



November 15, 2024

Koios Medical, Inc.  
% Michael Bocchinfuso  
Director of Regulatory Compliance and Quality  
242 West 38th Street  
14th Floor  
New York, NY 10018

Re: K242130

Trade/Device Name: Koios DS

Regulation Number: 21 CFR 892.2060

Regulation Name: Radiological computer-assisted diagnostic software for lesions suspicious of cancer

Regulatory Class: Class II

Product Code: POK, QIH

Dated: August 13, 2024

Received: August 19, 2024

Dear Michael Bocchinfuso:

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 (the 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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> identifies combination product submissions. 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.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (<https://www.fda.gov/media/99812/download>) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (<https://www.fda.gov/media/99785/download>).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these requirements, please see the UDI System webpage at <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system>.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems>.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance>) and CDRH Learn (<https://www.fda.gov/training-and-continuing-education/cdrh-learn>). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice>) for more information or contact DICE by email ([DICE@fda.hhs.gov](mailto:DICE@fda.hhs.gov)) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

**YANNA S. KANG -S**

Yanna Kang, Ph.D.

Assistant Director

Mammography and Ultrasound Team

DHT8C: Division of Radiological Imaging  
and Radiation Therapy Devices

OHT8: Office of Radiological Health

Office of Product Evaluation and Quality

Center for Devices and Radiological Health

Enclosure

## Indications for Use

510(k) Number (if known)

K242130

Device Name

Koios DS

Indications for Use (Describe)

Koios Decision Support (DS) is an artificial intelligence (AI)/machine learning (ML)-based computer-aided diagnosis (CADx) software device intended for use as an adjunct to diagnostic ultrasound examinations of lesions or nodules suspicious for breast or thyroid cancer.

Koios DS allows the user to select or confirm regions of interest (ROIs) within an image representing a single lesion or nodule to be analyzed. The software then automatically characterizes the selected image data to generate an AI/ML-derived cancer risk assessment and selects applicable lexicon-based descriptors designed to improve overall diagnostic accuracy as well as reduce interpreting physician variability.

Koios DS software may also be used as an image viewer of multi-modality digital images, including ultrasound and mammography. The software includes tools that allow users to adjust, measure and document images, and output into a structured report.

Koios DS software is designed to assist trained interpreting physicians in analyzing the breast ultrasound images of adult ( $\geq 22$  years) female patients with soft tissue breast lesions and/or thyroid ultrasounds of all adult ( $\geq 22$  years) patients with thyroid nodules suspicious for cancer. When utilized by an interpreting physician who has completed the prescribed training, this device provides information that may be useful in recommending appropriate clinical management.

Limitations:

- Patient management decisions should not be made solely on the results of the Koios DS analysis.
- Koios DS software is not to be used for the evaluation of normal tissue, on sites of post-surgical excision, or images with doppler, elastography, or other overlays present in them.
- Koios DS software is not intended for use on portable handheld devices (e.g. smartphones or tablets) or as a primary diagnostic viewer of mammography images.
- The software does not predict the presence of the thyroid nodule margin descriptor, extra-thyroidal extension. In the event that this condition is present, the user may select this category manually from the margin descriptor list.

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.

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## 510(k) Summary of Safety and Effectiveness

This 510(k) summary of safety and effectiveness information is submitted as part of the Premarket Notification in accordance with the requirements of 21 CFR Part 807, Subpart E and Section 807.92.

### 1. Identification of Submitter:

Submitter: Koios Medical Inc.  
Address: 242 West 38th Street, 14th Floor  
New York, NY 10018  
Phone: 732-529-5755  
Fax: 732-529-5757  
Contact: Michael Bocchinfuso  
Title: Director of Regulatory Compliance and Quality  
Phone: 732-529-5755  
Fax: 732-529-5757  
Summary Date: October 18, 2024

### 2. Identification of Product:

Device Name: Koios DS  
Version 3.6  
Device Common Name: Radiological Computer-Assisted Diagnostic Software  
Device Classification: 21 CFR 892.2060, Class II, POK (primary)  
21 CFR 892.2050, Class II, QIH (secondary)  
Classification Name: Radiological Computer-Assisted Diagnostic Software (CADx) for  
Lesions Suspicious for Cancer  
Manufacturer: Koios Medical, Inc.

### 3. Marketed Devices

In terms of safety and performance, this software medical device is substantially equivalent to the devices listed below:

Predicate device: Koios DS  
Manufacturer: Koios Medical, Inc.

#### 4. Device Description

Koios Decision Support (DS) is a software application designed to assist trained interpreting physicians in analyzing breast and thyroid ultrasound images. The software device is a web application that is deployed to a Microsoft IIS web server and accessed by a user through a compatible client. Once logged in and granted access to the Koios DS application, the user examines selected breast or thyroid ultrasound DICOM images. The user selects Regions of Interest (ROIs) of orthogonal views of a breast lesion or thyroid nodule for processing by Koios DS. The ROI(s) are transmitted electronically to the Koios DS server for image processing and the results are returned to the user for review.

##### **Breast Functionality:**

Koios DS software automatically classifies breast lesions suspicious for cancer based on image data into one of four ACR BI-RADS® Atlas<sup>1</sup> or European U1-U5 Classification System-aligned categories (Benign, Probably Benign, Suspicious or Indeterminate, or Probably Malignant) and also displays a continuous graphical Confidence Level Indicator depicting where the lesion falls within its respective category and its relation to neighboring categories. The software automatically classifies the shape (Round, Oval, Irregular) and orientation (Parallel, Not Parallel) of the selected lesion.

##### **Thyroid Functionality:**

Koios DS is a software medical device used to analyze ultrasound data to classify user-selected regions containing thyroid nodules suspicious for cancer. The software generates a set of user-editable sonographic nodule descriptor recommendations (Composition, Echogenicity, Shape, Margin, Echogenic Foci) along with an optional, deep-learning derived cancer risk assessment of the suspected nodule from two orthogonal views. Nodule descriptor recommendations are subsequently mapped to a categorical assessment and risk level rating via the ACR TI-RADS™ ATLAS or American Thyroid Association (ATA) risk stratification systems (RSSs) based on user preference. The software's direct, non-descriptor-based cancer risk assessment is presented as the Koios "AI Adapter" that, when used in conjunction with the ACR TI-RADS or ATA guidelines for nodule risk stratification, is shown to improve overall diagnostic performance of both systems. The AI Adapter operates as an optional lexicon-specific input used to modify the final categorization in the ACR TI-RADS and ATA RSSs. The AI adapter positively impacts performance through either a point-based modification (either positive or negative) or a risk-shift modification (either positive or negative) for ACR TI-RADS and the ATA systems, respectively.

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<sup>1</sup> BI-RADS® ATLAS is a registered trademark of American College of Radiology. All Rights Reserved.

This process creates an AI-augmented categorization that is meant to be used with no other modifications to the decision-making pathway of either RSS. A trained interpreting physician may choose to incorporate or exclude the Koios AI Adapter from the overall assessment when finalizing their diagnostic interpretation.

Koios DS enables the following functionality:

- Breast and Thyroid Diagnostic Core AI Engines enabled by state-of-the-art computer vision and machine learning techniques capable of reading, interpreting, analyzing, classifying and generating findings from ultrasound image data resulting in an automated risk assessment for breast lesions and thyroid nodules suspicious for cancer.
- Automatic classification of thyroid nodule TI-RADS and ATA Descriptors of: Composition, Echogenicity, Shape, Margin, and Echogenic Foci based on user-selected regions of interest (ROIs).
- Automatic classification of breast lesion BI-RADS and U1-U5 Descriptors Shape and Orientation based on user-selected or confirmed regions of interest (ROIs).
- Annotation and description of ultrasound images based on ACR BI-RADS Breast Imaging Atlas and U1-U5 for Koios DS Breast and ACR TI-RADS Atlas for thyroid lexicon classification forms and ATA classification guidelines for Koios DS Thyroid.
- Reporting forms for breast lesion or thyroid nodule identification and tracking in the Electronic Health Record.
- Smart Calipers - extraction of user-supplied ROI data (alternately referred to as Calipers) embedded in DICOM SR files from the ultrasound modality.
- Smart Click - for streamlining the manual ROI selection process. The Smart Click functionality enables the user to click on the center of a lesion in order to activate a system-generated region of interest surrounding the selected lesion for the user.
- Image Registration and Matching - allows users to select images and regions of interest through their own image viewers when interacting with Koios DS Breast and Koios DS Thyroid, and facilitates a flexible viewer agnostic workflow. When the Image Matching Engine is given a screenshot of a medical image with coordinates for a region of interest, it identifies the original full quality image and translates the coordinates to its frame of reference.
- Automatic Size and Position population using Optical Character Recognition (OCR) - the Koios DS Optical Character Recognition engine uses machine learning and rule-based methods to create a system which is capable of retrieving fast, accurate transcriptions of the text overlaid on ultrasound images. Given an ultrasound image that has been annotated by a radiologist or technician, the OCR function identifies all text in the image and extracts relevant information to the documentation of lesions or nodules.

This allows users to quickly interpret and transcribe the locations and measurements of ultrasound findings.

- Remote analysis interface to generate and view results within compatible software (e.g. ultrasound equipment or PACS workstation software).
- Installer and Configuration Wizard.
- Single Sign-on (SSO) Windows and LDAP Authentication.
- Operating system and platform-agnostic usage.
- Zero-footprint web-based HTML5 DICOM image viewer with image manipulation and annotation tools.
- Ability to save findings to PACS.
- Ability to export findings to reporting software.

**User Profile:**

Koios DS is for use by trained professionals only. Koios DS is not for use by patients. Users must have appropriate medical professional competence, such as trained sonographers and interpreting physicians.

**Use Environment:**

Koios DS is a software application for use within the healthcare setting (in a clinic or hospital) for the examination and assessment of breast lesions or thyroid nodules using ultrasound. It is a platform-agnostic web application that queries and accepts DICOM compliant digital medical files from any compliant device subject to the specified DICOM Conformance Statement for Koios DS. Processing of the image(s) occurs in conjunction with a trained interpreting physician's typical diagnostic case read. The output of the system is a digital display to be used as a concurrent read and report input that may be added as an addendum to the DICOM series selected for processing or exported directly into a patient's draft report.

**Operating Principle:**

Koios DS is an ASP.NET web application deployed to a web server inside a Windows operating system environment accessed by a user through a compatible client. The application provides image-derived data via web triggering and remote analysis.

Once logged in and granted access to the Koios DS application, the user examines selected breast and thyroid ultrasound DICOM images. For breast functionality, the user selects or confirms up to two ROIs, from up to two orthogonal views that represent a single breast lesion for processing by the system. For thyroid functionality, two ROIs are required for processing by the system. The first ROI must be drawn on the transverse view, with the second on the

longitudinal view of the nodule. For breast functionality, bench testing has verified a single ROI does not significantly decrease system AUC performance. The ROI(s) are transmitted electronically to the Koios DS server by the Koios DS Breast or Thyroid software for image processing and the results are returned to the user for review in the respective interface. Images and data can be stored, communicated, processed, and displayed within the system and/or across computer networks at distributed locations.

The Koios DS Client is an optional workflow enhancement tool installed as a desktop application on the user workstation that enables a user to draw ROIs natively within their image viewing software. The Koios DS Client captures a screenshot of the ROI selected by the user instead of being directly drawn on and captured with DICOM data. The ROI screenshot is transmitted electronically to the Image Matching Engine within the Koios DS Server. The Image Matching Engine processes the ROI screenshot and data, identifying and matching the correct DICOM image, and overlaying the ROI on that image. Once matched, the ROIs are returned to the user for review in the Koios DS Breast or Thyroid interface.

The software does not require any specialized hardware to return a diagnostic output, but the time to process ROIs will vary depending on the hardware specifications.

Koios DS contains two distinct AI/ML engines to characterize breast lesions and thyroid nodules. Based on the structured data that exists within the DICOM header for a patient study, the Koios DS system calls the corresponding engine for analysis of the identified lesion or nodule. Each system uses computer vision and machine learning techniques embedded within an engine capable of reading, interpreting, analyzing, and generating findings from ultrasound data. The underlying Breast and Thyroid engines draw upon knowledge learned from a large database of known cases, tying image features to their eventual diagnosis, to form a predictive model.

Koios DS results can be saved or transferred in three separate ways: in-transit transmission, saving to Picture Archiving and Communication System (PACS), and exporting results to third-party reporting software. In-transit transmission may be utilized when users wish to share analyses across viewing workstations. Results can be stored in in-transit memory for a preset period of time defined by a system administrator. After that preset period of time, all results are wiped from the local memory. Another method of saving is storing a report in the patient study on the PACS. After single or multiple lesion or nodule analyses have been performed and ultimately accepted by a trained interpreting physician, Koios DS can export a summary report to PACS as an addendum to the DICOM study that was selected for processing. This report serves as future reference and aid in the comparison of cases requiring follow up. This functionality is strictly reserved for approved users and must be configured by a site administrator.

Koios DS also supports exporting results to third-party reporting software to facilitate the reporting process. Saving or exporting preferences can be configured by the system administrator and user.

## **5. Indications for Use**

Koios Decision Support (DS) is an artificial intelligence (AI)/machine learning (ML)-based computer-aided diagnosis (CADx) software device intended for use as an adjunct to diagnostic ultrasound examinations of lesions or nodules suspicious for breast or thyroid cancer.

Koios DS allows the user to select or confirm regions of interest (ROIs) within an image representing a single lesion or nodule to be analyzed. The software then automatically characterizes the selected image data to generate an AI/ML-derived cancer risk assessment and selects applicable lexicon-based descriptors designed to improve overall diagnostic accuracy as well as reduce interpreting physician variability.

Koios DS software may also be used as an image viewer of multi-modality digital images, including ultrasound and mammography. The software includes tools that allow users to adjust, measure and document images, and output into a structured report.

Koios DS software is designed to assist trained interpreting physicians in analyzing the breast ultrasound images of adult ( $\geq 22$  years) female patients with soft tissue breast lesions and/or thyroid ultrasounds of all adult ( $\geq 22$  years) patients with thyroid nodules suspicious for cancer. When utilized by an interpreting physician who has completed the prescribed training, this device provides information that may be useful in recommending appropriate clinical management.

### **Limitations:**

- Patient management decisions should not be made solely on the results of the Koios DS analysis.
- Koios DS software is not to be used for the evaluation of normal tissue, on sites of post-surgical excision, or images with doppler, elastography, or other overlays present in them.
- Koios DS software is not intended for use on portable handheld devices (e.g. smartphones or tablets) or as a primary diagnostic viewer of mammography images.

- The software does not predict the presence of the thyroid nodule margin descriptor, extra-thyroidal extension. In the event that this condition is present, the user may select this category manually from the margin descriptor list.

## 6. Substantial Equivalence Chart

<b>Product</b>	Koios DS 3.0 (K212616)	Koios DS 3.6 (subject device)
<b>Physical Characteristics</b>	Software Package Operates on off-the-shelf hardware	Software Package Operates on off-the-shelf hardware
<b>Storage</b>	Storage not supported	Storage not supported
<b>Image Input</b>	DICOM	DICOM
<b>Characteristics</b>	Decision support device used to assist in the assessment and characterization of breast lesions and thyroid nodules using US image data.	Decision support device used to assist in the assessment and characterization of breast lesions and thyroid nodules using US image data.
<b>Intended Use/Indications for Use</b>	<p>Koios Decision Support (DS) is an artificial intelligence (AI)/machine learning (ML)-based computer-aided diagnosis (CADx) software device intended for use as an adjunct to diagnostic ultrasound examinations of lesions or nodules suspicious for breast or thyroid cancer.</p> <p>Koios DS allows the user to select or confirm regions of interest (ROIs) within an image representing a single lesion or nodule to be analyzed. The software then automatically characterizes the selected image data to generate an AI/ML-derived cancer risk assessment and selects applicable lexicon-based descriptors designed to improve overall diagnostic accuracy as well as reduce interpreting physician variability.</p> <p>Koios DS software may also be used as an image viewer of multi-modality digital images, including ultrasound and mammography. The software</p>	<p>Koios Decision Support (DS) is an artificial intelligence (AI)/machine learning (ML)-based computer-aided diagnosis (CADx) software device intended for use as an adjunct to diagnostic ultrasound examinations of lesions or nodules suspicious for breast or thyroid cancer.</p> <p>Koios DS allows the user to select or confirm regions of interest (ROIs) within an image representing a single lesion or nodule to be analyzed. The software then automatically characterizes the selected image data to generate an AI/ML-derived cancer risk assessment and selects applicable lexicon-based descriptors designed to improve overall diagnostic accuracy as well as reduce interpreting physician variability.</p> <p>Koios DS software may also be used as an image viewer of multi-modality digital images, including ultrasound and mammography. The software includes tools that allow users to adjust, measure and document images, and output into a</p>

	<p>includes tools that allow users to adjust, measure and document images, and output into a structured report.</p> <p>Koios DS software is designed to assist trained interpreting physicians in analyzing the breast ultrasound images of adult (<math>\geq 22</math> years) female patients with soft tissue breast lesions and/or thyroid ultrasounds of all adult (<math>\geq 22</math> years) patients with thyroid nodules suspicious for cancer. When utilized by an interpreting physician who has completed the prescribed training, this device provides information that may be useful in recommending appropriate clinical management.</p>	<p>structured report.</p> <p>Koios DS software is designed to assist trained interpreting physicians in analyzing the breast ultrasound images of adult (<math>\geq 22</math> years) female patients with soft tissue breast lesions and/or thyroid ultrasounds of all adult (<math>\geq 22</math> years) patients with thyroid nodules suspicious for cancer. When utilized by an interpreting physician who has completed the prescribed training, this device provides information that may be useful in recommending appropriate clinical management.</p>
<p><b>Target Population</b> (subset of above for comparison purposes)</p>	<p>Koios DS software is designed to assist trained interpreting physicians in analyzing the breast ultrasound images of adult (<math>\geq 22</math> years) female patients with soft tissue breast lesions and/or thyroid ultrasounds of all adult (<math>\geq 22</math> years) patients with thyroid nodules suspicious for cancer.</p>	<p>Koios DS software is designed to assist trained interpreting physicians in analyzing the breast ultrasound images of adult (<math>\geq 22</math> years) female patients with soft tissue breast lesions and/or thyroid ultrasounds of all adult (<math>\geq 22</math> years) patients with thyroid nodules suspicious for cancer.</p>
<p><b>Limitations for Use</b> (subset of above for comparison purposes)</p>	<p>Limitations:</p> <ul style="list-style-type: none"> <li>• Patient management decisions should not be made solely on the results of the Koios DS analysis.</li> <li>• Koios DS software is not to be used for the evaluation of normal tissue, on sites of post-surgical excision, or images with doppler, elastography, or other overlays present in them.</li> <li>• Koios DS software is not intended</li> </ul>	<p>Limitations:</p> <ul style="list-style-type: none"> <li>• Patient management decisions should not be made solely on the results of the Koios DS analysis.</li> <li>• Koios DS software is not to be used for the evaluation of normal tissue, on sites of post-surgical excision, or images with doppler, elastography, or other overlays present in them.</li> <li>• Koios DS software is not intended for use</li> </ul>

	<p>for use on portable handheld devices (e.g. smartphones or tablets) or as a primary diagnostic viewer of mammography images.</p> <ul style="list-style-type: none"> <li>The software does not predict the presence of the thyroid nodule margin descriptor, extra-thyroidal extension. In the event that this condition is present, the user may select this category manually from the margin descriptor list.</li> </ul>	<p>on portable handheld devices (e.g. smartphones or tablets) or as a primary diagnostic viewer of mammography images.</p> <ul style="list-style-type: none"> <li>The software does not predict the presence of the thyroid nodule margin descriptor, extra-thyroidal extension. In the event that this condition is present, the user may select this category manually from the margin descriptor list.</li> </ul>
<b>Modality Used for Analysis</b>	Breast Ultrasound Data Thyroid Ultrasound Data	Breast Ultrasound Data Thyroid Ultrasound Data
<b>Input</b>	Medical images provided in a DICOM format	Medical images provided in a DICOM format
<b>ROI Requirements</b>	<p>Breast</p> <p>The software requires a user to select up to two ROIs, from up to two orthogonal views, that represent a single lesion to be selected and processed.</p> <p>Thyroid</p> <p>Two ROIs that represent a single lesion to be selected and processed are required for analysis.</p> <p>The first ROI is drawn on the transverse view of the nodule. The second is drawn on the longitudinal view.</p>	<p>Breast</p> <p>The software requires a user to select up to two ROIs, from up to two orthogonal views, that represent a single lesion to be selected and processed.</p> <p>Thyroid</p> <p>Two ROIs that represent a single lesion to be selected and processed are required for analysis.</p> <p>The first ROI is drawn on the transverse view of the nodule. The second is drawn on the longitudinal view.</p>
<b>Output (Breast)</b>	Koios defined categorical and continuous outputs (confidence level indicator) that align to BI-RADS, U1-U5, and auto-classified shape and orientation.	Koios defined categorical and continuous outputs (confidence level indicator) that align to BI-RADS, U1-U5, and auto-classified shape and orientation.
<b>Output (Thyroid)</b>	Koios DS software automatically classifies thyroid nodules suspicious	Koios DS software automatically classifies thyroid nodules suspicious for cancer

	for cancer based on image data generating an output aligned to either the TI-RADS or ATA classification guidelines. The system automatically generates user-modifiable nodule descriptors (Composition, Echogenicity, Shape, Margin, Echogenic Foci) and a direct, image-derived cancer risk assessment that is translated into an optional lexicon-specific modifier.	based on image data generating an output aligned to either the TI-RADS or ATA classification guidelines. The system automatically generates user-modifiable nodule descriptors (Composition, Echogenicity, Shape, Margin, Echogenic Foci) and a direct, image-derived cancer risk assessment that is translated into an optional lexicon-specific modifier.
<b>Comparative Clinical Performance Testing (Breast)</b>	Metric: AUC Cases: 900 Readers: 15	Metric: AUC Cases: 900 Readers: 15
<b>Comparative Clinical Performance Testing (Thyroid)</b>	Metric: AUC Cases: 650 Readers: 15	Metric: AUC Cases: 650 Readers: 15

## 7. Description of Similarities and/or Differences

### Intended Use/Indications for Use (IFU)

The IFU of the subject and predicate devices are the same.

### Target Patient Population

Both the Koios DS predicate and the subject device are software applications designed to assist trained interpreting physicians in analyzing the ultrasound images of patients with soft tissue lesions who are being referred for further diagnostic ultrasound examination.

### Technological Characteristics

#### Modality

Koios DS shares the ultrasound modality requirements of Koios DS (K212616)

#### Technological Characteristics Comparison Table

	Koios DS 3.0 K212616	Koios DS 3.6 K242130
Diagnostic Engine	Breast (v 1.1.0) Thyroid (v2.2.0)	Breast (v. 3.0.0) Thyroid (v. 2.2.0)
Workflow Enhancements	Breast Smart Click  Breast Smart Calipers  Thyroid Smart Calipers	Breast Smart Click  Breast Smart Calipers  Thyroid Smart Click  Thyroid Smart Calipers  Image Registration and Matching

		OCR Automatic Size and Position Population
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**Input**

Per the respective device descriptions of Koios DS 3.6 and Koios DS (K212616), the following technical characteristics are included in the Koios DS 3.6 (K242130) version:

Thyroid Smart Click

If using this feature, the user can specify a Region of Interest with a single click near the center of the nodule. The Thyroid Smart Click Engine, based on this click, estimates the coordinates of the intended ROI in order to present these to the user. The Thyroid Smart Click engine produces an ROI which best matches the user’s Smart Click selection. The resulting ROI contains coordinates for the region. The user can adjust or overrule the resulting ROI if they deem it necessary, and the ROI can then be used as an input to the thyroid diagnostic engine.

Image Registration and Matching

If using this optional feature, the user draws ROIs on images within their image viewing software, which generates a screenshot. The Koios DS Client transmits the ROI screenshot to the Koios DS Server Image Matching Engine to generate the ROI on the underlying DICOM image and displays it to the user for review. The ROI and associated DICOM data are sent to the Koios DS Server for processing by the appropriate Diagnostic Engine.

The screenshots (or image region replicas) utilized during an image matching query are not saved. Image region replicas are captured by the software and stored as uncompressed bitmap data in memory and processed by the Image Matching engine as such. This process is agnostic to the underlying body part and functions generically, identically for any breast and/or thyroid image selection.

The image matching engine performs its search independently for each query region based purely and solely on image data, without external information pertaining to modality or other orthogonal views. The search candidates are limited in scope to database images from within the same study as the search query. As a result, if a search query is created from a thyroid image

from a specified thyroid study, only that specific thyroid study is searched for potential matching image regions. The same search query process is utilized for breast images; only the specific breast study is searched for matching image regions.

#### Auto-populate Size and Position using Optical Character Recognition (OCR)

If using this feature, the user provides an ultrasound image which has previously been annotated by a radiologist or technician. The OCR engine then identifies all the text in the image and parses out text which is relevant to the study of lesions or nodules. This functionality allows the user to quickly interpret and transcribe the locations and measurements of ultrasound findings.

#### **Output**

When comparing breast functionality, the subject Koios DS Breast Engine demonstrates a significant categorical output performance increase in AUC (1.6%), a significant increase in sensitivity (0.6%), and a significant increase (2.2%) in specificity. Koios DS retains the identical descriptor outputs and performance for the assessment of shape and orientation.

The Koios DS thyroid performance is unchanged from the predicate device including when accounting for new technological characteristics. Performance testing outlined in the next section demonstrates equivalence and non-inferiority for each new technical characteristic.

#### Auto-populate Size and Position using Optical Character Recognition (OCR)

The output of the OCR Engine consists of two categories - measurements and text. The measurements output consists of three elements: description (e.g. the length, height, or width of a nodule), value (a field representing the numerical value of measurement), and unit (the modifier to the value specifying a unit of measurement, e.g. cm or mm). The text output consists of two elements: a dictionary (with fields corresponding to each possible category of information present in the findings text), and values (corresponding to the predicted output for each field).

## **8. Performance Testing – Standalone Testing**

### **Breast Engine**

To compare the performance of the subject device to the predicate device (K212616, product codes POK, QIH), the subject device's updated breast classification engine was compared to the

predicate device on the same 900 case validation set. Bench testing was performed on the Koios DS 3.6 breast engine to ascertain the degree of concordance with trained interpreting physicians. Ground truth for malignancy risk classification was determined by pathology or 1-year follow-up for cases that were not biopsied. The system was analyzed on 900 lesions from 900 different patients set aside from the system's training data for the purpose of validating performance. Each lesion was represented by two orthogonal images (e.g. radial and anti-radial), providing a total of 1800 images. An expanded validation set of 1014, including these 900 and an additional 114 cases is used to test for dataset drift. System performance on the 900 cases reported an AUC of 94.5%, with a Sensitivity of 0.976 [0.960, 0.992] and a Specificity of 0.632 [0.588, 0.676].

The table below provides a detailed evaluation of the breast diagnostic engine across key performance metrics. Direct comparison with the Koios DS v3.0 breast engine's performance determined there is a significant increase in AUC (1.6%), a significant increase in sensitivity (0.6%), and a significant increase (2.2%) in specificity.

Koios DS Engine (Breast) Test	Engine Version 1.1.0 (Previous) <Subject Koios DS v3.0>	Engine Version 3.0.0 (Current) <Subject Koios DS v3.6>
1: Malignancy Risk Classifier AUC	0.929 [0.913, 0.945]	0.945 [0.932, 0.959]
2: Categorical Output		
Sensitivity	0.97 [0.96, 0.99]	0.976 [0.960, 0.992]
Specificity	0.61 [0.57, 0.66]	0.632 [0.588, 0.676]
3: Sensitivity to Region of Interest	0.019	0.012
4. Sensitivity to Transducer Frequency	High frequency ( $\geq 15$ MHz), AUC = 0.940 [0.907, 0.974]  Low frequency ( $< 15$ MHz), AUC = 0.924 [0.904, 0.944]	High frequency ( $\geq 15$ MHz), AUC = 0.948 [0.917, 0.978]  Low frequency ( $< 15$ MHz), AUC = 0.940 [0.925, 0.956]

5. Single Image vs Orthogonal Image Pair	Single Image: 0.914 [0.910 - 0.918]  Orthogonal Pair: 0.929 [0.913, 0.945]	Single Image: 0.932 [+/- 0.003]
6. Assessment of Categorical Agreement – Shape <i>(prior results continue to apply)</i>	0.738 [0.679, 0.797]	
7. Assessment of Categorical Agreement – Orientation <i>(prior results continue to apply)</i>	0.744 [0.675, 0.813]	

8. Operating Point	PLR: System= 2.52 [2.26, 2.79]  NLR: System=0.04 [0.02, 0.07]  PPV: System= 0.70 [0.67, 0.73]  NPV: System= 0.96 [0.94, 0.98]	PLR: System= 2.661 [2.338, 2.984]  NLR: System= 0.039 [0.013, 0.064]  PPV: System= 0.708 [0.672, 0.743]  NPV: System= 0.966 [0.944, 0.988]
9. Data Set Drift Analysis - Malignancy Risk Classifier AUC	ROCAUC = 0.930 [0.914, 0.946]	ROCAUC = 0.949 [0.936, 0.962]

10. Data Set Drift Analysis - Categorical Output	Sensitivity = 0.977 [0.967, 0.987] Specificity = 0.615 [0.578, 0.651]	Sensitivity = 0.973 [0.958, 0.989] Specificity = 0.659 [0.619, 0.700]
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Bench testing demonstrates that the system exceeds physician performance measured by AUC, sensitivity, and specificity. The engine's shape and orientation predictions have not been modified from the previously cleared device (which demonstrated the required level of agreement with the subjective categorizations assigned by physicians). Testing characterizes the system's sensitivity to shifts in the selected region of interests (ROI) and transducer frequency. Testing characterizes the system's Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) in comparison with physicians. Testing demonstrates that the performance of the engine does not demonstrate degradation when regions of interest are provided by the Smart Click or Smart Caliper system, as compared to manually drawn regions of interest. Therefore, the diagnosis engine is agnostic to the source of input ROI (Smart Click, Smart Calipers, physician drawn) and robust to shifts in ROI. In all tests, the Breast engine met or exceeded performance requirements.

### **Thyroid Engine**

Bench testing was performed on the thyroid engine to ascertain the degree of concordance with trained interpreting physicians utilizing both the ACR TI-RADS and ATA classification systems. Ground truth for malignancy risk classification was determined by pathology results only. The system was analyzed on 500 lesions from 500 different patients set aside from the system's training data for the purpose of validating performance. Each lesion was represented by two orthogonal images (e.g. radial and anti-radial), providing a total of 1000 images.

When applied to diagnoses made using ACR TI-RADS guidelines, the AI Adapter and descriptor predictors achieved an AUC of 79.8%, demonstrating a significant increase over the average physician AUC. When recommending biopsy, the system's sensitivity is 0.644 [0.545, 0.744] and specificity is 0.612 [0.566, 0.658]. When recommending follow-up, the system's sensitivity and specificity are 0.879 [0.812, 0.946] and 0.495 [0.446, 0.544], respectively. In both scenarios, bench testing of the system demonstrates a non-significant improvement in sensitivity and a significant improvement in specificity over the physician average.

Tests demonstrating AI Adapter impact on ATA classifications yielded similarly improved performance. With application of the AI Adapter, physician AUC demonstrates a significant increase of 9.135% [5.975, 12.294]. Sensitivity shows a non-significant increase of 0.511% [-5.182, 6.204], while specificity shows a significant increase of 18.741% [9.885, 27.596].

Bench testing included verification of standalone performance, performance with TI-RADS and ATA outputs, as well as performance when compared to a separate data set including data from independent sites (separate and apart from the sites/data used to train and tune the algorithm).

Testing demonstrates that application of the Koios DS AI Adapter exceeds physician performance as measured by AUC, sensitivity, and specificity. Descriptor predictions were tested objectively – against ground truth pathology. Testing demonstrated that performance requirements were met under ACR TI-RADS and ATA reporting systems as well as when compared against independent site data. Outputs were additionally tested subjectively and met the requirements for agreement with readers' descriptor categorizations. Testing characterized the sensitivity of the system with respect to shifts in the region of interest and variation in performance between high and low transducer frequencies. System performance on data acquired from independent sites meets performance requirements. In all tests, the Thyroid engine met or exceeded performance requirements.

#### Thyroid Smart Click

A dataset of 650 nodules with corresponding physician-drawn ROI's were used for testing the Koios DS Thyroid Smart Click Engine. These ROI's are the same as the reference ROI's used to validate the Koios DS Thyroid Engine. A user "click" will be simulated for testing the performance of the Smart Click engine by calculating the center of each nodule.

Non-inferiority testing is used to demonstrate that the use of the Smart Click engine does not degrade diagnostic performance when compared to physician-selected calipers. Each test will demonstrate that the lower 95% confidence bound of the difference in performance falls above a designated equivalence margin, delta ( $\delta$ ). In each case, delta is defined using the measured uncertainty in our performance metric and the variability observed on physicians' assessment of the data. Measurement uncertainty is computed via bootstrapping.

Testing further provides quantitative metrics which demonstrate how closely the automated Smart Click ROIs match the manual physician-drawn ROI's using standard segmentation evaluation metrics. In this case, the Dice Similarity Coefficient will be used. Specifically, the test will measure and report the average DICE score between the Smart Click and physician ROI's across all of the images present in the validation set. The objective of this test is to demonstrate the similarity between Smart Click ROI's and manually drawn ROI's.

Finally, testing demonstrates concretely that descriptors generated from Smart Click ROI's are not impacted by differences between them and manually drawn ROI's. Non-inferiority testing was used on a per-descriptor basis. Specifically, testing will show that the rate of agreement between the system's descriptors and the physicians' descriptors when utilizing smart click is non-inferior to the system's descriptors when using the manual ROI's. The Cohen's Kappa metric will be used to characterize agreement between system and reader in either case.

Superiority is evaluated using similar methodology. In this case, the lower bound of the difference in performance must fall above zero.

Koios DS Smart Click Engine Test	Smart Click Engine Version (TOR.2.0.X)
1: Non-inferiority Test - Sensitivity / Specificity	Sensitivity: Difference = -0.009 [-0.036, 0.018] Result: Non-inferior Specificity: Difference = -0.018 [-0.041, 0.005] Result: Non-inferior
2: Non-inferiority Test - AUC	Difference = -0.012 [-0.029, 0.006] Result: Non-inferior
3: Sub-optimal ROI Test	Difference = 0.026 [-0.009, 0.062] Result: Non-inferior
4: Detection DICE Coefficient	DICE= 0.913 +/- 0.075
5: Non-inferiority Test - Descriptor Agreement	Composition: Difference = 0.018 [0.001, 0.035] Result: Non-inferior Echogenicity: Difference = -0.005 [-0.022, 0.011] Result: Non-inferior

	<p>Shape:</p> <p>Difference = -0.033 [-0.093, 0.027]</p> <p>Result: Non-inferior</p> <p>Margin:</p> <p>Difference = -0.013 [-0.032, 0.007]</p> <p>Result: Non-inferior</p> <p>Echogenic Foci:</p> <ul style="list-style-type: none"> <li>- Large Comet-Tail Artifacts</li> </ul> <p>Difference = -0.019 [-0.048, 0.010]</p> <p>Result: Non-inferior</p> <ul style="list-style-type: none"> <li>- Macrocalcifications</li> </ul> <p>Difference = 0.017 [-0.035, 0.068]</p> <p>Result: Non-inferior</p> <ul style="list-style-type: none"> <li>- Peripheral (Rim) Calcifications</li> </ul> <p>Difference = 0.024 [-0.072, 0.120]</p> <p>Result: Non-inferior</p> <ul style="list-style-type: none"> <li>- Punctate Echogenic Foci</li> </ul> <p>Difference = 0.007 [-0.038, 0.053]</p> <p>Result: Non-inferior</p>
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Testing demonstrates that system performance does not fall below the computed value for the equivalence margin, delta. The confidence interval of the difference falls within the expected bounds.

The high value (DICE = 0.913 +/- 0.075) of the DICE coefficient demonstrates that Smart Click ROIs are, on average, a precise approximation to the ROIs that a physician would select. Test 5 contains a quantitative per-descriptor comparison of the predictions generated when using Smart Click ROIs to those generated using physician ROIs, via Non-Inferiority testing. Noninferiority was demonstrated for each descriptor using Smart

Click ROIs. Together, these results clearly demonstrate descriptor performance is not negatively impacted by the use of the Smart Click engine.

### Image Registration and Matching

A dataset consisting of 1,600 ultrasound studies of lesions in both breast (950 cases) and thyroid (650 cases) was used to evaluate the performance of the Koios DS Client ROI Match Engine in Tests 1-4 outlined below. Each study consists of one or more ultrasound images, wherein one or more contain a region of interest (ROI) that signifies the location of a lesion within the image.

Tests 5 & 6 utilized the breast validation dataset of 1014 cases. Tests 7 & 8 utilized the thyroid validation dataset of 650 cases.

Tests 5 & 7 measure the rate of incidence of each of the possible outcomes of the matching process.

- Successful Match: The system correctly identifies the image and image region corresponding to the query screenshot.
- No Match: The system is unable to identify a matching region of interest and returns no match for the query screenshot. Note: This is considered a positive outcome. If the system identifies that it cannot match a query screenshot, it should return that status rather than an incorrect result.
- Incorrect Match: The system identifies the correct image but returns an incorrect region within that image. Incorrect is defined as under 0.5 intersect-over-union with respect to the correct region.
- Incorrect Image: The system selects the wrong image as a match for the query screenshot.

These tests were run on each of the ROI's contained in the test dataset, which corresponds to 2028 breast ROI's and 1288 thyroid ROI's.

These tests are to tabulate how often the image matching process results in each of the four possible outcomes. This is reported both by total count and percent incidence.

Tests 6 & 8 investigate the quality of the resulting registration. This is measured by computing the average DICE coefficient for the set of matches which are in the successful match category.

A summary of performance statistics is outlined below.

Koios DS Image Registration and Matching Engine Test	Image Registration and Matching Engine Version (LAM.1.X.X)
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1: No Match Rate	No Match Rate = 0.32%
2: Match Time	<p>Average Time for Study Preprocessing: 2.39 +/- 0.48 seconds</p> <p>Average Time for Image Matching: 0.22 +/- 0.12 seconds</p> <p>Note: The average study size which was processed in this experiment was 53 +/- 11 images. The measured durations scale roughly linearly with study size.</p>
3: End-to-End Breast Engine Performance	<p>AUC = 0.946</p> <p>Sensitivity = 0.975</p> <p>Specificity = 0.637</p>
4: End-to-End Thyroid Engine Performance	<p>AUC = 0.801</p> <p>Sensitivity = 0.670</p> <p>Specificity = 0.603</p>
5: Breast Image Matching Outcomes	<p>Successful Match:</p> <p>Count: 2018</p> <p>Fraction: 0.995</p> <p>No Match:</p> <p>Count: 10</p> <p>Fraction: 0.005</p> <p>Incorrect Match:</p>

	<p>Count: 0</p> <p>Fraction: 0.000</p> <p>Incorrect Image:</p> <p>Count: 0</p> <p>Fraction: 0.000</p>
6: Breast Image Matching DICE Coefficient	DICE = 0.995 +/- 0.005
7: Thyroid Image Matching Outcomes	<p>Successful Match:</p> <p>Count: 1288</p> <p>Fraction: 1.000</p> <p>No Match:</p> <p>Count: 0</p> <p>Fraction: 0.000</p> <p>Incorrect Match:</p> <p>Count: 0</p> <p>Fraction: 0.000</p> <p>Incorrect Image:</p> <p>Count: 0</p> <p>Fraction: 0.000</p>
8: Thyroid Image Matching DICE Coefficient	DICE = 0.996 +/- 0.004

Auto-populate Size and Position using Optical Character Recognition (OCR)

A dataset of 1910 ultrasound B-Scans was manually annotated to test the OCR engine. These are a mix of thyroid and breast images that come from a variety of machines. Of these, a subset of 1226 images that come from the supported list of machines is used to carry out this test.

Tests will measure accuracy (percent correct) for each of the structured fields predicted by the engine. False positive, false negative, and misread text fields will count against the accuracy measurement of the engine.

Koios DS OCR Engine Test	Optical Character Recognition (OCR) Engine Version (GNO.1.1.X)
1: Breast Freetext Identification	Breast Side: 0.983 Location Type: 0.948 Clock Hour: 0.926 Clock Minute: 0.934 CMFN: 0.944 Plane: 0.976
2: Thyroid Freetext Identification	Thyroid Side: 0.965 Pole: 0.976 Region: 0.998 Plane: 0.970
3: Measurement Text Identification	Measurement Description: 0.943 Measurement Value: 0.948

	Unit of Measurement: 0.967
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In conclusion, the subject device has demonstrated substantially equivalent performance to the predicate by showing statistically significant results against similar success criteria in bench testing comparisons.

**9. Performance Testing – Clinical**

**Breast**

A clinical study was previously executed to determine the effect of Koios DS Breast (K190442) on reader performance. There were no new clinical studies performed for the design and development of Koios DS 3.0 (K212616), which used Koios DS Breast (K190442) as a predicate device during its regulatory submission. As discussed in the prior section, the performance of Koios DS 3.0 has been met or significantly improved across all measured metrics by Koios DS 3.6. This data continues to apply to the breast functionality within the subject device, with the understanding that its performance is superior, and it would therefore provide an equivalent or greater benefit. The below summary of the clinical study data has been included for ease of reference.

The study objective was to determine the impact on Interpreting Physician (Reader) performance as defined by the area under the Receiver Operating Characteristic (ROC) Curve (AUC) when Koios DS Breast and an ultrasound examination are combined (USE + DS), compared to USE Alone in patients that present with a soft tissue breast lesion through any form of imaging or physical examination and are referred for diagnostic ultrasound.

The study consisted of 15 readers with varying levels of training and experience providing analysis on a randomized set of 900 patient cases presented with USE + DS and USE Alone in two reading periods separated by a 1-month wash-out, totaling 1800 cases analyzed per reader. The reader set and dataset were distributed in accordance with FDA guidance and are explained in detail below:

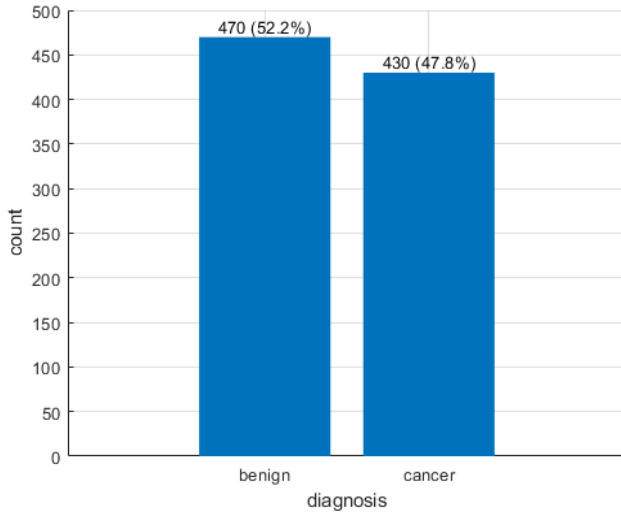
## Reader Background

Reader ID	Board Certification/ Specialty	Breast Fellowship Trained and/or Dedicated Breast Imager	Years of Experience – Mammography and/or Breast Ultrasound	Academic Institution Affiliation (Yes/No)	MQSA Qualified Interpreting Physician
1	Diagnostic Radiology	No	13 years	No	Yes
2	Diagnostic Radiology	No	4 years	No	No
3	Diagnostic Radiology	Yes	7 years	Yes	Yes
4	Breast Surgeon	No	0 years	No	No
5	OB/GYN	No	20 years	No	No
6	Diagnostic Radiology	No	13 years	Yes	No
7	Diagnostic Radiology	No	3 years	Yes	No
8	OB/GYN	No	0 years	No	No
9	Diagnostic Radiology	Yes	15 years	No	Yes
10	Diagnostic Radiology	No	13 years	No	No
11	Diagnostic Radiology	Yes	30 years	No	Yes
12	Diagnostic Radiology	Yes	10 years	Yes	Yes
13	Diagnostic Radiology	No	0 years	No	No
14	Interventional Radiology	No	4 years	No	No
15	Breast Surgeon	No	25 years	Yes	No

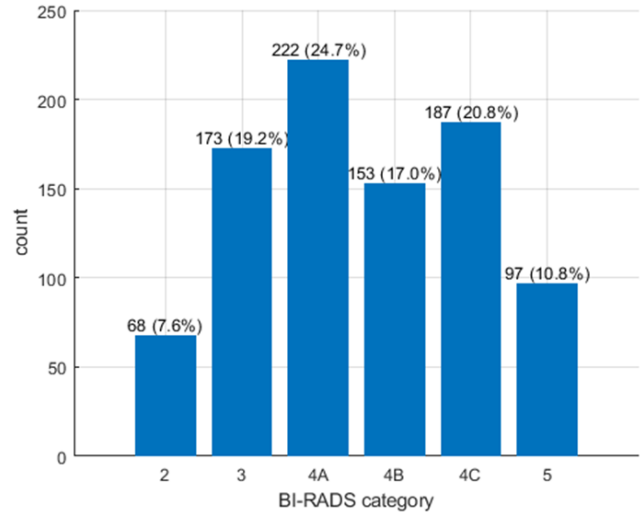
### Dataset Demographic Information

The Koios DS Breast engine was tested on images sourced from a wide variety of ultrasound hardware and data with the following patient demographics to ensure the system performance is generalizable to and representative of diverse populations. Patient demographic distribution was based upon data from the Breast Cancer Surveillance Consortium (2006-2009)<sup>2</sup>.

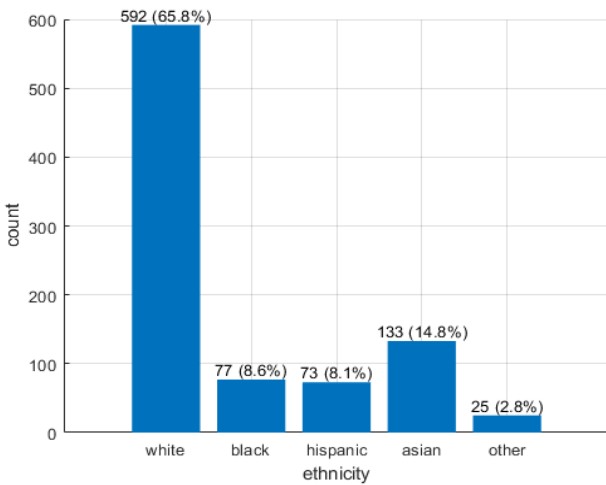
The following figures represent the final validation dataset (900 cases):



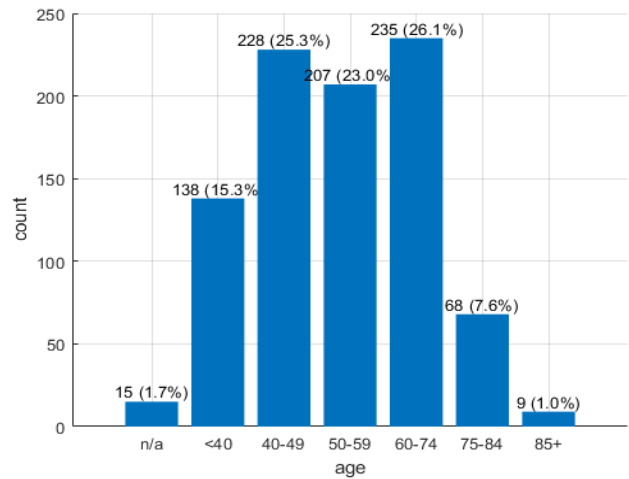
*Distribution of Malignancy in Final Validation Set*



*Distribution of BI-RADS Category in Final Validation Set*

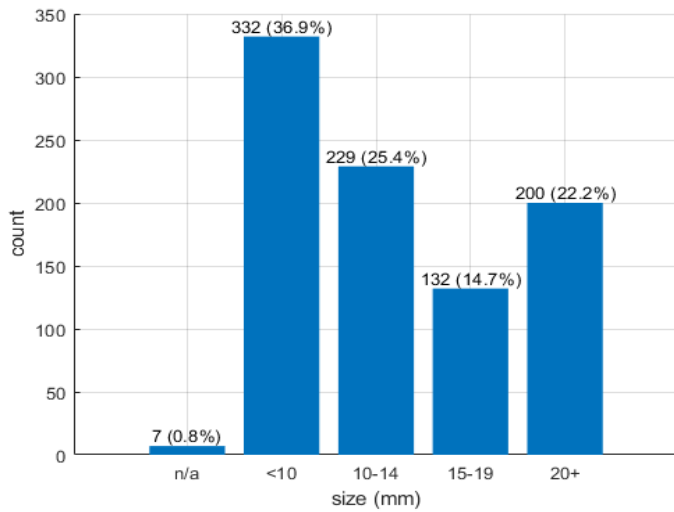


*Distribution of Ethnicity in Final Validation Set*

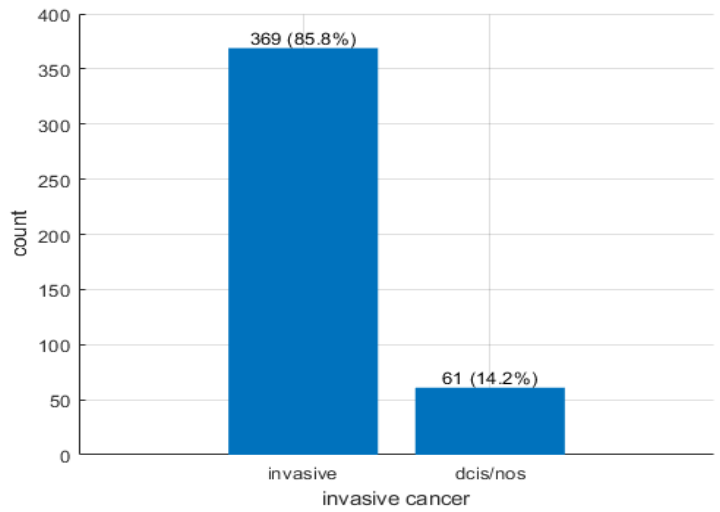


*Distribution of Age in Final Validation Set*

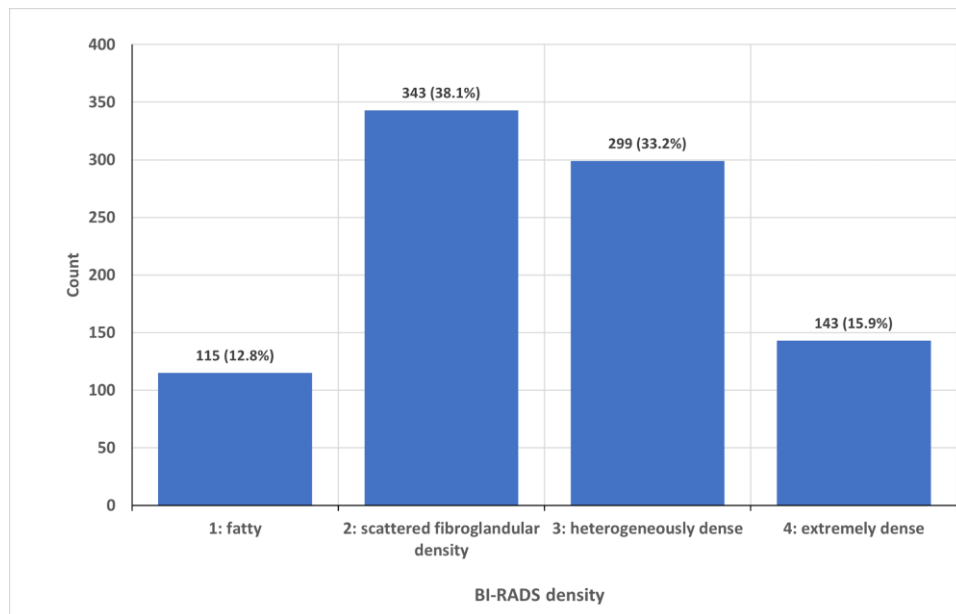
<sup>2</sup> Data were obtained from the Breast Cancer Surveillance Consortium, funded by the National Cancer Institute (HHSN261201100031C). From the Breast Cancer Surveillance Consortium website, <http://www.bscs-research.org/>



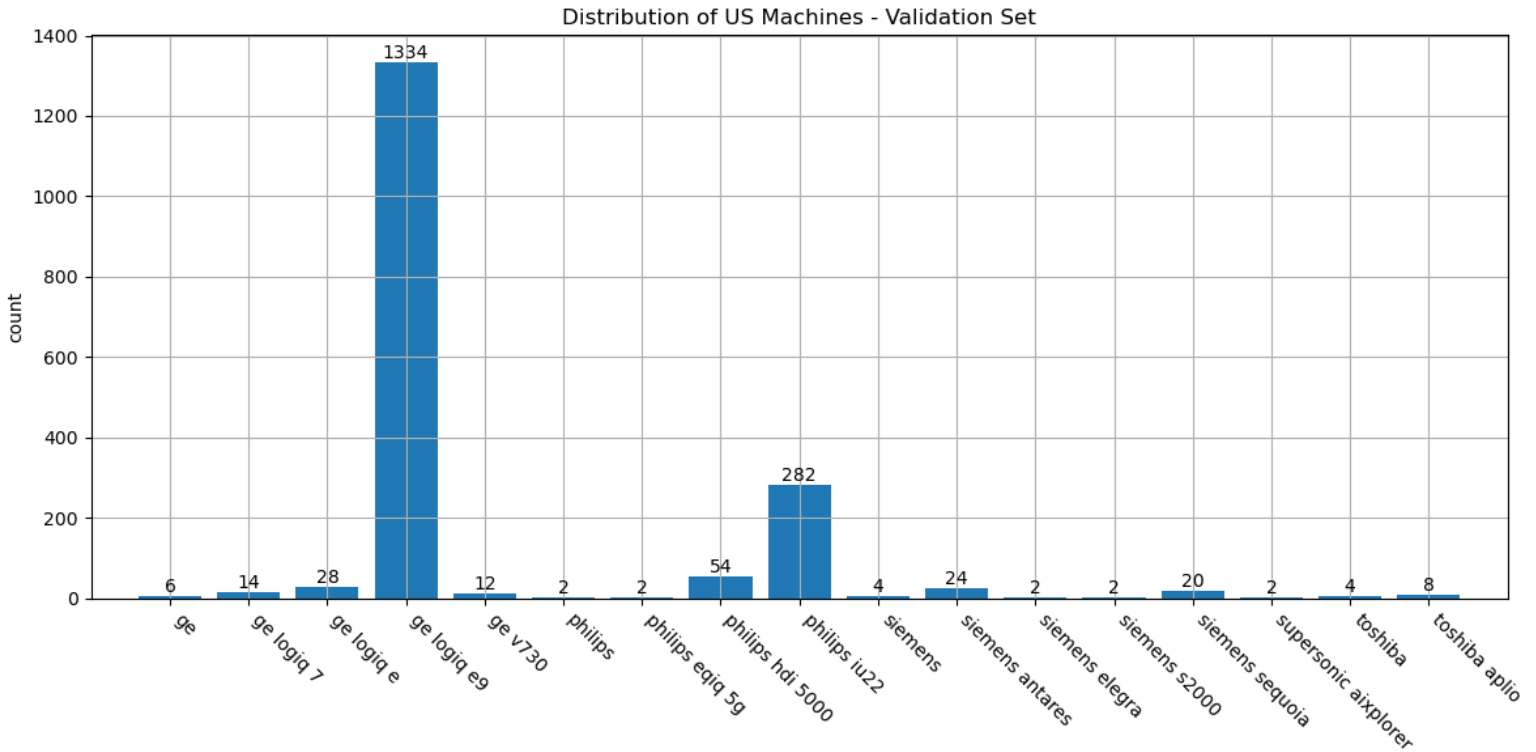
*Distribution of Lesion Size in Final Validation Set*



*Distribution of Invasive Cancer in Final Validation Set*



*Distribution of BI-RADS Density in Final Validation Set*



*Distribution of US Machines in Final Validation Set*

Per the primary endpoint of the study, ROC curves were generated and analyzed. All AUCs were computed via the trapezoidal approximation. Based on the standard error measurements, the error can be propagated to estimate the mean performance interface and 95% confidence interval. This was found to be 0.0370 (0.030, 0.044) at  $\alpha = .05$ , satisfying the success criteria for the primary endpoint.

To characterize the effect of Koios DS (USE + DS) system on inter-operator variability, the Kendall Tau-B correlation coefficient was computed in a pairwise manner for all readers. The metric is  $> 0$  for all reader pairs. The standard error for USE + DS and USE Alone was computed to assess if the shifts in the metric were significant. The average Kendall Tau-B of USE Alone was .5404 (.5301, .5507) and the average Kendall Tau-B of USE + DS was .6797 (.6653, .6941) with 95% CI demonstrating a significant increase in the metric ( $\alpha = .05$ ).

Also assessed was the effect of Koios DS on intra-operator variability leveraging 150 reads that did not switch from USE Alone to USE + DS across the washout session in the reader study (75 each). USE Alone class switching rate was 13.6% and the USE + DS class switching rate was 10.8% ( $p = 0.042$ ), demonstrating a statistically significant reduction in intra-reader variability when using USE + DS.

## Thyroid

An observational case-controlled, Multi-Reader, Multi-Case (MRMC) retrospective clinical trial (CRRS-3) was executed to determine the effect of Koios DS Thyroid on reader performance.

Effect on performance was defined by measuring the area under the Receiver Operating Characteristic (ROC) Curve (AUC) when Koios DS and an ultrasound examination were combined (USE + DS), compared to unassisted TI-RADS based Reader performance (USE Alone). All data analysis cases consisted of USE Alone and USE + DS image readings in patients that presented with a thyroid abnormality through any form of imaging or physical examination and were referred for diagnostic ultrasound where a nodule was subsequently discovered.

Data analysis in the CRRS-3 study was based on 650 retrospectively collected cases that were assigned a TI-RADS Assessment Category 1 through 5 at the time of initial review at study entry based upon the interpreting physician of the ultrasound evaluation. The study consisted of 15 readers reviewing and interpreting 650 cases twice (1300 total cases per reader). All data analysis was based on two randomized evaluations of each case with and without the assistance of Koios DS software with a 1-month washout period between corresponding presentations of the case and interpretations by physicians.

The study design called for a mixed population of physician readers (11/15 or 73% US based) and cases (500 or 77% US based) coming from both the US and Europe. Readers with a current medical license who met inclusion criteria and completed the study training protocol were considered trained interpreting physicians for study purposes. Readers possessed varying levels of training and experience, as detailed below:

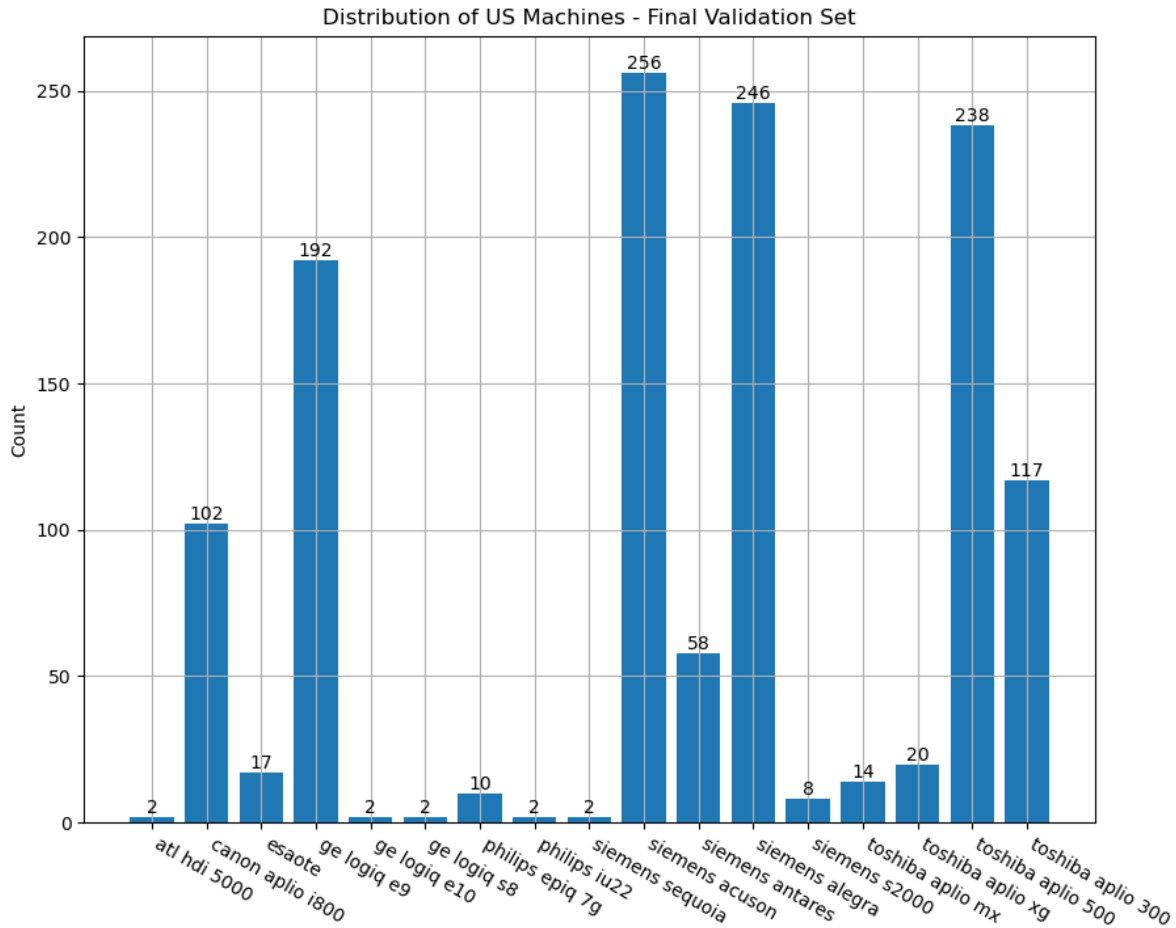
### Reader Experience

Reader ID	Reader Category	Experience (post-residency)
R1	Domestic Endocrinologist (End)	< 10 years
R2	Domestic Radiologist (Rad)	≥ 20 years
R3	Domestic Rad	≥ 20 years
R4	Domestic Rad	≥ 10 and < 20 years
R5	Domestic Rad	≥ 10 and < 20 years
R6	Domestic Rad	≥ 10 and < 20
R7	Domestic Rad	≥ 20 years
R8	Domestic Rad	< 10 years
R9	Domestic Rad	≥ 20 years
R10	Domestic Rad	≥ 20 years
R11	Domestic End	< 10 years
R12	European Rad	≥ 20 years
R13	European Rad	≥ 20 years
R14	European End	≥ 20 years
R15	European End	≥ 20 years

### Dataset Demographic Information

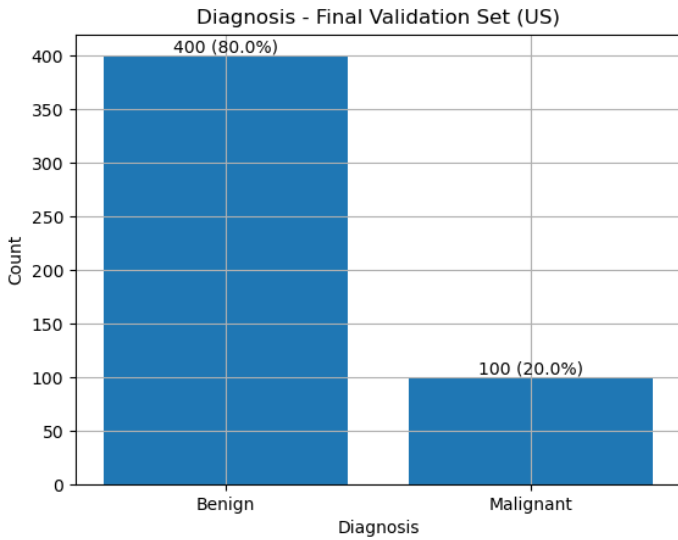
The Koios DS thyroid engine was tested on images sourced from a wide variety of ultrasound hardware and data with the following patient demographics to ensure the system performance is generalizable to and representative of diverse populations.

The following ultrasound hardware represents the final validation dataset (650 cases).

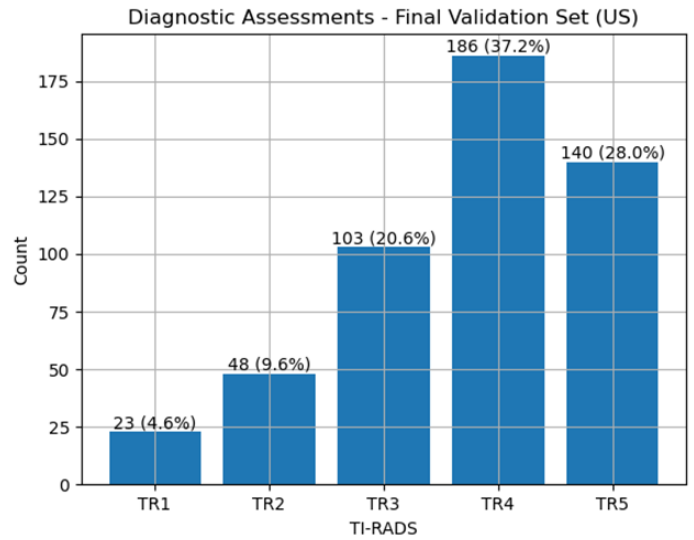


*Distribution of ultrasound machine models in the final validation set, by image*

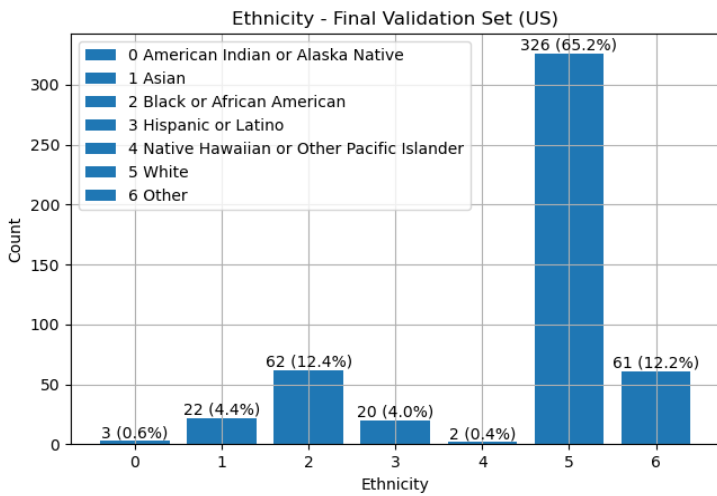
The final validation set data is divided into 2 subsets; 500 cases from United States locations and 150 cases from European locations. The following figures represent the United States patient demographics:



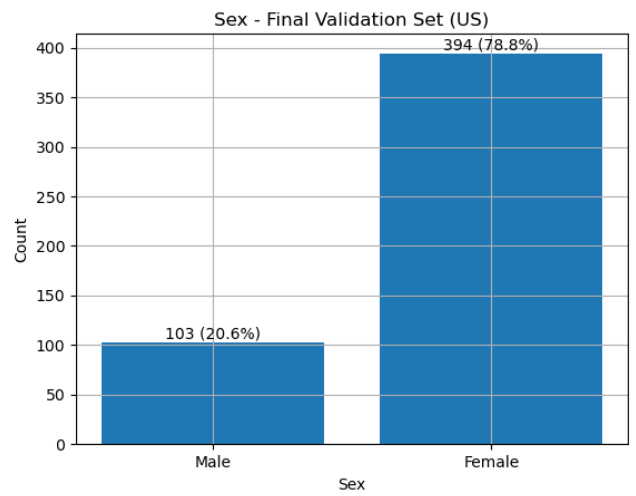
*Distribution of Malignancy in the Final Validation Set (United States)*



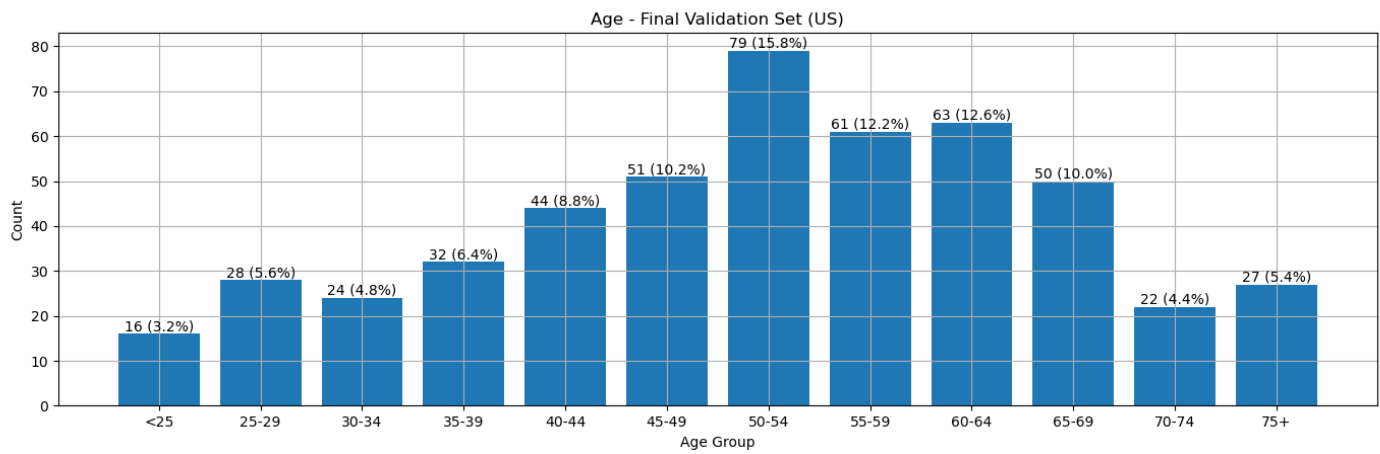
*Distribution of TI-RADS Assessment in the Final Validation Set (United States)*



*Distribution of Patient Ethnicity in the Final Validation Set (United States)*

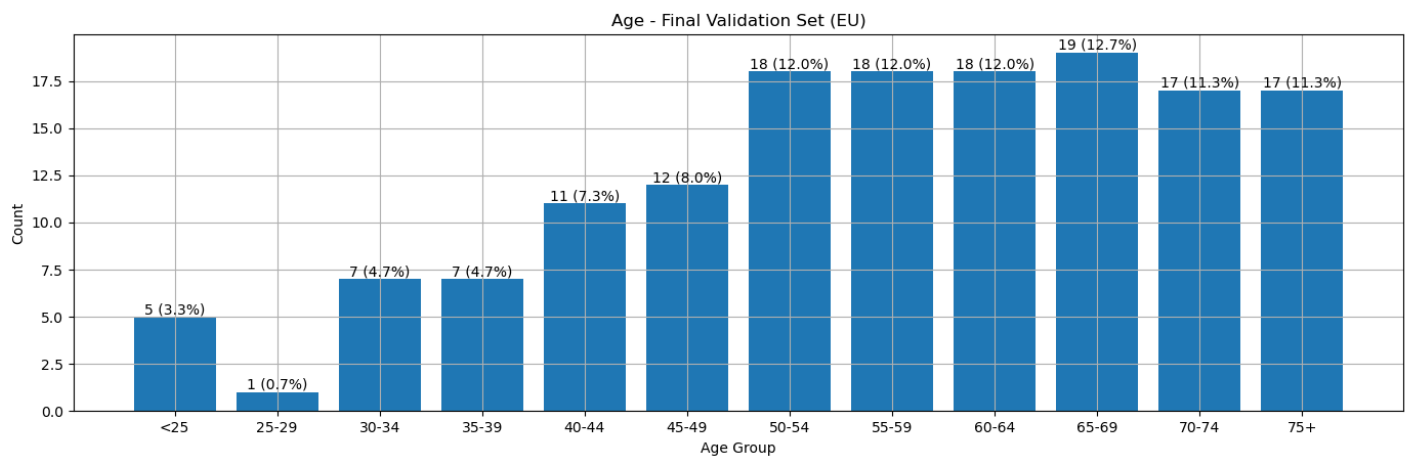


*Distribution of Patient Sex in the Final Validation Set (United States)*

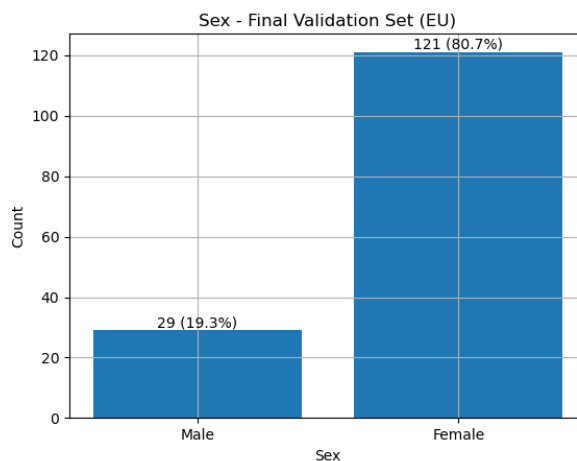


*Distribution of Patient Age in the Final Validation Set (United States)*

The following figures represent the European patient demographics:



*Distribution of Patient Age in the Final Validation Set (European)*



*Distribution of Patient Sex in the Final Validation Set (European)*

The primary CRRS-3 analysis was performed on the Readers' TI-RADS point total gradings from their review of the USE Alone and their review of the USE + DS for the Non-Cancer Case Set and Cancer Case Set. For each Reader, two ROC curves (Sensitivity vs. 1 – Specificity) were plotted using the USE Alone and the USE + DS primary analysis cases. Reader-specific AUC values for the primary analysis were derived from the trapezoidal approximation, whereas the mean AUC values and associated standard errors within- and between-modality across all Readers were derived from the DBM (Dorfman-Berbaum-Metz ANOVA after jackknife) method. This approach captures both reader variability and case variability and is the standard methodology for comparing AUCs in MRMC studies. All ROC curve analysis was done with respect to cyto-/histological or excisional pathology.

**Summary of All Primary Study Endpoints and Secondary Analyses (US data in bold)**

Analysis	Overview	Result
Primary Endpoint 1	Change in average AUC with Koios DS (all readers, all data)	+0.083 [0.066, 0.099] (parametric) +0.079 [0.062, 0.096] (non-parametric)
Primary Endpoint 2	<b>Change in average AUC with Koios DS (US readers, US data)</b>	<b>+0.074 [0.051, 0.098] (parametric)</b> <b>+0.073 [0.049, 0.096] (non-parametric)</b>
Secondary Analysis 1	Change in average Sensitivity and Specificity of FNA with Koios DS (all readers, all data)	+ 0.084 [0.054, 0.113] (sensitivity) + 0.140 [0.125, 0.155] (specificity)
	<b>Change in average Sensitivity and Specificity of FNA with Koios DS (US readers, US data)</b>	<b>+ 0.058 [0.017, 0.098] (sensitivity)</b> <b>+ 0.130 [0.110, 0.151] (specificity)</b>
	Change in average Sensitivity and Specificity of FNA with Koios DS (EU readers, EU data)	+0.125 [0.014, 0.237] (sensitivity) +0.171 [0.109, 0.233] (specificity)
Secondary Analysis 2 - – excluding cases recommended for FNA	Change in average Sensitivity and Specificity of Follow-up with Koios DS (all readers, all data)	+ 0.092 [0.043, 0.141] (sensitivity) + 0.242 [0.220, 0.264] (specificity)
	<b>Change in average Sensitivity and Specificity of Follow-up with Koios DS (US readers, US data)</b>	<b>+ 0.087 [0.023, 0.151] (sensitivity)</b> <b>+ 0.206 [0.176, 0.235] (specificity)</b>
	Change in average Sensitivity and Specificity of Follow-up with Koios DS (EU readers, EU data)	+0.084 [-0.133, 0.300] (sensitivity) +0.350 [0.267, 0.434] (specificity)
Secondary Analysis 2a – including cases recommended for	Change in average Sensitivity and Specificity of Follow-up with Koios DS (all readers, all data)	+0.060 [0.040, 0.080] (sensitivity) +0.206 [0.192, 0.219] (specificity)

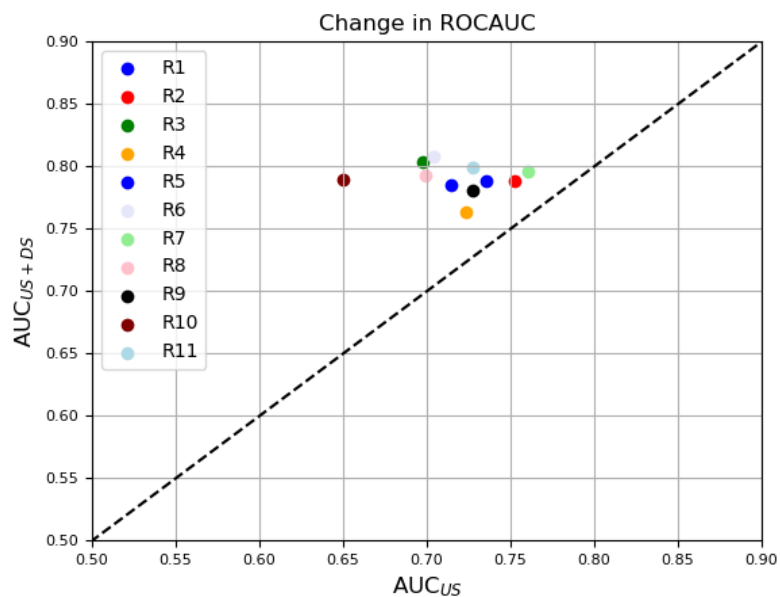
FNA	<b>Change in average Sensitivity and Specificity of Follow-up with Koios DS (US readers, US data)</b>	<b>+0.053 [0.026, 0.080] (sensitivity)</b> <b>+0.180 [0.161, 0.198] (specificity)</b>
	Change in average Sensitivity and Specificity of Follow-up with Koios DS (EU readers, EU data)	+0.060 [-0.009, 0.129] (sensitivity) +0.296 [0.238, 0.354] (specificity)
Secondary Analysis 3	Change in average AUC with Koios DS (EU Readers, EU Data)	+ 0.079 [0.024, 0.134] (parametric) + 0.066 [0.014, 0.118] (non-parametric)
Secondary Analysis 4	Inter-Reader Variability measuring the association of TI-RADS points assigned with and without decision support Difference (Relative Change %)	40.7% (all readers, all data) <b>37.4% (US readers, US data)</b> 49.7% (EU Readers, EU Data)
Secondary Analysis 5	Impact on Interpretation Time	-23.6% (all readers, all data) <b>-22.7% (US readers, US data)</b> -32.4% (EU Readers, EU Data)
Secondary Analysis 6	Change in average AUC with Koios DS descriptor classifiers only (without AI Adapter) (parametric)	+0.022 [0.005, 0.039] (all readers, all data) <b>+0.017 [-0.007, 0.041] (US readers, US data)</b> +0.010 [-0.051, 0.071] (EU Readers, EU Data)
	Change in average AUC with Koios DS descriptor classifiers only (without AI Adapter) (non-parametric)	+0.019 [0.001, 0.037] (all readers, all data) <b>+0.015 [-0.010, 0.039] (US readers, US data)</b> +0.004 [-0.054, 0.062] (EU Readers, EU Data)
	Change in average sensitivity and specificity of FNA with Koios DS descriptor classifiers only (without AI Adapter)	<u>Sensitivity:</u> +0.052 [0.022, 0.081] (all readers, all data) <b>+0.026 [-0.014, 0.066] (US readers, US data)</b> +0.109 [-0.004, 0.221] (EU Readers, EU Data)

		<p><u>Specificity</u> -0.009 [-0.024, 0.006] (all readers, all data)</p> <p><b>-0.001 [-0.022, 0.019]</b> <b>(US readers, US data)</b></p> <p>-0.032 [-0.095, 0.031] (EU Readers, EU Data)</p>
	<p>Change in average sensitivity and specificity of Follow-up with Koios DS descriptor classifiers only (without AI Adapter) – excluding cases recommended for FNA</p>	<p><u>Sensitivity</u> 0.079 [0.031, 0.128] (all readers, all data)</p> <p><b>0.072 [0.008, 0.135]</b> <b>(US readers, US data)</b></p> <p>0.133 [-0.068, 0.334] (EU Readers, EU Data)</p> <p><u>Specificity</u> 0.015 [-0.010, 0.040] (all readers, all data)</p> <p><b>0.012 [-0.021, 0.045]</b> <b>(US readers, US data)</b></p> <p>0.010 [-0.093, 0.113] (EU Readers, EU Data)</p>
	<p>Change in average sensitivity and specificity of Follow-up with Koios DS descriptor classifiers only (without AI Adapter) – including cases recommended for FNA</p>	<p><u>Sensitivity</u> +0.047 [0.026, 0.067] (all readers, all data)</p> <p>+0.037 [0.009, 0.065] (US readers, US data)</p> <p>+0.067 [0.000, 0.134] (EU Readers, EU Data)</p> <p><u>Specificity</u> +0.000 [-0.013, 0.012] (all readers, all data)</p> <p>+0.003 [-0.014, 0.019]</p>

		(US readers, US data)  -0.012 [-0.065, 0.041] (EU Readers, EU Data)
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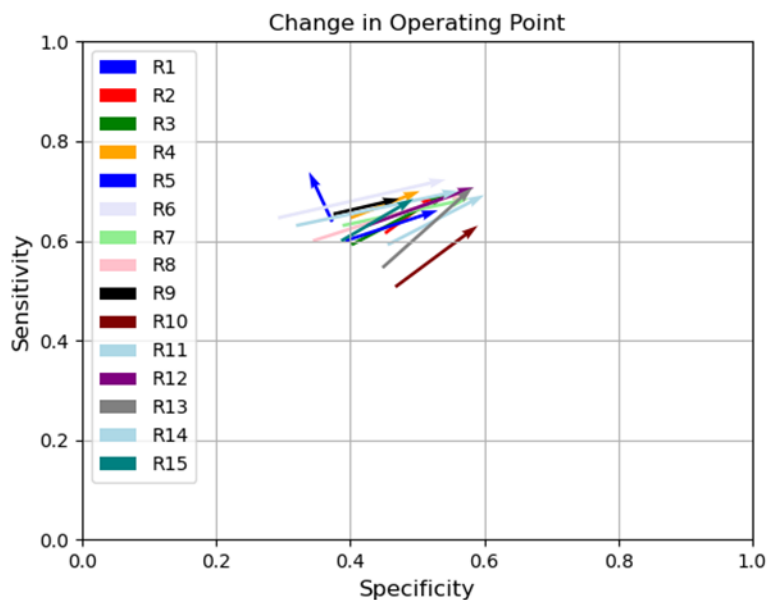
**Summary of System Clinical Performance Using TI-RADS RSS**

	All Readers, All Data	US Readers, US Data	EU Readers, EU Data
<b>Change in average Sensitivity/Specificity of FNA</b>			
TI-RADS categorization w/AI Adapter + size criteria	+0.084 [0.054, 0.113] (sensitivity) +0.140 [0.125, 0.155] (specificity)	+0.058 [0.017, 0.098] (sensitivity) +0.130 [0.110, 0.151] (specificity)	+0.125 [0.014, 0.237] (sensitivity) +0.171 [0.109, 0.233] (specificity)
TI-RADS categorization + size criteria	+0.052 [0.022, 0.081] (sensitivity) -0.009 [-0.024, 0.006] (specificity)	+0.026 [-0.014, 0.066] (sensitivity) -0.001 [-0.022, 0.019] (specificity)	+0.109 [-0.004, 0.221] (sensitivity) -0.032 [-0.095, 0.031] (specificity)
<b>Change in average Sensitivity/Specificity of Follow-up</b>			
TI-RADS categorization w/AI Adapter + size criteria	+0.060 [0.040, 0.080] (sensitivity) +0.206 [0.192, 0.219] (specificity)	+0.053 [0.026, 0.080] (sensitivity) +0.180 [0.161, 0.198] (specificity)	+0.060 [-0.009, 0.129] (sensitivity) +0.296 [0.238, 0.354] (specificity)
TI-RADS categorization + size criteria	+0.047 [0.026, 0.067] (sensitivity) +0.000 [-0.013, 0.012] (specificity)	+0.037 [0.009, 0.065] (sensitivity) +0.003 [-0.014, 0.019] (specificity)	+0.067 [0.000, 0.134] (sensitivity) -0.012 [-0.065, 0.041] (specificity)



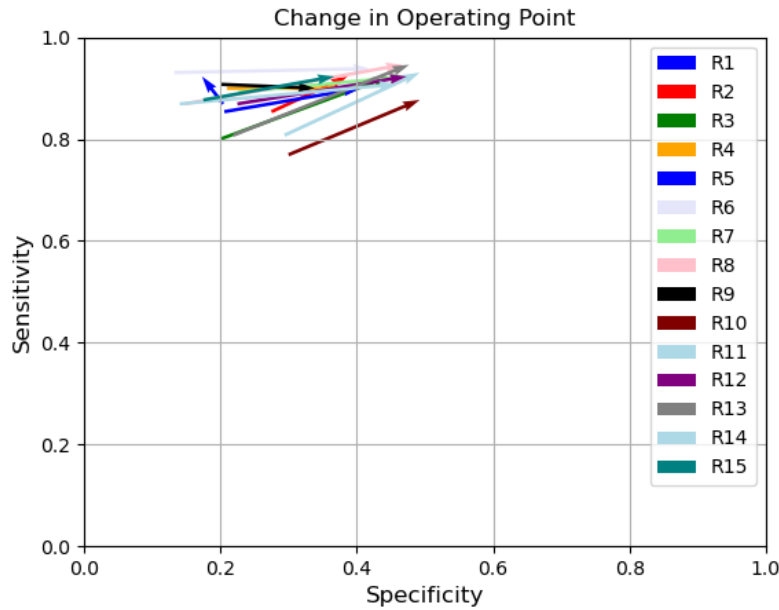
**Reader US (TI-RADS categorization) vs. US+DS (TI-RADS categorization w/AI Adapter)**

*Per reader non-parametric AUC comparing US to US+DS. The dashed line represents equivocal results with all points above this line demonstrating an improvement for the US+DS reading condition.*



**Reader US (TI-RADS categorization + size criteria) vs. US+DS (TI-RADS categorization w/AI Adapter + size criteria) Change in Operating Point (FNA)**

*Change in Sensitivity and Specificity of FNA Recommendations for all data for all readers. The base of the arrow represents the initial operating point, while the arrowhead represents the sensitivity and specificity of US+DS*



**Reader US (TI-RADS categorization + size criteria) vs. US+DS (TI-RADS categorization w/AI Adapter + size criteria) Change in Operating Point (Follow-up)**

*Change in Sensitivity and Specificity of Follow-Up Recommendations for all data for all readers. The base of the arrow represents the initial operating point, while the arrowhead represents the sensitivity and specificity of US+DS*

Primary endpoints were successfully met, demonstrating a **statistically significant improvement of 0.074 [0.051, 0.098] (95% confidence interval)** in overall reader performance of US-based readers when utilizing Koios DS for the interpretation of US-based thyroid ultrasound studies.

**10. Special Controls**

Design verification and validation and product labelling include all requirements proscribed in the 21 CFR 892.2060 Special Controls.

**11. Conclusion**

Nonclinical performance tests demonstrate that the Koios DS software device is as safe, as effective, and performs as well as or better than the legally marketed predicate Koios DS software. It has similar intended use, indications for use, technological characteristics, and principles of operation as its predicate device. The Koios DS product is substantially equivalent to K212616.