TaiHao Medical Inc.
℅ Hsin Hung
President
6F.-1, No.100, Sec. 2 Heping E. Rd., Da'an Dist.
Taipei, 10663
TAIWAN

December 21, 2021

Re: K210670
Trade/Device Name: BU-CAD
Regulation Number: 21 CFR 892.2090
Regulation Name: Radiological computer assisted detection and diagnosis software
Regulatory Class: Class II
Product Code: QDQ, LLZ
Dated: November 22, 2021
Received: November 22, 2021

Dear Hsin Hung:

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: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K210670

Device Name
BU-CAD

Indications for Use *(Describe)*
BU-CAD is a software application indicated to assist trained interpreting physicians in analyzing the breast ultrasound images of patients with soft tissue breast lesions suspicious for breast cancer who are being referred for further diagnostic ultrasound examination.

Output of the device includes regions of interest (ROIs) and lesion contours placed on breast ultrasound images assisting physicians to identify suspicious soft tissue lesions from up to two orthogonal views of a single lesion, and region-based analysis of lesion malignancy upon the physician's query. The region-based analysis indicates the score of lesion characteristics (SLC), and corresponding BI-RADS categories in user-selected ROIs or ROIs automatically identified by the software. In addition, BU-CAD also automatically classifies lesion shape, orientation, margin, echo pattern, and posterior features according to BI-RADS descriptors.

BU-CAD 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 (SR).

Patient management decisions should not be made solely on the basis of analysis by BU-CAD.

Limitations: BU-CAD is not to be used on sites of post-surgical excision, or images with Doppler, elastography, or other overlays present in them. BU-CAD is not intended for the primary interpretation of digital mammography images. BU-CAD 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.

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510(K) Summary

I. Identification of Submitter K210670

Submitter:	TaiHao Medical Inc.
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Contact:	HSIN HUNG (Simon) LAI
Title:	President
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Manufacturer:	TaiHao Medical Inc.

Additional Contact:	HONG HAO CHEN, Ph.D.
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Address:	6F.-1, No.100, Sec. 2, Heping E. Rd., Da'an Dist., Taipei City 106, Taiwan (R.O.C.)
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Email:	honghowc@taihaomed.com

Date of Prepared	December 16, 2021

II. Identification of Product

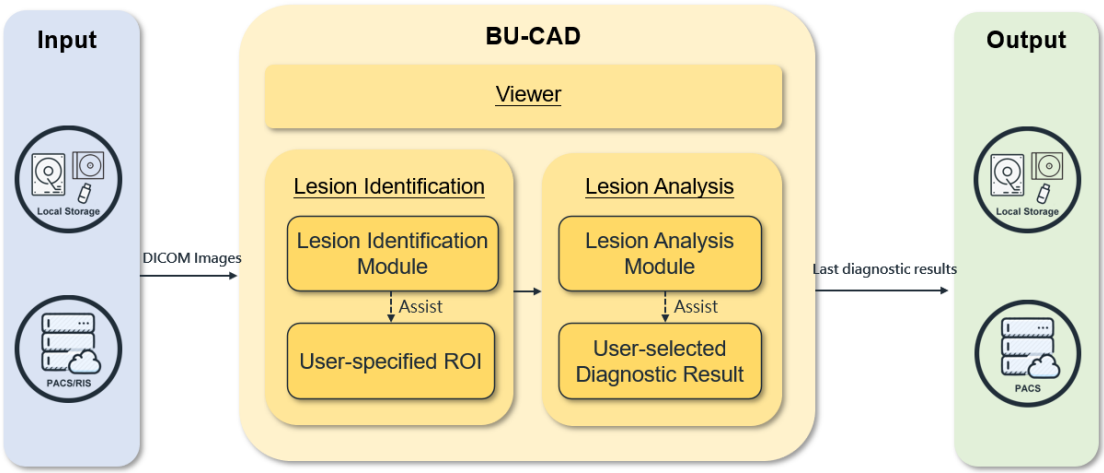
Device Name:	BU-CAD
Regulation Number:	892.2090
Device Classification:	Class II Classification Product Code: QDQ Subsequent Product Code: LLZ
Classification Name:	Radiological Computer Assisted Detection/Diagnosis Software For Lesions Suspicious For Cancer
Review Panel:	Radiology
Manufacturer:	TaiHao Medical Inc.

III. Predicate Device

Predicate Device:	Transpara™ (K181704) (primary), QuantX (K170195)
Reference Device:	Koios DS for Breast (K190442)

IV. Device Description

BU-CAD developed by TaiHao Medical Inc. is a software system designed to assist users in analyzing breast ultrasound images including identification of regions suspicious for breast cancer and assessment of their malignancy. The following figure shows the architecture chart of BU-CAD which consists of a Viewer, a Lesion Identification Module, and a Lesion Analysis Module.



Architecture chart of BU-CAD

The Viewer is able to load breast ultrasound and mammography images (FDA-cleared full-field digital mammography only) from local storage or a picture archiving and communication system (PACS) for review. The Viewer also includes tools that allow users to measure lesion size and adjust the image (such as window level and window width adjustment). Additionally, the report may be saved in local storage or uploaded to PACS. BU-CAD also supports exporting CAD results to third-party reporting software to facilitate the reporting process.

The Lesion Identification Module identifies regions of interest (automated ROIs) of a single suspicious soft tissue lesion in up to two orthogonal views of breast ultrasound images for assisting users in detecting soft tissue lesions. Additionally, the Lesion Identification Module generates an ROI and a lesion contour on each breast ultrasound image. The lesion contour on each image will be automatically delineated by the given ROI. The Lesion Analysis Module analyzes given ROIs of a breast lesion on ultrasound images, and generates a score of lesion characteristics (SLC) in terms of malignancy or benignity of a lesion, BI-RADS category, and BI-RADS descriptors (with limitations as described in the User Manual) for the concurrent read. The users are able to replace the automated ROIs with re-delineated rectangular ROIs for

analysis by Lesion Analysis Module. Only the last analysis results will be displayed on the user interface and are modifiable by the user. Note that the SLC is analyzed based on the rectangular ROIs, unless the user re-delineates the ROIs, the SLC will not be changed.

In clinical practice, after opening multi-modality digital images including ultrasound and mammography on the Viewer, the users may identify and analyze lesions with the assistance of the Lesion Identification Module and Lesion Analysis Module on the breast ultrasound images. Finally, the user confirms the diagnostic results (output from Lesion Analysis Module or modified by the user) shown on the user interface and saves them to the report.

Output of BU-CAD analysis

Region-based Analysis Item	Range
Score of lesion characteristics (SLC)	[0,100] The SLC ranging from 0 to 25 corresponds to BI-RADS 2, from 26 to 50 corresponds to BI-RADS 3, from 51 to 97 corresponds to BI-RADS 4, and from 98 to 100 corresponds to BI-RADS 5.
BI-RADS category	2 / 3 / 4a / 4b / 4c / 5
BI-RADS descriptors (mass)	Shape, Orientation, Margin, Echo Pattern, Posterior Features (with limitations specified in User Manual)

V. Indications for Use

BU-CAD is a software application indicated to assist trained interpreting physicians in analyzing the breast ultrasound images of patients with soft tissue breast lesions suspicious for breast cancer who are being referred for further diagnostic ultrasound examination.

Output of the device includes regions of interest (ROIs) and lesion contours placed on breast ultrasound images assisting physicians to identify suspicious soft tissue lesions from up to two orthogonal views of a single lesion, and region-based analysis of lesion malignancy upon the physician's query. The region-based analysis indicates the score of lesion characteristics (SLC), and corresponding BI-RADS categories in user-selected ROIs or ROIs automatically identified by the software. In addition, BU-CAD also automatically classifies lesion shape, orientation, margin, echo pattern, and posterior features according to BI-RADS descriptors.

BU-CAD 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 (SR).

Patient management decisions should not be made solely on the basis of analysis by BU-CAD.

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

VI. Comparison with Predicate Device/Reference Device

	BU-CAD	Transpara™ (K181704) Predicate Device	QuantX (K170195) Predicate Device
Manufacturer	TaiHao Medical Inc.	ScreenPoint Medical BV	Quantitative Insights, Inc.
Regulation Section	21 CFR 892.2090	21 CFR 892.2090	21 CFR 892.2050
Product Code	QDQ, LLZ	QDQ	LLZ
Intended Use	Intended to be used by clinicians interpreting radiological images, to help them with localizing and characterizing breast abnormalities. Intended to be used concurrently with the reading of images and are not intended as a replacement for the review of a clinician or their clinical judgement.	Intended to be used by clinicians interpreting radiological images, to help them with localizing and characterizing breast abnormalities. Intended to be used concurrently with the reading of images and are not intended as a replacement for the review of a clinician or their clinical judgement.	QuantX is a quantitative image analysis software device used to assist radiologists in the assessment and characterization of breast abnormalities using MR image data.
Characteristics	CADe and CADx software used to assist in localizing suspicious soft tissue lesions and region-based analyze of malignancy using ultrasound image data.	CADe and CADx software used to assist in localizing suspicious soft tissue lesions and suspicious calcifications; region-based analyze of malignancy using mammography image data.	The software automatically registers images, and segments and analyzes user-selected regions of interest (ROI). QuantX extracts image data from the ROI to provide volumetric and surface area analysis.
Target Population	Patients with soft tissue breast lesions who are being referred for ultrasound interpreting.	Patients with soft tissue breast lesions and suspicious calcifications who are being referred for	Patients who are being referred for breast MRI interpretation.

	BU-CAD	Transpara™ (K181704) Predicate Device	QuantX (K170195) Predicate Device
		mammogram interpreting.	
Anatomical Location	Breast	Breast	Breast
Design	Software-only device	Software-only device	Software-only device
Modality Used for Analysis	Breast ultrasound data	Mammography	Breast MRI
Input	Medical images provided in a DICOM format	Medical images provided in a DICOM format	Medical images provided in a DICOM format
Output	ROIs and lesion contours placed on suspicious soft tissue lesion. A region-based score of lesion malignancy, a BI-RADS category, and BI-RADS descriptors.	Marks placed on suspicious soft tissue lesion and suspicious calcifications. A region-based score of lesion malignancy, and an overall score of the mammogram.	QuantX extracts image data from the ROI to provide volumetric and surface area analysis.
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
Comparative Performance Testing (MRMC)	Metric: AUC Cases: 628 Readers: 16	Metric: AUC Cases: 240 Readers: 14	N/A
Modality Used for Viewing	Breast Ultrasound and Mammography (FFDM)	N/A	Breast MRI, breast ultrasound, and mammography
Primary Interpretation of Digital Mammography Images	BU-CAD is not intended for the primary interpretation of digital mammography images.	N/A	QuantX is not intended for primary interpretation of digital mammography images

◆ **Intended Use**

The intended use of BU-CAD is the same as that of the legally marketed predicate device, Transpara™. Both are intended to be used by clinicians interpreting radiological images, to help them with localizing and characterizing breast abnormalities. BU-CAD and the predicate device are both intended to be used concurrently with the reading of images and are not intended as a replacement for the review of a clinician or their clinical judgement.

◆ **Indications for Use**

Both BU-CAD and Transpara™ are intended to identify regions suspicious for breast cancer and provide computer analytics that are then synthesized by an artificial intelligence algorithm into a single value. Both BU-CAD and Transpara™ generate region-based scores indicating the malignancy. Both BU-CAD and Koios DS for Breast characterizes a lesion based on categorical output and auto-classifies BI-RADS descriptors.

◆ **Intended Use Population and Modality**

BU-CAD and Transpara™ differ in the type of medical images the devices process, however, they are both aligned to the generic FDA device type for radiological computer-assisted detection and diagnosis for lesions suspicious for cancer. Transpara™ is intended for aiding physicians interpreting screening mammograms, while BU-CAD is intended for aiding physicians interpreting diagnostic ultrasound examination.

BU-CAD shares the intended use population and modality requirements of Koios DS for Breast. Both BU-CAD and the Koios DS for Breast are intended to be used for assisting trained interpreting physicians in analyzing patients with soft tissue breast lesions which are being referred for further diagnostic ultrasound examination.

BU-CAD and QuantX may also be used as image viewers of multi-modality digital images, including ultrasound and mammography, and are not intended for the primary interpretation of digital mammography images.

◆ **Input**

According to the respective device descriptions of Transpara™ and BU-CAD, 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.

Both BU-CAD and Koios DS for Breast analyzes breast lesion from up to two orthogonal views of a single lesion.

◆ **Output**

The outputs between BU-CAD and Transpara™ are not exactly the same. Outputs of Transpara™ consist of highlighted locations of detected suspicious soft tissue lesions and suspicious calcifications, and region-based scores (Transpara™ Score). Output of BU-CAD

consists of highlighted locations (ROI(s) and lesion contour(s)) of detected suspicious soft tissue lesion, region-based score (SLC), BI-RADS category, and BI-RADS descriptors.

Both BU-CAD and Koios DS for Breast characterizes a lesion based on categorical output and auto-classifies BI-RADS descriptors.

◆ **Interface**

Transpara™ consists of a processing server and an optional viewer. Processing results of Transpara™ can be transmitted to external destinations that allows PACS workstations to implement the interface of Transpara™ in mammography reading applications. BU-CAD is intended to be used as an image viewer of multi-modality digital images which provides analysis of breast ultrasound abnormalities.

Both BU-CAD 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.

◆ **Performance Testing**

Both BU-CAD and Koios DS for Breast are intended to be used for assisting trained interpreting physicians in analyzing patients with soft tissue breast lesions which are being referred for further diagnostic ultrasound examination.

When comparing clinical validation between BU-CAD, Transpara™, and Koios DS for Breast, the devices were evaluated using similar endpoints in their clinical studies and the Area Under the Curve (AUC) shift was used when comparing the performance of users alone versus users with the aid of the software platform. The number of cases evaluated in the MRMC reader study of Koios DS for Breast was 750 (150 additional cases for intra-operator variability evaluation without switching the reading condition), the number of cases evaluated in the MRMC reader study of Transpara™ was 240, while the BU-CAD MRMC reader study evaluated a total of 628 cases. The number of readers utilized in the Koios DS for Breast MRMC reader study was 15 (11 radiologist, 2 breast surgeon, and 2 OB/GYN), the number of readers utilized in the Transpara™ MRMC reader study was 14 radiologists, while the BU-CAD MRMC reader study used a total of 16 readers (14 radiologists and 2 breast surgeons).

The AUC shift between users alone and users with the aid of the software platforms (Transpara™, Koios DS for Breast, and BU-CAD) was similar. The results of Koios DS for Breast MRMC reader study showed a mean AUC shift of +0.037, the results of Transpara™ MRMC reader study showed mean AUC shift of +0.02, the BU-CAD MRMC reader study showed a mean shift +0.0374.

The standalone performance of BU-CAD reported an AUC_LROC of 0.8203 (AUC from 0.8 to 0.9) compared to the reference device Koios DS for Breast of 0.882. For the BI-RADS descriptors, Koios DS for Breast provided BI-RADS descriptors of Shape and Orientation which the level of agreement between readers is similar to the agreement between readers and system. The MRMC showed that BU-CAD improved readers' determination of BI-RADS descriptors (Shape, Orientation, Margin, Echo Pattern, and Posterior Features) for at least one or more subcategories for each descriptor. In conclusion, the BU-CAD MRMC reader study has demonstrated substantially equivalent performance to Transpara™ and Koios DS for Breast by showing a statistically significant aided read performance using similar success criteria compared to Transpara™ and Koios DS for Breast.

- **Discussion of the Comparison to Support Substantial Equivalence (SE) Determination**

BU-CAD has the same intended use as the legally marketed predicate device, Transpara™. They are intended to be used by clinicians interpreting radiological images, to help them with localizing and characterizing breast abnormalities.

The input of BU-CAD and the predicate devices is composed of medical images provided in a DICOM format. The output of BU-CAD is similar to the predicate devices by providing ROIs and lesion contours placed on suspicious soft tissue lesion and region-based score are similar to Transpara™, while providing BI-RADS category and BI-RADS descriptors are similar to Koios DS for Breast.

Although BU-CAD and Transpara™ differ in the type of medical images the devices process, they are both aligned to the generic FDA device type for radiological computer-assisted detection and diagnosis for lesions suspicious for cancer (product code: QDQ). BU-CAD has similar intended use compared to the predicate devices that aim to localize and characterize breast abnormalities. Artificial intelligence algorithm of each device may have different technological characteristics from the legally marketed predicate devices. Therefore, a fully crossed multiple reader multiple case (MRMC) reader study was conducted in the US.

Compared to Transpara™ and QuantX as the primary and secondary predicates, and in consideration of the technological characteristics and test methods used in the legally marketed Koios DS for Breast, BU-CAD does not raise different questions of safety and effectiveness.

VII. Clinical Performance Data

◆ Summary of the Reader Study

The performance of physicians without and with the aid of BU-CAD decision support in interpreting breast ultrasound images was compared by using a fully crossed multi-reader multi-case receiver operating characteristic (MRMC-ROC) retrospective study (also known as Obuchowski-Rockette Dorfman-Berbaum-Metz MRMC-ROC or OR-DBM MRMC-ROC).

The study consisted of 628 cases, of which 456 cases (189 malignant and 267 benign) were collected from the United States and 172 cases (65 malignant and 107 benign) were collected from Taiwan. Sixteen readers participated in the study. Each reader was asked to identify the lesion, provide a linear score of lesion characteristics (SLC), select a BI-RADS category and select BI-RADS descriptors for an ultrasound breast lesion with or without the aid of BU-CAD.

Dataset Demographic

A total of 628 cases collected from two institutions were used in the reader study. The source of cases is listed below.

- U.S.: 456 cases
- Taiwan: 172 cases

The BI-RADS category distribution included in this study were listed below:

- BI-RADS 2: 5 cases
- BI-RADS 3: 123 cases
- BI-RADS 4A: 204 cases
- BI-RADS 4B: 111 cases
- BI-RADS 4C: 105 cases
- BI-RADS 5: 80 cases

The number of benign and malignant cases included in this study were listed below.

- Benign cases
    - Pathology proof benign: 197 cases
    - Two-year follow-up benign: 177 cases

- Malignant cases
    - Ductal carcinomas in situ (DCIS): 17 cases
    - invasive ductal carcinoma (IDC): 193 cases
    - Invasive lobular carcinoma (ILC): 40 cases
    - Other cancer types: 4 cases

The imaging hardware distribution included in this study were listed below:

- GE: 451 cases
- Acuson: 5 cases
- Philips: 100 cases
- Canon/Toshiba: 72 cases

Reader Experience

Study Reader	Specialty	MQSA	Received Breast Image Fellowship	Year of experience as a radiologist
Dr. X01	Radiologist	Yes	No	24
Dr. X02	Radiologist	Yes	Yes	3
Dr. X03	Radiologist	Yes	No	13
Dr. X04	Radiologist	Yes	No	14
Dr. X05	Radiologist	Yes	No	8
Dr. X06	Radiologist	Yes	Yes	5
Dr. X07	Radiologist	Yes	Yes	2
Dr. X08	Radiologist	Yes	No	10
Dr. X09	Radiologist	Yes	Yes	12
Dr. X10	Radiologist	Yes	No	11
Dr. X11	Breast Surgeon	No	No	> 30 (breast surgeon)
Dr. X12	Breast Surgeon	No	No	> 30 (breast surgeon)
Dr. X13	Radiologist	Yes	No	21
Dr. X14	Radiologist	Yes	No	1
Dr. X15	Radiologist	Yes	No	13
Dr. X16	Radiologist	Yes	No	5

Primary Objective

The primary objective of this clinical study is to prove that the user's performance (AUC of location-specific ROC) aided by the BU-CAD software is superior to the unaided performance. The aided AUC of the location-specific ROC for BU-CAD was superior to that of the unaided scenario for the diagnosis of breast ultrasound images. The mean AUC of location-specific ROC shift of 0.0374.

Primary Results of the Pivotal Study

Reading Scenario	AUC_LROC	95% CI	*p*-value
Unaided	0.7786	(0.7463, 0.8109)	
Aided	0.8160	(0.7862, 0.8458)	
Aided – Unaided	0.0374	(0.0190, 0.0557)	0.0001

Subgroup Analysis

Subgroup of reader specialty (with and without MQSA certification), with and without breast image fellowship training, ultrasound systems (GE, Acuson, Philips, and Canon/Toshiba), benign types (pathology proof benign and two-year follow-up benign), cancer types (DCIS, IDC, ILC, and others), lesion sizes (less than 1 cm, between 1 cm and 2 cm, and larger than 2 cm), lesion locations (center and not in center), ages (≤ 50 years, > 50 years, ≤ 55 years, and >55 years), and source of cases (U.S. and Taiwan) were performed. Except for the subgroup of Acuson ultrasound system, where the sample size was relatively low, the readers aided by the BU-CAD achieved higher performance than unaided reading in the other subgroups.

Secondary Objective

The secondary objective of this clinical study is to compare that the user's performance (sensitivity, specificity, PPV, and NPV) between the unaided and aided readings. Sensitivity, specificity, PPV, and NPV produced from the aided arm were higher than unaided. The specificity, unadjusted PPV, and unadjusted NPV differed significantly from zero between the aided and unaided sessions.

Sensitivity, Specificity, PPV, and NPV between Unaided and Aided Reading Scenarios

Statistical Parameter	Unaided (95% CI)	Aided (95% CI)
Sensitivity	0.9225 (0.8896, 0.9554)	0.9353 (0.9050, 0.9655)
Specificity	0.3165 (0.2694, 0.3636)	0.3611 (0.3124, 0.4098)
NPV (unadjusted)	0.8623 (0.8048, 0.9198)	0.8945 (0.8456, 0.9434)
NPV_U.S. (adjusted)	0.9982 (0.9902, 1.0000)	0.9986 (0.9918, 1.0000)
NPV_Taiwan (adjusted)	0.9969 (0.9767, 1.0000)	0.9975 (0.9809, 1.0000)
PPV (unadjusted)	0.4876 (0.4433, 0.5319)	0.5056 (0.4607, 0.5505)
PPV_U.S. (adjusted)	0.0108 (-0.0001, 0.0216)	0.0113 (0.0000, 0.0225)
PPV_Taiwan (adjusted)	0.0256 (-0.0002, 0.0514)	0.0283 (0.0006, 0.0560)

Although the specificity in the aided scenario is 36.11%, the following confusion table summarizes the event count from a false-positive (FP) unaided to a true-negative (TN) when aided by BU-CAD or a reverse for all 374 benign cases. A total of 790 FP events unaided were changed to TN events aided by BU-CAD for all 16 readers, and a total of 523 TN events

unaided were changed to FP events aided by BU-CAD for all 16 readers. The overall benefit was +267 events and shows that BU-CAD is able to assist the majority of readers in reducing false positives even for datasets where readers have a low specificity performance in the unaided scenario.

Confusion Table FP to TN Net Benefit for Benign Cases

All benign (374)	X01	X02	X03	X04	X05	X06	X07	X08	X09	X10	X11	X12	X13	X14	X15	X16	Total
FP (unaided) → TN (aided)	83	24	93	23	86	33	44	73	34	46	30	46	24	41	69	41	790
TN (unaided) → FP (aided)	33	28	18	70	16	67	16	52	38	33	22	47	4	20	17	42	523
Difference	50	-4	75	-47	70	-34	28	21	-4	13	8	-1	20	21	52	-1	267

In addition, BU-CAD software was found to significantly decrease readers' interpretation times (by ~40%) which was shown in analyses including and excluding outliers. Statistical analyses also indicated that BU-CAD improved readers' determination of BI-RADS descriptors (Shape, Orientation, Margin, Echo Pattern, and Posterior Features), where at least one or more subcategories for each descriptor demonstrated improved aided read performance, with limitations described in the User Manual.

Accuracy of BI-RADS Descriptors

Reading Scenario	Shape	Orientation	Margin	Echo Pattern	Posterior Features
Unaided	78.14%	82.15%	79.22%	76.49%	66.51%
Aided	78.92%	82.20%	77.34%	66.52%	67.53%
BU-CAD Standalone	71.91%	75.24%	73.57%	66.73%	58.03%

◆ **Summary of the Standalone Study**

A total of 1139 cases (628 reader study cases plus 511 extended cases) collected from multiple institutions were used in the standalone study.

Dataset Demographic

The source of cases is listed below.

- North America: 531 cases
- Europe: 36 cases
- Taiwan: 572 cases

The BI-RADS category distribution included in this study were listed below:

- BI-RADS 2: 31 cases

- BI-RADS 3: 223 cases
- BI-RADS 4A: 356 cases
- BI-RADS 4B: 218 cases
- BI-RADS 4C: 181 cases
- BI-RADS 5: 130 cases

The number of benign and malignant cases included in this study were listed below.

- Benign cases
    - Pathology proof benign: 465 cases
    - Two-year follow-up benign: 177 cases
- Malignant cases
    - Ductal carcinomas in situ (DCIS): 53 cases
    - invasive ductal carcinoma (IDC): 361 cases
    - Invasive lobular carcinoma (ILC): 51 cases
    - Other cancer types: 32 cases

The imaging hardware distribution included in this study were listed below:

- GE: 634 cases
- Siemens: 188 cases
- Canon/Toshiba: 90 cases
- Philips: 111 cases
- Supersonic: 24 cases
- Others: 92

Lesion Identification Module (CADe) Performance

A total of 59 benign cases (including 11 of the 20 missing cases) and 18 malignant cases (including 9 of the 20 missing cases) did not meet the objective performance criteria (automated ROI center must be within ground truth ROI with at least 50% overlap in ROI area). The accuracy of the lesion identification algorithm was 93.24% (1062/1139). For the LROC analysis, 18 malignant cases were penalized due to wrong location or undetected by BU-CAD.

Comparison between Standalone and Unaided Reading Performance

The standalone performance of BU-CAD was measured in AUC_LROC on the 628 reader study cases and the standalone study cases (combined the 628 reader study cases and 511

extended cases), a total of 1,139 cases (497 malignant and 642 benign). Table below shows the standalone AUC_LROCs in both datasets are higher than that of unaided reading performance.

Standalone and Unaided Reading Performances

Reading Scenario	AUC_LROC	95% CI
BU-CAD Standalone (628 reader study cases)	0.7987	(0.7626, 0.8348)
BU-CAD Standalone (1,139 standalone study cases)	0.8203	(0.7947, 0.8458)
Unaided Reading (628 reader study cases)	0.7786	(0.7463, 0.8109)

Summary of Subgroup Analysis

Subgroup of the different ultrasound systems (GE, Siemens, Canon/Toshiba, Philips, Supersonic, and others), benign types (pathology proof benign and two-year follow-up benign), cancer types (DCIS, IDC, ILC, and others), lesion size (less than 1 cm, between 1 cm and 2 cm, and larger than 2cm), Lesion Locations (center and not in center), view type (two view vs. single view), ages (≤ 50 years, > 50 years, ≤ 55 years, and >55 years), and sources of cases (North America, Europe, and Taiwan) were performed. The performance of distinguishing between benign and malignant in Siemens ultrasound system, DCIS and ILC cancer type, cases where the lesion is not in the center, two-orthogonal views, and source of North America and Europe achieved acceptable discrimination (AUC_LROC from 0.7 to 0.8). The remaining subgroups achieved excellent (AUC_LROC from 0.8 to 0.9) or outstanding (AUC_LROC > 0.9) discrimination.

Sensitivity, Specificity, PPV, and NPV

The standalone performances of sensitivity and specificity were assessed by using the 1,139 cases and summarized in Table 9. Results show the standalone sensitivity and specificity were 88.53% and 57.94%. In addition, the adjusted PPV of U.S. and Taiwan were 1.28% and 4.74% respectively, the adjusted NPV of U.S. and Taiwan were 99.83% and 99.67% respectively. Because both the prevalence rates of U.S. and Taiwan are relatively low, the adjusted PPVs were relatively low and the adjusted NPVs were relatively high. However, the standalone PPVs in U.S. and Taiwan were higher than those of unaided and aided scenarios.

Standalone Sensitivity, Specificity, PPV, NPV

Statistical Parameter	Standalone (Frequency)	95% CI
With Modification for Wrong-location Penalty)		
Sensitivity (%)	88.33 (439/497)	(0.8551, 0.9115)
Specificity (%)	57.94 (372/642)	(0.5413, 0.6176)
PPV (%) [unadjusted]	61.92 (439/709)	(0.5834, 0.6549)
PPV_US (%)	1.28	(0.0011, 0.0245)*
PPV_TW (%)	4.74	(0.0246, 0.0703)*
NPV (%) [unadjusted]	86.51 (372/430)	(0.8328, 0.8974)
NPV_US (%)	99.82	(0.9921, 1.0000)*
NPV_TW (%)	99.67	(0.9895, 1.0000)*

* The 95% Confidence Interval (CI) was estimated conditioning on the obtained prevalence rates of 0.72% and 1.94% in U.S. and Taiwan, respectively.

The following table showed the calculated sensitivity and specificity using each BI-RADS category as the threshold. Since the clinical decision threshold for cancer vs. non-cancer is BI-RADS 3 vs BIRADS 4a and the BI-RADS fifth edition concluded that patients with category ≥ 4a lesions are recommended to undergo biopsy, the analysis of sensitivity and specificity are still based on BI-RADS 4a as the cutoff point (i.e., a BI-RADS category of 4a or higher defines a positive call for cancer diagnosis).

Standalone Sensitivity and Specificity by Using Different Cut-Off Points

Statistical Parameter	3	4A*	4 B	4C	5
Sensitivity	0.9416 (0.9210, 0.9623)	0.8833 (0.8551, 0.9115)	0.8249 (0.7915, 0.8584)	0.6962 (0.6557, 0.7366)	0.4588 (0.4149, 0.5026)
Specificity	0.3302 (0.2938, 0.3666)	0.5794 (0.5413, 0.6176)	0.6994 (0.6639, 0.7348)	0.8271 (0.7979, 0.8564)	0.9252 (0.9049, 0.9456)

* The cut-off value used in the standalone study.

Robustness of the Lesion Analysis Module (CADx)

To evaluate the robustness of the CADx algorithm (Lesion Analysis Module) when different rectangular ROIs are drawn around the same lesion on a given single-view image or two-view images, two reproducibility experiments of the same lesion cropped by different rectangular ROIs were conducted. In the first reproducibility experiment, each corner point of an ROI was shifted by randomly changing the horizontal and vertical dimensions up to 20% respectively from the ground truth ROI defined by the expert panel. The experiment was repeated 20 times with all 1139 test cases (the original dataset was 628 cases and the

extended dataset was 511 cases). The results show that randomly enlarging the width and height of the ROIs did not affect the performance of the BU-CAD CADx algorithm (Lesion Analysis Module). The AUC remained stable between 0.840 and 0.846.

In the second reproducibility experiment, each corner point of ground truth ROI was altered by systematically shrinking the horizontal and vertical dimensions respectively from 1% to 30%. The experiment was conducted with all 1139 cases. The new ROIs and their corresponding images were then processed by the BU-CAD CADx algorithm (Lesion Analysis Module) to produce analysis outputs. The results show that as long as the shrinking percentage of the width and height of the ROIs is within 16%, the AUC remained above 0.8.

VIII. Non-Clinical Performance Data

In the design and development of BU-CAD, TaiHao applied the following voluntary FDA recognized standards:

Standard	Standard Title
ISO 14971:2007	Medical Devices - Application Of Risk Management To Medical Devices
IEC 62304:2015	Medical Device Software - Software Life Cycle Processes
DEN180005	Evaluation of automatic class III designation for OsteoDetect – Decision summary with special controls

The following guidance documents were used to support this submission:

FDA Guidance	Issued Date
Guidance for Industry and FDA Staff - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.	May 11, 2005
Guidance for Industry and Food and Drug Administration Staff - Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data – Premarket Notification [510(k)] Submissions.	July 3, 2012
Guidance for Industry and FDA Staff - Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data in - Premarket Notification (510(k)) Submissions.	January 22, 2020

FDA Guidance	Issued Date
Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)].	July 28, 2014
Draft Guidance for Industry and Food and Drug Administration Staff - Content of Premarket Submissions for Management of Cybersecurity in Medical Devices.	October 18, 2018

BU-CAD is a software-only device. The level of concern for BU-CAD is identified as Moderate Level of Concern. Developmental testing was conducted to verify requirements according to the BU-CAD specifications. The purpose of the verification test was to assure that the software application satisfied the software requirements. Validation testing consisted of determining standalone performance of the algorithms in BU-CAD using a multiple-vendor testing dataset of breast ultrasound images. The testing dataset was not used for training of BU-CAD algorithms.

IX. Conclusions

TaiHao has applied a risk management process in accordance with FDA recognized standards to identify, evaluate, and mitigate all known hazards related to BU-CAD. Non-clinical and clinical performance tests demonstrate that BU-CAD performs similarly to the legally marketed predicates, and thatall identified risks are effectively mitigated. Therefore, it can be concluded that BU-CAD is as safe and effective as the identified predicates, Transpara™ (K181704) and QuantX (K170195)