

# **SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)**

## **I. GENERAL INFORMATION**

Device Generic Name: Computer-aided Detection System

Device Trade Name: QVCAD System

Device Procode: MYN

Applicant's Name and Address: QView Medical, Inc.  
4546 El Camino Real, Suite 215,  
Los Altos, CA 94022

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150043

Date of FDA Notice of Approval: November 9, 2016

## **II. INDICATIONS FOR USE**

The QVCAD System is indicated for use as an aid to the reader during screening procedures in searching images of female breasts produced by the somo.v Automated Breast Ultrasound System (screening mammography BI-RADS® Assessment Category 1 or 2, and BI-RADS Composition/Density c or d) to detect mammography-occult lesions in regions not known to have suspicious findings. The indicators produced by the QVCAD System are not intended to be used for diagnostic characterization of suspicious findings.

## **III. CONTRAINDICATIONS**

There are no known contraindications.

## **IV. WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the QVCAD System labeling.

## **V. DEVICE DESCRIPTION**

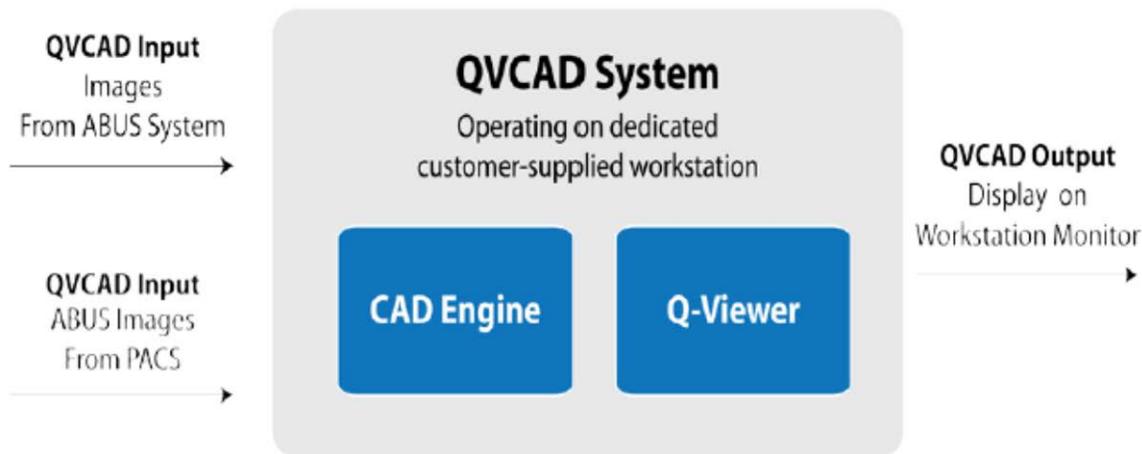
The QVCAD system is a proprietary CAD and image processing software device intended to aid in the reading of 3D Breast Ultrasound images generated by the somo.v ABUS (P110006) system ("ABUS"). QVCAD is designed to process and display a projection image using the ABUS image stack on a customer supplied computer and monitor for review, with certain areas highlighted and/or marked for attention. The user

is instructed to review the original ABUS images concurrently with the CAD generated output before making their final assessment of the case.

QVCAD is supplied as a software package consisting of the following two software components:

- i) The QVCAD CAD engine that comprises the CAD and image processing algorithms;
- ii) The QVCAD Q-Viewer that formats the ABUS images together with the output of the QView CAD engine for display on the monitor.

The QVCAD CAD engine and Q-Viewer are integrated and require each other to operate. The QVCAD system receives input images directly from the ABUS acquisition system or from a PACS system, via a standard DICOM interface. The QVCAD System is intended to process 3D Breast Ultrasound images originally acquired by the ABUS system. The native images from the ABUS system together with the output of the QVCAD CAD Engine are concurrently displayed on the Q-Viewer. Figure 1 shows a schematic of the QVCAD system.



**Figure 1 QVCAD System**

The QVCAD CAD engine employs several image pattern recognition processes and artificial neural networks to detect suspicious areas of breast tissue 5mm or more in diameter that have characteristics similar to breast lesions. It inspects every tissue location in the 3-D ABUS images it processes with dedicated algorithms that characterize the volumetric region surrounding each location by automatically extracting features that have been determined to represent suspicious signs. These features include typical ultrasound image features described in the radiological literature such as region boundary, margin, echo pattern, orientation, posterior enhancement, architectural distortions, etc. Using those features, the QVCAD CAD engine generates a score for each suspicious area to distinguish potential breast lesions from normal breast tissue.

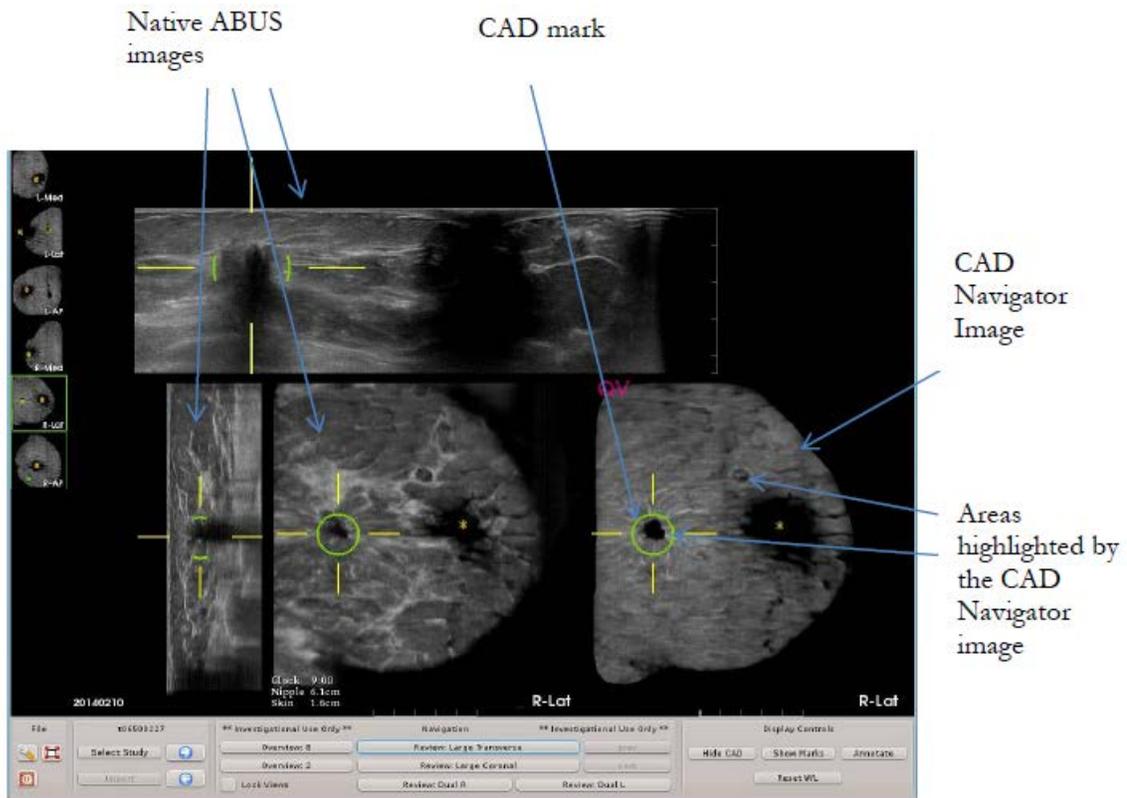
The training database consists of a large number of cancer, benign and normal cases. All cancers and benign lesions are biopsy proven. Normal cases were confirmed by follow-up exams. The cancers cases include all those encountered during clinical practice without selection. The benign and normal cases are randomly selected from available

cases. The training algorithm employs a cross validation technique on this database to achieve optimal performance of the QVCAD CAD engine.

The locations and types of the cancers and benign lesions in the images are annotated as the reference standard by ultrasound experts based on radiology and pathology reports. Using the reference standard and the ultrasound image features extracted from the ABUS images in this training database, the QVCAD CAD engine is trained to distinguish breast lesions from normal breast tissue.

The CAD-generated output from the QVCAD system is presented in two forms:

- i) A QVCAD CAD Navigator image of each ABUS volume or view, which is a modified minimum intensity projection combined with a line texture projection of the coronal image data in areas where CAD has detected possible abnormalities. This is intended to bring attention to certain areas of interest by enhancement of dark areas and/or radial spiculations and retraction patterns. The enhancements may be applied to both malignant and benign lesions.
- ii) CAD marks presented as colored circles around areas of interest and displayed over the CAD Navigator image and over the corresponding original ABUS images. CAD marks are intended to highlight potentially malignant lesions.

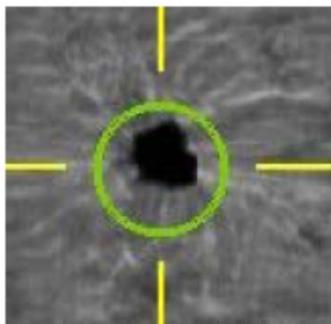


**Figure 2 Sample Q-Viewer Display with native ABUS images, the CAD Navigator Image and CAD mark.**

The user is instructed to use both the CAD Navigator image and the CAD marks in support of their review of the ABUS case. See Figure 2 and Figure 3 for an example of a CAD Navigator image and CAD marks.

The CAD Navigator image is a roadmap displayed concurrently with the original ABUS images (sagittal, transverse and coronal). The user may select any CAD mark or other area of interest on the CAD Navigator image and the corresponding original ABUS images will be displayed. This is intended to serve as a review and navigation tool, enabling the user to efficiently review the entire ABUS case, focusing on certain areas of interest. It is designed to improve user productivity while preserving the accuracy of diagnosis.

Installation, commissioning and training on the use of the QVCAD System is performed by qualified QView Medical, Inc. personnel only. A comprehensive user training program is conducted after installation to instruct the user/s on the operation of the QVCAD System. This training includes modules on system operation, guided case-study, user self-study and a final proficiency assessment.



**Figure 3 Close-up detail of CAD mark on the CAD Navigator Image**

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

QView Medical's QVCAD system is intended for use with the somo.v ABUS system to aid in the reading of 3D Breast Ultrasound images generated by the ABUS system. For breast cancer detection during screening procedures, mammography and ABUS are accepted imaging practices used by physicians, where ABUS is intended as an adjunct to mammography for breast cancer screening in women with dense breast parenchyma. Mammography and ABUS cases can be read by the physician in a conventional, unaided manner. Multi-modality approaches are also accepted as a way for the physician to improve his/her accuracy of breast cancer detection, such as CAD (computer-aided detection) for mammography.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## **VII. MARKETING HISTORY**

The QVCAD System has not been marketed in the United States or any foreign country.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

There are no known direct safety or health risks caused by or related to use of the QVCAD system. The QVCAD system is used as an aid in the interpretation of existing ABUS images. It does not modify the existing ABUS image acquisition process nor alter the native ABUS images. Additionally, the use of the software does not directly involve the patient. Indirect inherent risks are that

- a. QVCAD system may not mark or highlight all regions that are indicative of cancer.
- b. QVCAD system may mark or highlight regions that do not contain cancer.

These possibilities are explained in the Warnings section of the device labeling. Proper use of the information generated by QVCAD system is explained in the labeling section of the QVCAD User Manual.

If a radiologist determines that a false positive CAD mark indicates an area that is suspicious enough for follow-up, then the patient may be subjected to unnecessary anxiety and/or biopsy.

## **IX. SUMMARY OF NONCLINICAL STUDIES**

QView Medical performed verification and validation testing on the QView Medical QVCAD System 3.0. Verification testing consisted of software unit testing, software integration testing, and software system testing. The purpose of the verification test was to assure that the software application satisfied the software requirements. Verification testing was successfully completed. It was found that several minor anomalies remain in the software application. These anomalies have no impact on the safety and effectiveness of the device and no impact on the operator usage.

Device validation testing consisted of measuring CAD Algorithm standalone performance (including sensitivity, specificity and false positives rate (per volume)) and validating that the proper integration of the CAD Algorithm into the QVCAD software release load image (i.e. software release package). The results of CAD Algorithm standalone performance testing, using QView's internal clinical image evaluation database of 398 cases (including 154 cancers and 244 non-cancers) and, a total of 1908 image volumes were:

- Overall CAD marker case sensitivity was 85%;
- Case specificity was 36%, and
- False positive rate was 0.2 per volume.

The performance of the CAD Algorithm on the in-house QView's internal clinical image evaluation database suggests it has the potential to perform satisfactorily on an independent clinical validation dataset.

After the CAD Algorithm performance test was complete, it was integrated into the software release load image and installed on a verification test computer system. Several cases that were included in the CAD Algorithm standalone performance test were processed by the integrated CAD Algorithm. The results of the test were identical to the CAD Algorithm standalone performance test, confirming that the CAD Algorithm was properly integrated into the software release load image.

## **X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)**

QView Medical, Inc (“QView”) completed a pivotal clinical study (“Study”) to demonstrate the safety and effectiveness of its QVCAD System (“QVCAD”) for the proposed indication for use. The clinical protocol for the Study was reviewed and approved by the Institutional Review Board as IRB13-1404. In the Study, radiologists performed interpretation of automated breast ultrasound (“ABUS”) images with and without the aid of QVCAD, with the endpoints being (1) area under the receiver operating characteristic (ROC) curve (AUC) to characterize cancer detection performance, and (2) average per case interpretation time to characterize radiologist productivity.

### **A. Study Design**

The study was a retrospective, multi-reader multi-case (MRMC) ROC study. The study used a fully crossed design in which all readers review all the cases under two reading conditions:

- a) Arm 1: ABUS image alone, without QVCAD assistance;
- b) Arm 2: ABUS image with concurrent QVCAD assistance.

The Study was designed to test a pair of co-primary hypotheses:

- a) The reader with ABUS plus QVCAD assistance is non-inferior to the reader with the ABUS image alone. This will be evaluated using the difference in the areas under the Receiver Operating Characteristic (ROC) curves (AUCs), evaluated for non-inferiority (non-inferiority margin =  $-0.05$  for  $AUC_{ABUS+QVCAD} - AUC_{ABUS\ alone}$ );
- b) The reader interpretation time for QVCAD and ABUS combined is reduced demonstrating superiority to ABUS alone.

Both co-primary hypotheses must be supported to declare that the primary objectives of the pivotal study were met.

The initial reader selection criteria specified in the protocol is as follows:

- Fellowship-Trained in Breast Imaging and/or have 10 years' experience in breast imaging in which the radiologist's practice was at least 70% breast imaging.
- Currently meets the minimum mammography interpretation requirements per MQSA
- Review rate of at least 1,000 mammograms annually
- Review rate of at least 500 breast ultrasounds annually

One hundred and thirty radiologists were surveyed by QView Medical for their interest and availability in participating in the study. Thirty radiologists responded with both interest to participate and available time. Based on the responses, specific study sessions were scheduled and 19 radiologists were able to commit for the entire duration of the study. All 19 radiologists were accepted with the anticipation of the possible inability of some to complete the study while still achieving the target participation of 16 readers.

All of the 19 readers were MQSA certified radiologists. Of these, 1 radiologist withdrew before enrolling due to personal medical reasons. The remaining 18 radiologists were enrolled and all completed the study<sup>1</sup>. The 18 radiologists were from practices in 9 US states (California, Connecticut, Florida, Illinois, Kansas, New York, North Carolina, Ohio, and Pennsylvania) and the District of Columbia. Their practice and experience characteristics are summarized in Table 1. These 18 radiologists represent a broad spectrum of experience in breast imaging and practice types, and they are expected to be a representative sample of the anticipated user population.

All the readers successfully completed an eight-hour hands-on training session in preparation for their participation in the reader study. The objectives of the training sessions were to instruct the readers on:

- a) proper operation of the QVCAD system,
- b) proper interpretation of ABUS images with the aid of the QVCAD system, and
- c) specific reader-study instructions.

The training sessions were conducted by a qualified breast-imaging radiologist with extensive experience in the review of ABUS studies and significant experience with the QVCAD system.

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<sup>1</sup> Of the 18 readers, 3 readers did not meet the initial reader selection criteria but were included to broaden the reader profile. The first reader (not breast imaging fellowship trained) had more than 10 years' experience as a radiologist but breast imaging represented less than 70% of the practice. The second reader was breast imaging fellowship trained, had more than 10 years' experience as a breast imaging specialist but had mammography/ultrasound review volumes in 2014 less than the imaging volume criteria due to medical leave and part time employment. The third reader (not breast imaging fellowship trained) had less than 10 years' experience but met both the mammogram and ultrasound reading volume criteria. All three readers were from community hospital settings. They were all included in this study to broaden the reader profile to include less experienced readers as well as increased representation of community radiology practices

**Table 1 Practice and experience characteristics of radiologist readers.**

Practice or Experience Characteristics	N (%)
<b>Practice type</b>	
Academic (research)	3 (17%)
Academic (clinical)	8 (44%)
Private	3 (17%)
Community	4 (22%)
Total	18 (100%)
<b>Years of breast imaging</b>	
< 3 years	1 (6%)
3–10 years	5 (28%)
> 10 years	12 (67%)
Total	18 (100%)
<b>Weight of breast imaging in practice</b>	
≤ 70%	2 (11%)
> 70%	16 (89%)
Total	18 (100%)
<b>Numbers of screen mammograms or breast-tomosynthesis read in 2014</b>	
< 1,000	1 (6%)
1,000–2,500	5 (28%)
2,500–5,000	6 (33%)
> 5,000	6 (33%)
Total	18 (100%)
<b>Numbers of hand-held breast ultrasound read in 2014</b>	
< 500	1 (6%)
500–1,000	4 (22%)
1,000–2,000	9 (50%)
> 2,000	4 (22%)
Total	18 (100%)
<b>Total number of automated breast ultrasound read (all years)</b>	
None	2 (11%)
1–100	4 (22%)
101–250	5 (28%)
251–500	—
501–1,000	5 (28%)
> 1,000	2 (11%)
Total	18 (100%)

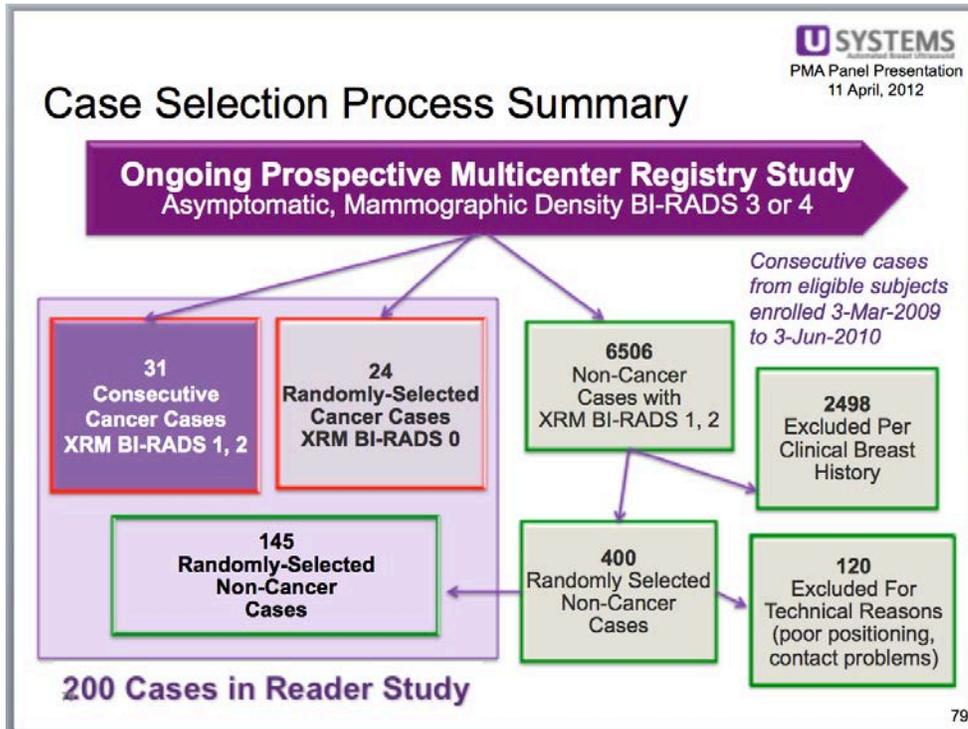
## **B. Study Cases/ Accountability of PMA Cohort and Population**

The pivotal study consisted of 185 cases (52 contained breast cancer and 133 did not contain breast cancer). These 185 cases were a subset of 200 cases that were the entire set of cases from a previous pivotal study on the somo•v ABUS system sponsored by U-Systems, Inc. FDA approved the somo•v ABUS system in September 2012 (P110006) . The remaining 15 (3 out of the 24 BI-RADS 0 cancer cases and 12 non-cancer cases) of the 200 cases contained only mammograms and no ABUS images, and thus were not used in this pivotal study. The entire 200 cases were kept in quarantine, and QView Medical did not have access to these cases.

The source of the 200 cases was a consecutive case series of breast cancer screening mammogram and ABUS exams collected prospectively from 13 US clinical sites from March, 2009 to June 2010 according to U-Systems PMA filing (P110006). All cases were prospectively given a BI-RADS breast composition (or density) rating of 3 or 4 by the Registry Clinical Site Investigator who interpreted the screening mammogram.

Slide 1 and Slide 2 below (copied from Page 79 and 80 of U-Systems PMA panel presentation on April 11, 2012) show the case selection process, and Table 2 below summarizes the composition of the 185 pivotal study cases by prospective screening mammogram interpretation (P110006). Since the 185 pivotal study cases were a subset of 200 cases that were the entire set of cases from a previous pivotal study on the somo•v ABUS system, the clinical inclusion and exclusion criteria are consistent with those for the ABUS pivotal study that included 200 breast screening cases. See detailed inclusion and exclusion criteria on page 10 -11 of the Summary of Safety and Effectiveness Data for the somo•v ABUS system.

Slide 1 U-Systems Case Collection



(Note: the data collection part of the study was completed in June, 2010)

Slide 2 U-Systems Reader Study Cases (15 cases were mammogram only cases)

**U SYSTEMS**

### Reader Study: 200 cases

Modalities in a Complete Case	Non-Cancer Cases BI-RADS 1 or 2 for XRM	Cancer Cases BI-RADS 1 or 2 for XRM	Cancer Cases BI-RADS 0 for XRM
XRM+ABUS	133 <sup>P</sup>	31 <sup>P</sup>	21 <sup>S</sup>
XRM Alone	12 <sup>S</sup>	0	3 <sup>S</sup>

<sup>P</sup> Cases used in Primary Analysis (N=164)  
(BI-RADS 1 or 2 on XRM as deemed by the site investigator)

<sup>S</sup> Supplemental Cases (N=36)

- 24 XRM BI-RADS 0 cancer cases to make case mix closer to that in clinical practice
- 15 XRM Alone cases to maintain Reader's vigilance and reduce bias caused by anticipation that an ABUS exam would follow after interpretation of XRM Alone

80

**Table 2 . Composition of the 185 pivotal study cases  
(200 U-Systems cases less 15 mammogram-only cases).**

	Cancer Cases		Non-Cancer Cases		
N	31	21	6	104	23
BI-RADS Assessment (Mammogram alone)	1 or 2	0	1 or 2	1 or 2	1 or 2
BI-RADS Density (Mammogram alone)	3 or 4	3 or 4	3 or 4	3 or 4	3 or 4
Confirmation	Biopsy	Biopsy	Follow-up within 365 days	Follow-up beyond 365 days	Presumed

Cancer Cases (n = 52)

All 52 cancers presented as masses. The first set is a set of 31 cancer cases proven by biopsy no later than 365 days after the screening mammogram, and prospectively given a BI-RADS final assessment category of 1 or 2. The second set is a set of 21 cancer (invasive carcinoma) cases proven by biopsy, and prospectively given a BI-RADS final assessment category of 0 based on screening mammogram alone.

Although the ABUS system is approved for both diagnosis and screening and patients with mammographic BI-RADS 0, 1 and 2 as expected inputs to the ABUS system in the actual clinical environment, the QView Study included only the 31 BI-RADS 1 and 2 cancer cases in the primary analysis. The reason for this is that the study data contained no BI-RADS 0 non-cancer cases (for the same reason, in the U-Systems study (P110006), BI-RADS 0 cancer cases were only used as control cases).

Non-cancer Cases (n = 133)

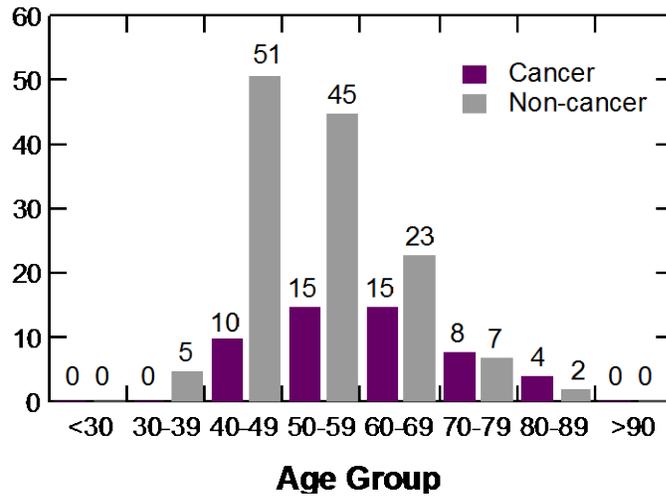
The first set is a set of 6 cases confirmed by a follow-up exam demonstrating no breast cancer within 365 days after the screening mammogram, and prospectively given a BI-RADS final assessment category of 1 or 2 based on screening mammogram alone by the Registry Clinical Site Investigator who interpreted the screening mammogram. These cases were a random sample of the eligible cases.

The second set is a set of 104 cases confirmed by a follow-up exam demonstrating no breast cancer more than 365 days after the screening mammogram, and prospectively given a BI-RADS final assessment category of 1 or 2 based on screening mammogram alone by the Registry Clinical Site Investigator who interpreted the screening mammogram. These cases were a random sample of the eligible cases.

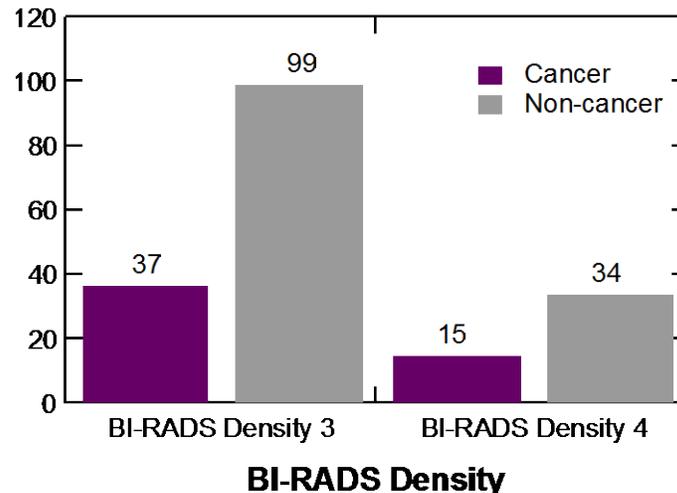
The third set is a set of 23 cases without follow-up exam confirmation (presumed to be non-cancer), and prospectively given a BI-RADS final assessment category of 1 or

2 based on screening mammogram alone by the Registry Clinical Site Investigator who interpreted the screening mammogram. These cases were a random sample of the eligible cases.

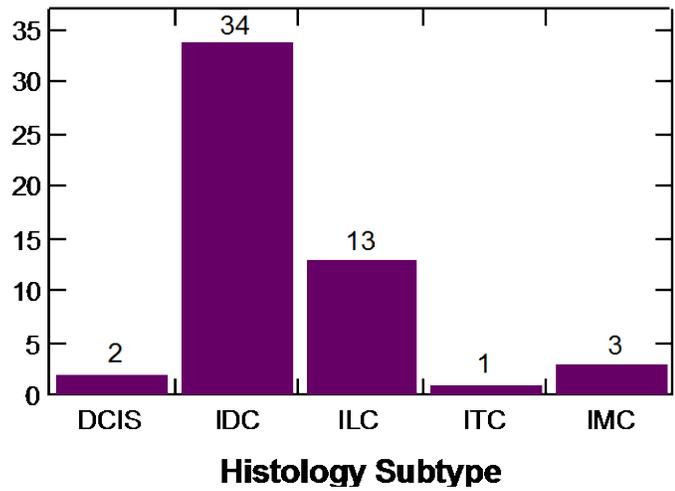
Figures 4–8 below show detailed information on patient age, breast density, tumor histology, nodal status, and TNM stage for the 52 cancer and 133 non-cancer cases.



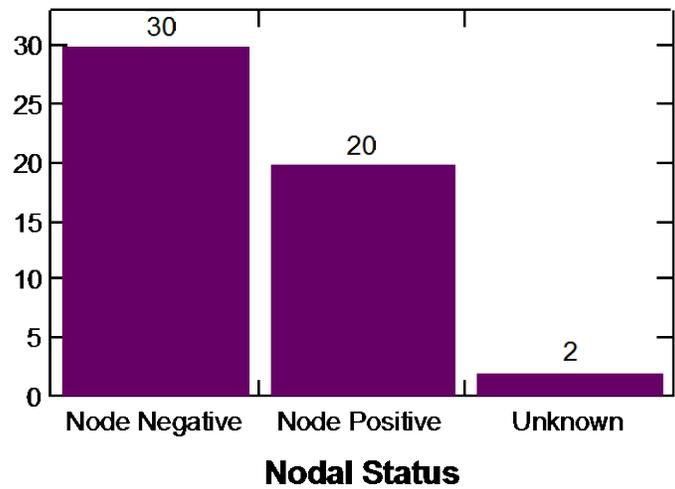
*Figure 4 Age distribution of 52 cancer and 133 non-cancer cases*



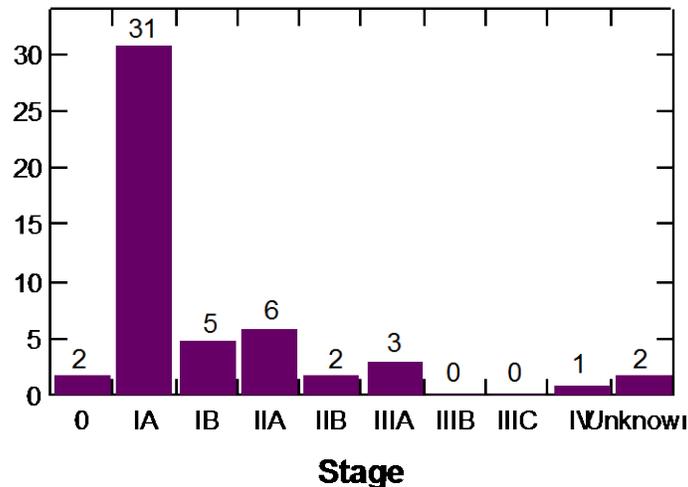
*Figure 5 BI-RADS density distribution of 52 cancer and 133 non-cancer cases*



*Figure 6 Tumor histological subtypes of 53 cancers in 52 cancer cases*



*Figure 7 Nodal status of 52 cancer cases*



*Figure 8 TNM stage of 52 cancer cases*

During study execution care was taken to mimic the clinical radiology reading environment, including ambient light, temperature, noise, and level of reader comfort.

Cases were presented to readers in random order. The entire set of 185 cases were divided into 4 subsets (A-D), with each subset containing 13 randomly selected cancer cases and 33 randomly selected non-cancer cases, except that subset D contained 34 non-cancer cases. Following that, eight "reading patterns" were defined following the principle of counterbalancing by "Latin squares" and each reader was randomly assigned one of the eight reading patterns.

Each reader interpreted each case twice, once interpreting ABUS images with the aid of QVCAD, and once interpreting ABUS images alone. These 2 separate sessions were separated by a washout period of at least 4 weeks. The combination of case randomization and washout period is intended to control for any bias effect of readers recalling individual case/s and any specific findings.

Each reader performed the following tasks when he or she interpreted ABUS images with the aid of QVCAD:

- a) Interpret ABUS images with the aid of QVCAD.
- b) Record "with QVCAD" assessment.

Each reader performed the following tasks when he or she interpreted ABUS images alone:

- a) Interpret ABUS images (QVCAD not available).
- b) Record "without QVCAD" assessment.

The "with QVCAD" and "without QVCAD" assessments consisted of the following information:

- Lesion(s) location

- Lesion-specific BI-RADS (1, 2, 3, 4a, 4b, 4c, 5)
- Lesion-specific LOS (level of suspicion, on a quasi-continuous scale of 1–100)
- Case-level BI-RADS (1, 2, 3, 4a, 4b, 4c, 5)
- Case-level LOS

For the calculation of the reader interpretation time, the elapsed time for review of each case by each reader was recorded automatically by the QVCAD Q-Viewer application.

### Pivotal Study Statistical Methods

The primary statistical analysis of breast cancer detection performance was the Dorfman-Berbaum-Metz (DBM) analysis of jackknife and ANOVA for estimation of multi-reader and multi-case ROC curves when radiologists interpret ABUS images with the aid of QVCAD compared with when they interpret ABUS images alone.

The statistical analysis of interpretation time was based on references for ROC analysis<sup>1-8</sup>, the ANOVA approach<sup>9</sup>, and sample size estimation<sup>10-13</sup>. This analysis, treating both readers and cases as random effects, estimated the average interpretation time of: (1) when radiologists interpret ABUS images with the aid of QVCAD, (2) when radiologists interpret ABUS images alone, and (3) the differences between the interpretation times of these two modalities.

The co-primary hypotheses on AUC and interpretation time were tested hierarchically in a fixed sequence to control type-I error rate at  $p=0.05$ : the superiority hypothesis of interpretation time was tested only after the non-inferiority hypothesis of AUC was tested successfully.

All estimates of  $p$  values and confidence intervals were two-sided.

## **C. Safety and Effectiveness Results**

### **1. Safety Results**

The QVCAD system is used as an aid in the interpretation of existing ABUS images. It does not modify the existing ABUS image acquisition process nor alter the native ABUS images. Additionally, the use of the software does not directly involve the patient. Therefore, there is no known direct safety or health risks caused by, or related to, the use of the device.

The risks from false-positive or false-negative results for diagnostics are:

- i) When reading ABUS images with the aid of QVCAD, there is a chance that users will be influenced in their final decision by the QVCAD results, potentially leading to additional diagnostic work-up on QVCAD findings to determine true positive or negative. The potential additional workup may include diagnostic imaging and breast biopsy.

- ii) When reading ABUS images with the aid of QVCAD, there is a chance that users may rely too heavily on the absence of QVCAD findings without sufficiently assessing the native ABUS images. This may result in missing cancers that may have otherwise been found.

**Adverse effects that occurred in the PMA clinical study:**

There were no adverse events reported by the Radiologists (Readers) or Principal Investigator as part of the Pivotal Clinical Retrospective Reader Study.

2. Effectiveness Results

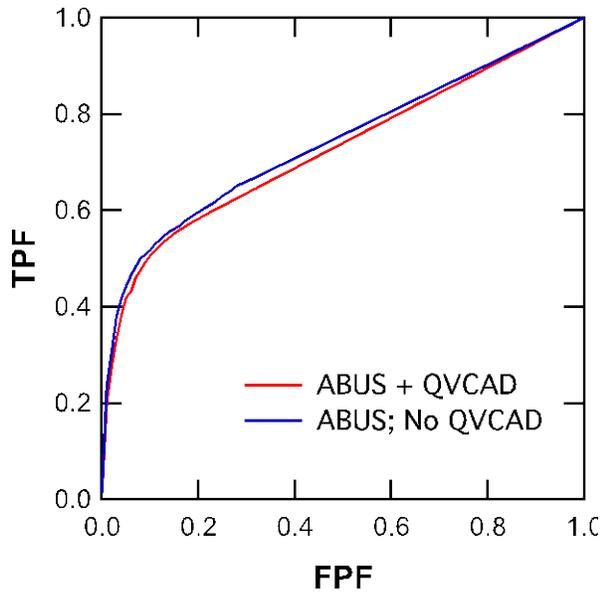
Pivotal Study Primary Analysis Results

The pivotal study has two co-primary objectives: to determine whether radiologists' performance in the detection of breast cancer is non-inferior when they interpret ABUS images with the aid of QVCAD compared with when they interpret ABUS images alone, and whether their interpretation time is shorter when they interpret ABUS images with the aid of QVCAD compared with when they interpret ABUS image alone.

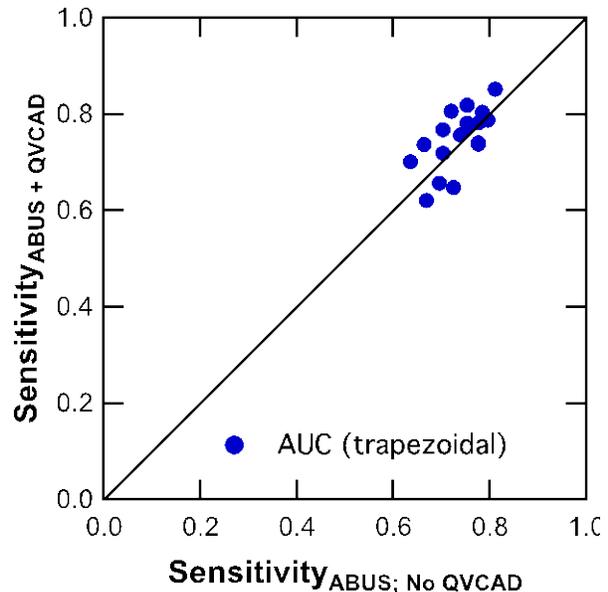
The hypothesis of non-inferiority in AUC ( $\Delta AUC = AUC_{ABUS + QVCAD} - AUC_{ABUS; No QVCAD}$ ) was tested successfully on the 31 mammographic BIRADS 1 or 2 cancer cases and the 133 non-cancer cases (Table 3). These results show that the lower limit of the 95% confidence interval on  $\Delta AUC$  was approximately -0.0442, which lies above the pre-specified non-inferiority margin of -0.05. Therefore, these results support the conclusion that the average AUC value when radiologists interpret ABUS images with the aid of QVCAD is statistically non-inferior to the average AUC value when they interpret ABUS images alone. Figure 9 shows the "average" trapezoidal ROC curves of the two interpretation modalities across all readers, and Figure 10 shows a comparison of each reader's trapezoidal AUC values between the two interpretation modalities.

**Table 3 First co-primary result of the pivotal study: Non-inferiority of trapezoidal AUC.**

	AUC	95% CI of AUC	p-value
$AUC_{ABUS + QVCAD}$	0.7353		
$AUC_{ABUS; No QVCAD}$	0.7493		
$AUC_{ABUS + QVCAD} - AUC_{ABUS; No QVCAD}$	-0.0141	[-0.0442, 0.0160]	0.0102



**Figure 9 Comparison of "average" trapezoidal ROC curves across the 18 readers between the two interpretation modalities**



**Figure 10 Comparison of trapezoidal AUC estimates of the 18 readers between the two interpretation modalities.**

The hypothesis of superiority in interpretation time ( $\Delta\text{Time} = \text{Time}_{\text{ABUS; No QVCAD}} - \text{Time}_{\text{ABUS + QVCAD}}$ ) was tested successfully (Table 4). These results show that the estimated  $\Delta\text{Time}$  per case is 71 seconds (33% of the average  $\text{Time}_{\text{ABUS; No QVCAD}}$ ), which is statistically significantly greater than zero ( $p=0.000016$ ). These results support the conclusion that the average interpretation time when radiologists interpret ABUS images with the aid of QVCAD is statistically superior to (shorter than) the average interpretation time when they interpret ABUS images alone.

**Table 4 Second co-primary result of the pivotal study: Superiority of interpretation time (per case).**

	Interpretation Time (s)	95% CI of Time (s)	p-value
$\text{Time}_{\text{ABUS; No QVCAD}}$	215		
$\text{Time}_{\text{ABUS + QVCAD}}$	144		
$\text{Time}_{\text{ABUS; No QVCAD}} - \text{Time}_{\text{ABUS + QVCAD}}$	71	[46, 97]	$1.6 \times 10^{-5}$

These results demonstrate that both co-primary objectives were met, and demonstrate that radiologists who interpret ABUS images with the aid of QVCAD can be expected to produce non-inferior performance of breast cancer detection from ABUS images in a significantly shorter interpretation time than when they interpret ABUS images alone.

### 3. Subgroup Analyses

Several supplemental (or secondary) analyses were conducted of the pivotal study data. The purpose of these additional analyses was to assess the strength of the primary conclusion of the pivotal study.

Table 5 and Figure 11 show the average sensitivity and specificity estimates. Table 5 also shows bootstrapping estimates of uncertainty in these estimates. These results show that sensitivity and specificity are similar between the two interpretation modalities. These results support the primary conclusion of the pivotal study.

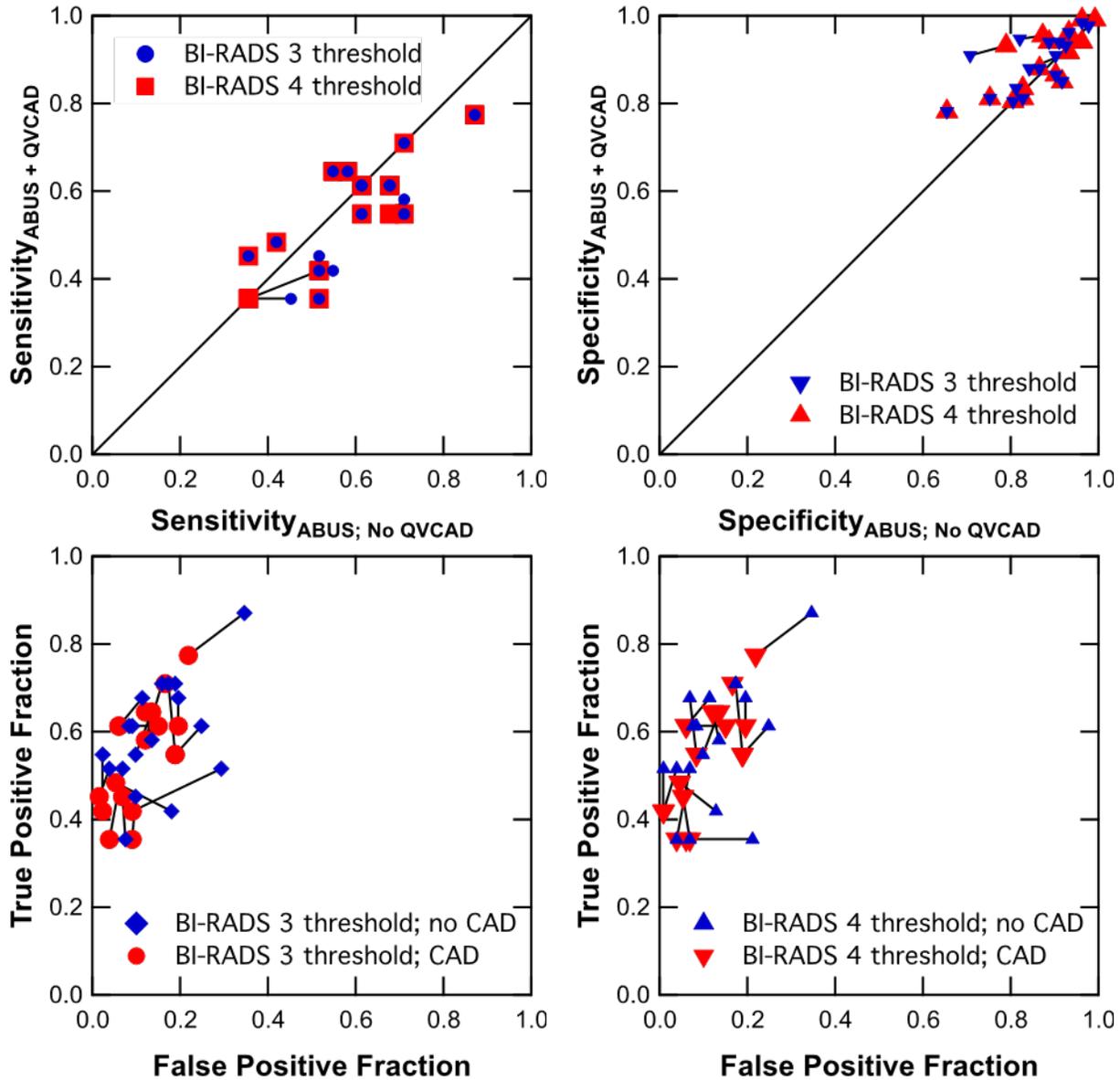
In Figure 11 top row, short line segments link each reader’s sensitivity or specificity at the BI-RADS 3 threshold and the BI-RADS 4 threshold. In Figure 11 bottom row, short line segments link each reader’s sensitivity and false-positive fraction in the two interpretation modalities.

**Table 5 Supplemental analysis of the pivotal study: Sensitivity and specificity.**

BI-RADS Threshold (cancer call)	Interpretation Modality	Sensitivity (%)		Specificity (%)	
		Average*	95% CI	Average*	95% CI
≥ 3	ABUS; No QVCAD	59.0±12.5	[46.2, 72.0]	85.5±8.8	[80.7, 89.9]
	ABUS + QVCAD	54.6±12.1	[40.9, 68.8]	89.0±6.4	[85.1, 92.6]
	Δ	-4.4±8.5	[-11.6, 2.5]	3.5±6.4	[-0.3, 7.7]
≥ 4	ABUS; No QVCAD	57.2±14.2	[43.7, 70.4]	87.4±8.6	[83.0, 91.9]
	ABUS + QVCAD	53.9±12.7	[40.0, 68.1]	89.8±6.8	[85.7, 93.5]
	Δ	-3.3±8.3	[-10.0, 3.2]	2.4±5.4	[-1.1, 5.8]

Δ = (ABUS + QVCAD) – (ABUS; No QVCAD)

\*Mean ± standard deviation



*Figure 11: Comparison of sensitivity and specificity estimates of 18 readers between the two interpretation modalities*

Conventional ROC and MRMC analyses do not require correct localization of cancerous lesions. Therefore, additional secondary location-specific analyses were conducted to test whether or not the radiologists in the study found cancers in the correct locations. These analyses required one modification from the conventional MRMC and sensitivity and specificity analyses: for cancer cases, if none of a radiologist's identified lesion(s) matched the location of known cancer(s), then the radiologist's case-level LOS was treated as the lowest possible (1 on the scale of 1–100). Thus, radiologists' scores were penalized in location-specific analyses for identifying non-cancer lesion(s) while missing cancer(s). The criterion for a radiologist-identified lesion to match a known cancer was that the distance between the geometrical centers of the marked lesion and the known

cancer must be less or equal to 15 mm. The MRMC analysis of trapezoidal AUC and analysis of sensitivity and specificity were repeated with location-specific analyses, and these results are shown in Tables 6 and 7, respectively. These results support the primary conclusion of the pivotal study.

**Table 6 . Supplemental analysis of co-primary results of the pivotal study: Non-inferiority of location-specific trapezoidal AUC.**

	AUC	95% CI of AUC	p-value
$AUC_{ABUS + QVCAD}$	0.6946		
$AUC_{ABUS; No QVCAD}$	0.6975		
$AUC_{ABUS + QVCAD} - AUC_{ABUS; No QVCAD}$	-0.0030	[-0.0412, 0.0353]	0.0082

**Table 7 Supplemental analysis of the pivotal study: Location-specific sensitivity and specificity.**

BI-RADS Threshold (cancer call)	Interpretation Modality	Sensitivity (%)		Specificity (%)	
		Average*	95% CI	Average*	95% CI
≥ 3	ABUS; No QVCAD	49.0±12.9	[35.1, 64.2]	85.5±8.8	[80.7, 89.9]
	ABUS + QVCAD	46.3±11.0	[31.4, 62.0]	89.0±6.4	[85.1, 92.6]
	Δ	-2.7±8.5	[-9.9, 5.9]	3.5±6.4	[-0.3, 7.7]
≥ 4	ABUS; No QVCAD	48.4±12.9	[34.6, 63.6]	87.4±8.6	[83.0, 91.9]
	ABUS + QVCAD	46.1±11.1	[31.2, 61.6]	89.8±6.8	[85.7, 93.5]
	Δ	-2.3±8.3	[-9.7, 5.7]	2.4±5.4	[-1.1, 5.8]

Δ = (ABUS + QVCAD) – (ABUS; No QVCAD)

\*Mean ± standard deviation

The results in Table 3 compare the readers’ performance with and without the aid of the QVCAD System on all 31 mammographic BI-RADS 1 and 2 cancer cases that were included in the study. However, of those 31 cancer cases, 15 were of patients who had prior breast interventions (PBI), for which ABUS is contra-indicated. The remaining 16 were of patients who had no prior breast interventions (no-PBI). All but one of the 133 normal cases used in the study had

**Table 8 Supplemental analysis of the pivotal study: MRMC analysis of 16 no-PBI cancer cases and 132 no-PBI non-cancer cases**

	AUC	95% CI of AUC	p-value
$AUC_{ABUS+QVCAD}$	0.7572		
$AUC_{ABUC; \text{No QVCAD}}$	0.7764		
$AUC_{ABUS+QVCAD} - AUC_{ABUC; \text{No QVCAD}}$	-0.0192	[-0.0637, 0.0252]	0.3931

no PBI. Thus an additional analysis was performed on the 16 no-PBI cancer cases and the 132 no-PBI non-cancer cases (Table 8). The results of this supplemental analysis are consistent with those of the primary analysis, but statistical significance was not established in this supplemental analysis presumably because, at least in part, of the smaller number of cancer cases in this supplemental analysis.

#### Standalone Performance

The standalone performance of QVCAD System was measured on the dataset with 31 cancer cases and 133 normal cases. As described in Section IV Device Description, the CAD output has two forms of indicators, CAD marks and CAD enhanced dark areas in the CAD Navigator Image.

Tables 9-14 below show the standalone performance for each of the indicator types of the QVCAD System. The sensitivity was measured as the number of cancer cases where at least one CAD indicator is present divided by the total number of cancer cases; the specificity was measured as the number of normal cases without any CAD indicators divided by the total number of normal cases; the false-positive (FP) rate (per volume) was measured twice: 1) for non-cancer cases (NCC) - as the total number of CAD indicators in non-cancer cases divided by the total number of volumes in non-cancer cases; 2) for non-cancer volumes (NCV) - as the total number of CAD indicators in non-cancer volumes in all cases divided by the total number of non-cancer volumes in all cases. The type of indicator used in each of the following tables is defined in the table captions. Figure 12 below shows the QVCAD System standalone FROC curve.

**Table 9 . QVCAD standalone test results (CAD marks)**

	By-Patient Sensitivity	By-Patient Specificity	FP rate (NCC)	FP rate (NCV)
CAD mark	71.0% [53.7%, 84.6%]	49.6% [41.2%, 58.1%]	0.12 [0.09, 0.14]	0.11 [0.09, 0.14]

**Table 10 . QVCAD standalone test results (enhanced dark areas)**

	By-Patient Sensitivity	By-Patient Specificity	FP rate (NCC)	FP rate (NCV)
CAD Navigator	96.8% [85.9%, 99.7%]	6.0% [2.8%, 11.0%]	0.66 [0.59, 0.74]	0.67 [0.60, 0.74]

**Table 11. QVCAD standalone sensitivity by lesion size (CAD marks).**

Lesion size	Sensitivity (%)	
	Estimate	95% CI
<10 mm	75.0	[37.9, 91.4]
≥ 10 mm & < 20 mm	70.6	[46.3, 88.2]
≥ 20 mm	87.5	[48.9, 99.0]

**Table 12 QVCAD standalone sensitivity by lesion size (enhanced dark areas).**

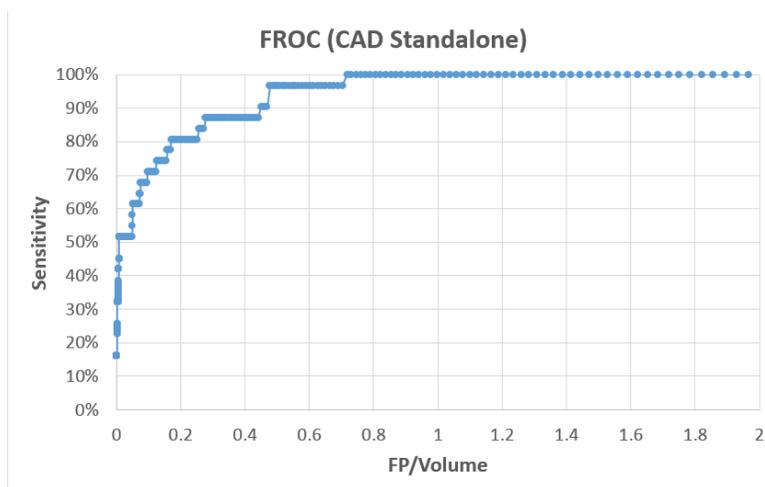
Lesion size	Sensitivity (%)	
	Estimate	95% CI
<10 mm	100.0	[76.2, 99.9]
≥ 10 mm & < 20 mm	94.1	[74.9, 99.4]
≥ 20 mm	100.0	[67.0, 99.9]

**Table 13 QVCAD standalone sensitivity, specificity, and false-positive rate by BI-RADS breast density (CAD marks).**

Bi-RADS Breast Density	Sensitivity (%)		Specificity (%)		FP rate (NCC)		FP Rate (NCV)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
	e				e			
C	70.0	[48.3, 86.4]	49.0	[39.3, 58.8]	0.12	[0.09, 0.15]	0.11	[0.09, 0.14]
D	72.7	[43.5, 91.7]	52.8	[36.4, 68.8]	0.10	[0.06, 0.14]	0.11	[0.07, 0.15]

**Table 14 QVCAD standalone sensitivity, specificity, and false-positive rate by BI-RADS breast density (enhanced dark areas).**

Bi-RADS Breast Density	Sensitivity (%)		Specificity (%)		FP rate (NCC)		FP Rate (NCV)	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
C	95.0	[78.9, 99.5]	4.9	[1.9, 10.5]	0.68	[0.60, 0.76]	0.68	[0.61, 0.76]
D	100.0	[80.0, 100.]	11.1	[3.7, 24.8]	0.60	[0.46, 0.75]	0.64	[0.51, 0.78]



**Figure 12: QVCAD System Standalone FROC curve**

4. Pediatric Extrapolation

This device is intended for use with the mammography patient population which is defined as women over the age of 40. There is no pediatric population in this disease space.

**D. Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included one investigator. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c),

and (f). The information provided does not raise any questions about the reliability of the data.

## **XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION**

Note that the 185 pivotal study cases, which were a subset of 200 cases that were the entire set of cases from a previous pivotal study on the somo.v ABUS system, consisted of 31 cancer cases with BI-RADS score 1 or 2 and 133 non-cancer cases. Based on the information provided in the ABUS SSED (page 22-27), of the 31 cancer cases, 15 had breast intervention > 1 year prior to the screening exam. In contrast, non-cancer cases having any prior breast intervention were excluded from the ABUS CRSS-4 study (however, one non-cancer case with prior breast intervention was accidentally enrolled). Because of the inconsistency between cancer and non-cancer cases in the inclusion/exclusion criteria of study CRSS-4, a supplemental analysis of CRSS-4 was performed, excluding the 15 cancer cases with prior breast intervention. By doing this, the cancer and non-cancer cases were comparable with respect to no prior breast interventions and were consistent with the IFU of ABUS:

“The somo.v Automated Breast Ultrasound System (ABUS) is indicated as an adjunct to mammography for breast cancer screening in asymptomatic women for whom screening mammography findings are normal or benign (BI-RADS Assessment Category I or 2), with dense breast parenchyma (BI-RADS Composition/Density 3 or 4), and have not had previous clinical breast intervention. The device is intended to increase breast cancer detection in the described patient population.”

Although the IFU of QVCAD does not explicitly exclude women with prior breast intervention, the pivotal study, which was based on the case selection criteria of the ABUS study, has limitation of having different selection criteria for cancer and non-cancer cases. To address this inconsistency and support QVCAD to be used in the screening population, QView excluded the 15 cancers and 1 non-cancer with prior breast intervention and conduct additional analyses. Therefore, estimates of ROC AUC, average per case interpretation time, sensitivity and specificity based on the study population that excludes patients with prior breast interventions are presented next.

### **Additional Analyses**

Among the 133 designated non-cancer cases, 23 lacked 1-year follow-up to confirm their non-cancer status at the time of screening (baseline). Analyses of robustness to the missing verification of true disease status were conducted.

QView conducted sensitivity analyses to assess the impact of missing follow-up data on the study results. There are 23 possible different analyses in which one of the 23 unconfirmed non-cancer cases is assumed to be cancer. The results of these 23 different analyses are that the non-inferiority criterion in the trapezoidal AUC of ABUS+QVCAD to ABUS alone (lower bound of 95% CI of AUC difference > -0.05) was met in all 23 analyses. The range of the lower bound of 95% CIs was -0.019 to -0.024.

## **XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION**

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Radiological Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

The radiologist can expect to achieve a statistically significant reduction in average interpretation time with no decrease in the performance of detecting breast cancer.

The interpretation time of ABUS images is important in several ways:

- i) It affects the patient throughput rate.
- ii) It affects facilities' decisions to use ABUS to benefit their patients with dense breasts.

The reduction of interpretation time of ABUS images may improve patient throughput and may facilitate wider adoption of ABUS to improve radiologist performance compared to mammography alone, particularly in dense breasts.

### **B. Safety Conclusions**

The QVCAD system is used as an aid in the interpretation of existing ABUS images. It does not modify the existing ABUS image acquisition process nor alter the native ABUS images. Additionally, the use of the software does not directly involve the patient. Therefore, there is no known direct safety or health risks caused by, or related to, the use of the device.

The risks from false-positive or false-negative results for diagnostics are:

- i) When reading ABUS images with the aid of QVCAD, there is a chance that users will be influenced in their final decision by the QVCAD results, potentially leading to additional diagnostic work-up on QVCAD findings to determine true positive or negative. The potential additional workup may include diagnostic imaging and breast biopsy.
- ii) When reading ABUS images with the aid of QVCAD, there is a chance that users may rely too heavily on the absence of QVCAD findings without sufficiently assessing the native ABUS images. This may result in missing cancers that may have otherwise been found.

### **C. Benefit-Risk Determination**

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefits outweigh the probable risks. The average difference in AUC was -0.0141, which is statistically non-inferior. The average difference in interpretation time was 71 seconds (one-third decrease), which is statistically superior.

Summary of the Benefits. The radiologist can expect to achieve a statistically significant reduction in average interpretation time with no decrease in the performance of detecting breast cancer.

The interpretation time of ABUS images is important in several ways:

- i) It affects the patient throughput rate.
- ii) It affects facilities' decisions to use ABUS to benefit their patients with dense breasts.

The reduction of interpretation time of ABUS images improves patient throughput and facilitates wider adoption of ABUS to improve radiologist performance compared to mammography alone, particularly in dense breasts.

Summary of the Risks. The QVCAD system is used as an aid in the interpretation of existing ABUS images. It does not modify the existing ABUS image acquisition process nor alter the native ABUS images. Additionally, the use of the software does not directly involve the patient. Therefore, there is no known direct safety or health risks caused by, or related to, the use of the device.

The risks from false-positive or false-negative results for diagnostics are:

- i) When reading ABUS images with the aid of QVCAD, there is a chance that users will be influenced in their final decision by the QVCAD results, potentially leading to additional diagnostic work-up on QVCAD findings to determine true positive or negative. The potential additional workup may include diagnostic imaging and breast biopsy.
- ii) When reading ABUS images with the aid of QVCAD, there is a chance that users may rely too heavily on the absence of QVCAD findings without sufficiently assessing the native ABUS images. This may result in missing cancers that may have otherwise been found.

Summary of other Factors. The risk of the radiologist using the CAD concurrently rather than a second reader is mitigated by good awareness of how CAD software should be employed and clear instructions for use in labelling.

The possibility of increasing the false positive or false negative rate is mitigated by having the radiologist make the final interpretation. Based on the study results of non-inferior diagnostic performance and enhanced workflow, the use of the QVCAD System does not lead to any additional risk of misdiagnosis compared to other breast cancer diagnostic aids.

### Patient Perspective

This submission did not include specific information on patient perspectives for this device.

Conclusion. The QVCAD system does not modify the existing ABUS image acquisition process nor alter the native ABUS images. The patient has no risk of direct harm resulting from the addition of the CAD software to the screening ABUS workup, any benefit that results from the use of the CAD software is a benefit to the patient. The risk that the device presents is increased false positives or negatives; however, this risk is mitigated by the fact that a radiologist is always making the final decision. Also the MRMC study provided sufficient evidence that the QVCAD system achieves a statistically significant reduction in average interpretation time with no decrease in the performance of detecting breast cancer. The available information above, the data support that for the indication for use of the device the probable benefits outweigh the probable risks.

### **D. Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The device is likely to produce some benefits to the patient at the cost of minimal additional risk. The probable benefits outweigh the probable risks. The average difference in AUC was -0.0141, which is statistically non-inferior. The average difference in interpretation time was 71 seconds (one-third decrease), which is statistically superior.

The QVCAD system does not modify the existing ABUS image acquisition process nor alter the native ABUS images. The patient has no risk of direct harm. The risk that the device presents to the patient is increased false positives or negatives; however, this risk is mitigated by the fact that a radiologist is always making the final decision. The MRMC study provided sufficient evidence that the QVCAD system achieves a statistically significant reduction in average interpretation time with no decrease in the performance of detecting breast cancer.

In summary, the device is safe and effective likely to produce some benefits to the patient at the cost of minimal additional risk. The data support that for the indication for use of the device the probable benefits outweigh the probable risks.

### **XIV. CDRH DECISION**

CDRH issued an approval order on November 9, 2016.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## **XV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

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