contact Name: Jennifer Butsch

DEFICIENCY LIST

(b)(4)
Right, since they did not plan multiplicity for reading time, it cannot be described using word **significantly**.

They can report reading time for each modality and individual confidence interval. They are report difference of reading times. But not CI for the difference and p-value.

Qin Li, Ph.D.
Diagnostics Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
WO66 Rm 2268
10903 New Hampshire Avenue,
Silver Spring, MD 20993
Ph: 301-796-5311 Fax: 301-847-8123
Email: Qin.Li@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
https://www.research.net/s/cdrhcrowerservice?O=600&D=660&B=663&E=&S=F

---

**From:** Kang, Yanna
**Sent:** Wednesday, July 27, 2016 4:04 PM
**To:** Li, Qin
**Subject:** RE: statistical review of K161201/S001, Riverain ClearRead Lung CT

Qin,

One more quick question: the sponsor states in the 510k Summary that “ClearRead CT was found to significantly decrease read times with and without outliers.” Although the sponsor did not say “statistically significant”, does it imply that this conclusion was based on the hypothesis testing results, which is not allowed to be reported for reading time?

Best regards,
Yanna

---

**From:** Li, Qin
**Sent:** Wednesday, July 27, 2016 10:20 AM
**To:** Kang, Yanna
**Subject:** RE: statistical review of K161201/S001, Riverain ClearRead Lung CT

Yanna,
Let’s rephrase it to “…because the third session was necessary for precise estimation of the modality effect since the first two reading sessions are completely confounded with modality. In addition, leaving session and order effects in…”.

Sorry about it.
Qin Li, Ph.D.
Diagnostics Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
WO66 Rm 2268
10903 New Hampshire Avenue,
Silver Spring, MD 20993
Ph: 301-796-5311 Fax: 301-847-8123
Email: Qin.Li@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received: https://www.research.net/s/cdrhcustomerservice?

From: Kang, Yanna
Sent: Wednesday, July 27, 2016 10:04 AM
To: Li, Qin
Subject: RE: statistical review of K161201/S001, Riverain CLeaRead Lung CT

Qin,

Thanks so much for your thorough review! I have a quick clarification question:

(b)(4)

Best regards,
Yanna

From: Li, Qin
Sent: Tuesday, July 26, 2016 9:47 PM  
To: Kang, Yanna  
Cc: Pennello, Gene; Li, Meijuan; Ballyns, Jeffrey; Gavrielides, Marios A  
Subject: statistical review of K161201/S001, Riverain CLeaRead Lung CT

Yanna,

Please see attachment for my review. let me know if you have any questions.

Thanks,

Qin Li, Ph.D.  
Diagnostics Devices Branch  
Division of Biostatistics  
Office of Surveillance and Biometrics  
Center for Devices and Radiological Health  
WO66 Rm 2268  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993  
Ph: 301-796-5311 Fax: 301-847-8123  
Email: Qin.Li@fda.hhs.gov

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

I think the model should be described briefly but non-technically. Thus, on p. 25 I would suggest replacing

Data from all three reader arms was pooled and analyzed based on established test hypotheses

with

Data from all three reader arms was pooled and analyzed based on established test hypotheses for reading modality (unaided or aided with ClearRead CT). Measures of performance (pAUC, sensitivity, specificity, NPV, PPV, reading time) were estimated in each reading modality after adjustment for design effects (arm, case block, order, reader).

On p.24, after

to unaided interpretations was measured.

I suggest adding the following:

LROC pAUC was evaluated per reader and scaled to have a maximum value of 1 according to the formula

\[ pAUC = \frac{\text{max}(\text{sensitivity}_m)}{m} \times \frac{\text{max}(1 - \text{specificity}_m)}{m} \]

where m denotes a reading modality (unaided or aided with ClearRead CT). The maximum values of sensitivity and 1 - specificity across the modalities were used to define the range over which the unscaled pAUC (numerator in formula) was calculated.

I suggest also adding the same description of LROC pAUC as a footnote to the table “LROC pAUC ClearRead CT - Unaided” on p. 2.

Gene Pennello, PhD, Team Leader
FDA/CDRH/AMS/DRS/Diagnostic Statistics Branch
15505 New Hampshire Avenue, WO66 rm 2268, Silver Spring, MD 20993
Ph: 301-796-5999 Fax: 301-443-3382 Email: gene.pennello@fda.hhs.gov

From: Kang, Yanna
Sent: Thursday, September 08, 2016 9:51 AM
To: Li, Qin
Cc: Pennello, Gene; Ballyns, Jeffrey; Cadotte, Alex
Subject: RE: K161201/S002, Riverain, formal response

Thanks, Qin.

Gene – Could you please let me know if you have additional comments on the labeling? I plan to send the final labeling comments to the sponsor today and close out this file Friday or Monday. Thanks so much!

Best regards,

Yanna

From: Li, Qin
Sent: Wednesday, September 07, 2016 5:30 PM
To: Kang, Yanna
Cc: Pennello, Gene; Ballyns, Jeffrey; Cadotte, Alex
Subject: RE: K161201/S002, Riverain, formal response

Yes, I think the definition of pAUC should be briefly described.

Also for the random effect model, I will talk to Gene. There should be a description for the three arm study design. And in the model description, they can mention cases and readers were treated as random effect.

Qin Li, Ph.D.
Diagnostics Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
WO66 rm 2268
10903 New Hampshire Avenue,
Silver Spring, MD 20993
From: Kang, Yanna  
Sent: Wednesday, September 07, 2016 5:10 PM  
To: Li, Qin  
Cc: Pennello, Gene; Ballyns, Jeffrey; Cadotte, Alex  
Subject: RE: K161201/5002, Riverain, formal response  

Thanks, Qin. They didn’t describe how they define pAUC in the labeling. Regarding the description of the pAUC, for which they used scaled pAUC, do they need to describe the following equation briefly in text?  

In addition to this, do you think the modeling data (fixed and random effect data) are needed in the labeling? I’m not sure if the user will understand this and benefit from this. Thanks.

Best regards,  
Yanna

From: Li, Qin  
Sent: Wednesday, September 07, 2016 4:56 PM  
To: Kang, Yanna  
Cc: Pennello, Gene; Ballyns, Jeffrey; Cadotte, Alex  
Subject: RE: K161201/5002, Riverain, formal response  

Thanks, Yanna.

I think the labelling should also describe how pAUC was defined in addition to the results.

Qin Li, Ph.D.  
Diagnostics Devices Branch  
Division of Biostatistics  
Office of Surveillance and Biometrics  
Center for Devices and Radiological Health  
WO66 Rm 2268  
10903 New Hampshire Avenue,  
Silver Spring, MD 20993  
Ph: 301-796-5311 Fax: 301-847-8123  
Email: Qin.Li@fda.hhs.gov  

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:  
https://www.research.net/s/cdrhcustomerservice?0=600&D=660&B=663&E=R5=E  

From: Kang, Yanna  
Sent: Wednesday, September 07, 2016 4:52 PM  
To: Li, Qin  
Cc: Pennello, Gene; Ballyns, Jeffrey; Cadotte, Alex  
Subject: K161201/5002, Riverain, formal response  

Hi Qin,  

Riverain’s formal response 5002 just came in. Based on our previous interactions with the sponsor, their modeling approaches and the analysis results look fine. I believe this formal statistical review will determine if and what modeling data will need to be included in the labeling. Their current labeling reports the following LSMean difference for pAUC of LROC, which pools data from all three...