Koios Medical, Inc.
℅ Mr. Lev Barinov
VP of Clinical Excellence and Applied Research
500 7th Avenue, 8th Floor
NEW YORK NY 10018

July 3, 2019

Re: K190442
Trade/Device Name: Koios DS for Breast
Regulation Number: 21 CFR 892.2060
Regulation Name: Computer-assisted diagnostic software for lesions suspicious for cancer
Regulatory Class: Class II
Product Code: POK
Dated: June 27, 2019
Received: June 28, 2019

Dear Mr. Barinov:

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. 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 located 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.

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) for devices or postmarketing safety reporting (21 CFR 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 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

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 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) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

For

Thalia T. Mills, Ph.D.
Director
Division of Radiological Health
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

# Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
*See PRA Statement below.*

510(k) Number *(if known)*
K190442

Device Name
Koios DS for Breast

Indications for Use *(Describe)*
Koios Decision Support (DS) for Breast is a software application designed to assist trained interpreting physicians in analyzing the breast ultrasound images of patients with soft tissue breast lesions who are being referred for further diagnostic ultrasound examination. Koios DS for Breast is a machine learning-based decision support system, indicated as an adjunct to diagnostic ultrasound for breast cancer. Koios DS for Breast automatically classifies user-selected region(s) of interest (ROIs) containing a breast lesion into four BI-RADS-aligned categories (Benign, Probably Benign, Suspicious, Probably Malignant), and displays a continuous graphical confidence level indicator of where the lesion falls across all categories. Koios DS for Breast also automatically classifies lesion shape and orientation according to BI-RADS descriptors.

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. When utilized by an interpreting physician who has completed the prescribed training, this device provides information that may be useful in rendering an accurate diagnosis. Patient management decisions should not be made solely on the results of the Koios DS for Breast analysis. This device is intended to help trained interpreting physicians improve their overall accuracy as well as reduce inter- and intra-operator variability.

Koios DS for Breast 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.

Limitations: Koios DS for Breast is not to be used on sites of post-surgical excision, or images with doppler, elastography, or other overlays present in them. Koios DS for Breast is not intended for the primary interpretation of digital mammography images. Koios DS for Breast is not intended for use on mobile devices.

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
*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."*

# 5. 510(k) Summary of Safety and Effectiveness

This 510(k) summary of safety and effectiveness information is submitted as part of the Pre-Market 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: 500 7th Avenue
8th Floor
New York, NY 10018
Phone: 732-529-5755
Fax: 732-529-5757
Contact: Lev Barinov
Title: VP of Clinical Excellence & Applied Research
Phone: 732-529-5755
Fax: 732-529-5757
Summary Date: February 21, 2019

**2. Identification of Product:**

Device Name: Koios DS for Breast, Version 2.0
Device Common Name: Radiological Computer-Assisted Diagnostic Software
Device Classification: 21 CFR 892.2060, Class II, POK
Classification Name: Radiological Computer-Assisted Diagnostic Software (CADx) For Lesions Suspicious For Cancer
Manufacturer: Koios Medical, Inc.

**3. Marketed Devices**

The Koios DS for Breast system is designed to assist trained interpreting physicians in analyzing the breast ultrasound images of patients with soft tissue breast lesions who have been referred for further diagnostic ultrasound examination. Ultrasound images of the breast should be acquired with a small parts linear array or dedicated breast ultrasound linear array transducers. The system provides a generated categorical output that aligns with or exceeds the sensitivity and specificity of radiologist chosen BI-RADS® categorizations using computer vision and machine learning techniques. In terms of safety and performance, this software medical device is substantially equivalent to the devices listed below:

Model: QuantX
Manufacturer: Quantitative Insights, Inc.
510(k) Number: DEN170022

Model: ClearView cCAD, Version 1.0
Manufacturer: ClearView Diagnostics, Inc.
510(k) Number: K161959

**4. Device Description**

Koios Decision Support (DS) for Breast is a software application designed to assist trained interpreting physicians in analyzing breast ultrasound images. The system provides image derived data via web triggering and remote analysis. 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 for Breast application, the user examines selected breast ultrasound DICOM images. The user selects up to two Regions of Interest (ROIs) of two orthogonal views of a breast lesion for processing by Koios DS for Breast. The ROI(s) are transmitted electronically to the Koios DS for Breast server for image processing and the results are returned to the user for review.

The Koios DS for Breast core engine characterizes image features using the ROI data to generate a categorical output that aligns to BI-RADS categories. The engine uses computer vision and machine learning techniques embedded within a software capable of reading, interpreting, analyzing, and generating findings from ultrasound data. The underlying engine draws upon knowledge learned from a large database of known cases, tying image features to their eventual diagnosis, to form a predictive model. The categorical output of the Koios DS for Breast engine is divided into four categories (Benign, Probably Benign, Suspicious, Probably Malignant), separated by three operating points, aligning with or exceeding the sensitivity and specificity of radiologist chosen BI-RADS categorizations. . The output of the system is a digital display to be used as a concurrent read. Koios DS for Breast is intended to support compliance with the ACR BI-RADS ultrasound lexicon classification form. The engine additionally classifies the region of interest on the basis of shape (Oval, Round, Irregular) and orientation (Parallel to Skin, Not Parallel).

Koios DS for Breast results can be saved or transferred in three separate ways: in-transit transmission, PACS saving, 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. These results are never locally cached, written to disk, or otherwise stored outside of in-transit memory. 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 series on the PACS. After single or multiple breast lesion analyses have been performed and ultimately accepted by a trained interpreting physician, Koios DS for Breast can export a summary report to PACS as an addendum to the DICOM series that was selected for processing. This report serves as future reference and aid in comparison of cases requiring follow up. This functionality is strictly reserved for approved users.

Koios DS for Breast 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.

The Koios DS for Breast software is an ASP.NET web application that is deployed to an IIS Web Server inside a Windows operating system environment. The software does not require any specialized hardware, but the time to process ROIs will vary depending on the hardware specifications. If utilizing the recommended technical specifications, the time to generate and present results for two analyzed ROIs will be <= 2 seconds. The Koios DS for Breast processing software is a platform agnostic web service that queries and accepts DICOM compliant digital medical files from any DICOM compliant device.

Koios DS for Breast is intended to be used on patients with soft tissue breast lesions who are being referred for further diagnostic ultrasound examination.

**5. Indications for Use**

Koios Decision Support (DS) for Breast is a software application designed to assist trained interpreting physicians in analyzing the breast ultrasound images of patients with soft tissue breast lesions who are being referred for further diagnostic ultrasound examination. Koios DS for Breast is a machine learning-based decision support system, indicated as an adjunct to diagnostic ultrasound for breast cancer. Koios DS for Breast automatically classifies user-selected region(s) of interest (ROIs) containing a breast lesion into four BI-RADS-aligned categories (Benign, Probably Benign, Suspicious, Probably Malignant), and displays a continuous graphical confidence level indicator of where the lesion falls across all categories. Koios DS for Breast also automatically classifies lesion shape and orientation according to BI-RADS descriptors.

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. When utilized by an interpreting physician who has completed the prescribed training, this device provides information that

may be useful in rendering an accurate diagnosis. Patient management decisions should not be made solely on the results of the Koios DS for Breast analysis. This device is intended to help trained interpreting physicians improve their overall accuracy as well as reduce inter- and intra-operator variability.

Koios DS for Breast 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.

Limitations: Koios DS for Breast is not to be used on sites of post-surgical excision, or images with doppler, elastography, or other overlays present in them. Koios DS for Breast is not intended for the primary interpretation of digital mammography images. Koios DS for Breast is not intended for use on mobile devices.

## 6. Substantial Equivalence Discussion

| Product | QuantX (DEN270022) | ClearView cCAD (K161959) | Koios DS for Breast |
|---|---|---|---|
| **Characteristics** | CADx device used to assist in the assessment and characterization of breast abnormalities using MR image data. | Decision support device used to assist in the assessment and characterization of breast lesions using US image data. | Decision support device used to assist in the assessment and characterization of soft tissue breast lesions using US image data. |
| **Intended Use** | Diagnostic Aid using Machine Learning to characterize image features with user provided ROIs to generate a single value relative to reference abnormalities (QI Score). | Diagnostic Aid using Machine Learning to generate BI-RADS shape and orientation assessments coupled with additional user input BI-RADS descriptors to generate a preliminary BI-RADS bucket assessment. | Diagnostic Aid using Machine Learning to characterize image features with user provided ROIs to generate categorical output that aligns to BI-RADS and auto-classified shape and orientation. |
| **Target Population** | High-risk screening; diagnostic workup; evaluation of known disease | Any patient that has an identified breast lesion that is referred for diagnostic ultrasound examination; excludes high-risk screening | Patients with soft tissue breast lesions who are being referred for further diagnostic ultrasound examination. |
| **Modality Used for Analysis** | Breast MR Data | Breast Ultrasound Data | Breast Ultrasound Data |
| **Input** | Medical images provided in a DICOM format | Medical images provided in a DICOM format | Medical images provided in a DICOM format |
| **Output** | "QI" score mapped onto histograms of distributions of malignant and benign lesions | BI-RADS bucket assessment of lesions based on auto-classified shape and orientation and user supplied inputs | Koios defined categorical and continuous outputs (confidence level indicator) that align to BI-RADS and auto-classified shape and orientation |
| **Comparative Performance Testing** | Metric: AUC<br>Cases: 111<br>Readers: 19 | N/A | Metric: AUC<br>Cases: 900<br>Readers: 15 |
| **Physical Characteristics** | Software Package Operates on off-the-shelf hardware | Software Package Operates on off-the-shelf hardware | Software Package Operates on off-the-shelf hardware |
| **Storage** | Storage not supported | Storage not supported | Storage not supported |
| **Image Input** | DICOM | DICOM | DICOM |

**Description of Similarities and/or Differences:**

**Indications for Use (IFU)**

Comparing the IFU of the primary predicate device QuantX (DEN170022) and Koios DS for Breast, there are several key similarities and differences outlined below:

Both devices are intended to be utilized as diagnostic aids that operate on user-supplied Regions of Interest (ROIs). Koios DS for Breast's core classification engine does not rely on registration or segmentation to function sothese requirements are not present in its IFU as compared to those for QuantX. In the case of QuantX, the IFU states "(t)he software automatically registers images, and segments and analyzes user-selected regions of interest (ROI)." Accordingly, the IFU for Koios DS for Breast does not contain a similar provision. The IFU for Koios DS for Breast requires that a user select up to two ROIs from up to two orthogonal views that represent a single lesion to be selected and processed.

Both devices provide computer analytics based on morphological and enhancement characteristics that the QuantX device refers to as imaging (or radiomic) features that are then synthesized by an artificial intelligence algorithm into a single value. While the QuantX device generates a "QI score" which is analyzed relative to reference abnormalities, Koios DS for Breast generates a probability output that analyzes imaging features relative to a dataset of known ground truth that is then used to generate a categorical assessment. The categorical assessment provided by Koios DS for Breast aligns to BI-RADS and auto-classifies shape and orientation.

The intended use population for QuantX includes patients presenting for high-risk screening, diagnostic imaging workup, or evaluation of known disease. Koios DS for Breast is intended to be used for assisting trained interpreting physicians in analyzing patients with soft tissue breast lesions who are being referred for further diagnostic ultrasound examination. This intended use includes patients presenting with any soft tissue breast lesion through any form of imaging or physical examination resulting in a referral for diagnostic ultrasound - thus covering diagnostic imaging workup or the evaluation of known disease. Koios DS for Breast is not indicated to be used for the evaluation of patients presenting for high-risk screening, which is the only clear difference in target populations between the predicate and Koios DS for Breast.

Both the QuantX device and Koios DS for Breast are intended to be used as image viewers of multi-modality digital images including ultrasound and mammography. Both

sets of software include tools to allow users to measure and document images, and output the findings in structured DICOM formats. Neither platform is intended for primary interpretation of digital mammography images. Both platforms contain labeling instructions with a list of warnings.

The secondary predicate device, cCAD (K161959), which was also developed by Koios Medical (fka ClearView Diagnostics, Inc.), differs in that it relied upon user-supplied BI-RADS descriptors and generated a BI-RADS bucket assessment. Similar to cCAD, Koios DS for Breast automatically assesses shape and orientation for user selected ROIs, but does not support the addition of user supplied BI-RADS descriptors to suggest a BI-RADS bucket assessment. In addition, although Koios DS for Breast may be utilized as a primary diagnostic viewer for ultrasound, warnings explicitly limit users from utilizing the platform for primary interpretation of mammography images along with labeling instructions with a list of warnings, precautions and contraindications.

**Modality**

QuantX is intended to be utilized on breast MR data, while Koios DS for Breast is intended to be utilized on breast ultrasound data. While this clearly differentiates the products, they are both aligned to the generic FDA device type (per DEN170022) for radiological computer-assisted software (CADx) for lesions suspicious for cancer.

Koios DS for Breast shares the modality requirements of cCAD.

**Input**

Per the respective device descriptions of QuantX and Koios DS for Breast, the input to each consists of medical images provided in a DICOM format. While there are modality differences that are addressed above, the technical implementation for ingesting images for processing occurs via the same DICOM based interface.

Koios DS for Breast shares the input requirements of ClearView Diagnostics' cCAD product.

**Output**

The output of both systems differs in both information and style of display. The QuantX system outputs a "QI" score that is then mapped onto distributions of malignant and benign lesions. It does not explicitly compute a likelihood of malignancy, but instead relies on the user to interpret the QI score and its respective position in the benign/malignant histograms to impact their assessment of the lesion's underlying risk. Conversely, Koios DS for Breast directly characterizes a lesion based on categorical and continuous outputs (confidence level

indicator) that are aligned to BI-RADS and auto-classifies shape and orientation. This allows for users to interpret the automated assessment alongside an existing risk stratification and feature description lexicon.

In addition, Koios DS for Breast implements an automated assessment of shape and orientation as done by cCAD. The results are presented in a form substantially similar to the form provided by cCAD.

Koios DS for Breast, does not provide a BI-RADS bucket assessment of lesions as cCAD does. Instead, Koios DS for Breast aligns its risk assessment to BI-RADS with categories chosen such that they align with or exceed the sensitivity and specificity of BI-RADS categorizations.

**Algorithm**

Koios DS for Breast and cCAD share a similar algorithm set, training data, and validation approach for automated shape and orientation assessment.

While Koios DS for Breast and QuantX both aim to characterize lesions suspicious for cancer, their respective differences in modality necessitate differences in the algorithmic approach applied. Due to the fact that QuantX does not disclose their algorithmic approach, Koios Medical cannot speculate as to the underlying architecture of their system. Instead, Koios Medical aims to demonstrate equivalence through performance impact.

**Performance Testing**

Koios DS for Breast and cCAD share a similar algorithm set, training data, and validation approach for automated shape and orientation assessment. As such their performance results are directly comparable.

When comparing clinical validation between Koios DS for Breast and QuantX, the sponsors used similar endpoints in their clinical studies. Both sponsors evaluated an Area Under the Curve (AUC) shift when comparing the performance of users alone versus users utilizing the respective software platform. The number of cases evaluated in the QuantX study was 111, while the Koios DS for Breast study evaluated a total of 900 cases. The number of readers utilized in the QuantX study was 19, while the Koios DS for Breast study used a total of 15 readers.

While the results of QuantX study showed a mean AUC shift of +0.0487, the Koios DS for Breast study showed a mean shift of +0.037. The 95% CI was noticeably tighter for the AUC with a standard error of .0036 for Koios DS for Breast compared to .0254 when computing the MRMC estimated AUC via the trapezoidal rule. Further, the AUC of both

the first and second reads is considerably higher in the Koios DS for Breast study set than in the QuantX study with an AUC shift of .7090 to .7577 for QuantX and a shift from .836 to .873 for Koios DS for Breast. While the absolute values for AUC may differ based on reader, data, and modality; the range for possible improvement has a smaller lower bound in the Koios DS for Breast clinical evaluation. In conclusion, the Koios DS for Breast study has demonstrated substantially equivalent performance to QuantX by showing a statistically significant acceptance of similar success criteria to QuantX with a smaller standard error.

**7. Clinical Performance Data**

A clinical study was executed to determine the effect of Koios DS for Breast on reader performance. 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 for 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 Experience**

| 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 |

*Reader Experience Breakdown*

**Dataset Demographic Information**

The following patient demographics, as measured by the Breast Cancer Surveillance Consortium (2006-2009), were met to ensure populations representative of national rates:

592 White women
73 Hispanic women
77 African American women
133 Asian women
25 cases that do not fall in the above categories

The age distribution of patients included within the study were:

- <40: 15.3% = 138
- 40-49: 25.3% = 228
- 50-59: 23.0% = 207
- 60-74: 26.1% = 235
- 75-84: 7.6% = 68
- 85+: 1.0% = 9
- N/A: 1.7% = 15

Breast Density information for the clinical study was as follows:

- BI-RADS 1: 12.8%
- BI-RADS 2: 38.1%
- BI-RADS 3: 33.2%
- BI-RADS 4: 15.9%

The lesion sizes included within the study ranged from 3-80mm with 332/900 (36.9%) <10mm, 229/900 (25.4%) 10-14mm, 132/900 (14.7% 15-19mm, and 200/900 (22.2%) > 20mm. Size was unavailable for 7 lesions (0.8%). The minimum lesion size was 3mm.

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.

**8. Non-Clinical Performance Data**

Malignancy Risk Classification:

Bench testing was performed 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 is represented by two orthogonal images (e.g. radial and anti-radial), providing a total of 1800 images. System performance on the 900 cases reported an AUC of 88.2%.

BI-RADS Descriptors:

Bench testing was performed to ascertain the degree of concordance with trained interpreting physicians. Ground truth for shape and orientation was supplied by three MQSA certified radiologists. These physicians, all with over 20 years of experience and at least 3000 images read per year, evaluated this dataset on the aforementioned parameters. The system was used to analyze these 1300 cases on the same parameters. In the first test, the system was analyzed on 1204 cases which had a majority decision on shape and 1227 lesions which had a majority decision on orientation. The Koios DS for Breast system was able to achieve overall accuracy that fell within the 95% confidence interval of the radiologists' performance, rendering them statistically equivalent.

| Category | Koios DS for Breast properly Identified | Koios DS for Breast Proportion | 95% CI | Cut Off for Proportion Point estimate | Conclusion |
|---|---|---|---|---|---|
| Lesion orientation | 1125 | 91.12% | [**89.43%** 92.60%] | **86.12%** | Within criteria established for clinical equivalence |
| Lesion shape | 1066 | 87.62% | [**85.68%** 89.36%] | **83.54%** | Within criteria established for clinical equivalence |

*Koios DS performance for shape and orientation classification, when measured against majority decision*

In the second test, categorical agreement between each pair of readers was compared to agreement between each reader and the system. For this test, majority agreement was not enforced and all cases were analyzed for reader-reader and reader-system agreement. Agreement was estimated by means of calculating the Cohen's Kappa coefficient for each pair. On average, for both shape and orientation, the level of agreement between two pairs of readers was not found to statistically differ from the level of agreement between readers and the system.

| | $\kappa$: Reader vs Reader | $\kappa$: System vs Reader |
|---|---|---|
| **Shape** | 0.769 [0.711, 0.826] | 0.738 [0.679, 0.797] |
| **Orientation** | 0.728 [0.655, 0.801] | 0.744 [0.675, 0.813] |

*Average kappa coefficient and 95% confidence intervals for reader vs reader and system vs reader categorizations*

**9. Conclusion**

Based on the substantial equivalence evaluation, which is derived from the nonclinical and clinical tests that demonstrate that the device is as safe, as effective, and performs as well as or better than the legally marketed device predicates, we have determined that the Koios DS for Breast product is substantially equivalent to DEN170022 and K161959.