QVIEW'S ARTIFICIAL INTELLIGENCE TECHNOLOGY THE "QVCAD"

AND

ITS POTENTIAL IMPACT

ON

BREAST CANCER SCREENING

AND

A CLEAR PATH TO SAVING MANY MORE LIVES

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SUMMARY

Current breast cancer screening modalities, with over 100 million exams per year globally, are primarily X-ray based and are increasingly found to be insufficient in breast cancer detection, especially in women with dense breast tissue. This paper describes how QView's artificial intelligence (AI) deep-learning neutral network algorithm, the QVCAD, coupled with automated breast ultrasound systems, ABUSs, could serve as a powerful supplemental to current screening modalities.

Breast ultrasound has long been shown by multiple studies to be a promising and more appropriate supplemental screening modality with a detection rate of 3.5 cancers per 1,000 mammo-negative patients[1]. Most East Asian countries, due partly to the growing cancer rate in younger women, a higher percentage of women with dense breast tissue, concern with radiation, and lack of mammography legacy, have almost completely entrusted breast cancer screening to ultrasound – opening up a potential market for ultrasound-based breast cancer screening many times the current size.

An analysis of the probable causes of the 40,000/yr U.S. breast cancer deaths based on two important studies (by Sickles[2] and Webb[3]), shows that: (a) from Sickles study, 25,000/yr deaths are from symptomatic patients with prior mammograms (due mainly to breast density), and (b) from Webb study, 20,000/yr deaths are from young women with an initial cancer diagnosis below the age of 50. (Please note that some of the young women in (b) could be a part of the symptomatic patients with priors in (a), such that (a)+(b) does not exceed 40,000/yr). Screening both of these two groups will require breast ultrasound to play a central role.

The growing global awareness of the significant issues with breast density and the higher rate of cancers in younger women will substantially increase breast ultrasound's use for screening exams, not just in Asia, but also in U.S. and Europe. Several Automated Breast Ultrasound Systems (ABUSs) have been introduced recently to provide consistency, reduce operator dependence and variability, and improve workflow for automated breast cancer screening using ultrasound.

However, the studies[4] on actionable prior mammograms reveal that CAD is needed to reduce these actionable priors plus "obvious oversights". ABUS systems produce approximately 2,000 2D sectional images per exam vs. fewer than 100 2D images per exam for 3D DBT mammography, and 4 2D images per exam for 2D mammography, thereby creating a significant reading challenge and physician burden.

The solution to this challenge is QVCAD, the first and only FDA PMA and CE-Mark approved deep-learning software system using AI algorithms for breast cancer detection in ABUS images. Three recently published studies (a U.S. FDA study[5a], a study in Europe[5b] and a study in China[5c]), show that by using QVCAD, ABUS images can be read in less time, with greater confidence and without any compromise in performance. It is anticipated that in future studies, QVCAD will also reduce actionable priors plus "obvious oversights". This important tool will accelerate the adoption of ABUS as the

standard of care for breast cancer screening, especially in women with dense breast tissue.

As the performance of ABUS and QView AI technology improves with time, QVCAD, combined with ABUS, is anticipated to be used as the first reader (without a human reader), removing perhaps 80% to 90% of the benign cases in a mass screening program to substantially reduce the screening costs. This will further accelerate the growth of the ABUS market. This projection is based on the massive amount of volumetric information available from ABUS images and the increasing ability for QVCAD to utilize this information. A typical ABUS, much like CT, generates 2,000 truly sectional 2D images such that a typical 1 cm lesion is sliced into 20 truly sectional images to depict its fine features. This capability of QVCAD/ABUS is unique due to the massive amount of volumetric data available for AI Deep-Learning analysis and is unmatched by X-ray based modalities. Currently, based on U.S. FDA studies on QVCAD, approx. 55% of the normal cases show no QVCAD marks. If these QVCAD negative cases were ignored, it would miss a cancer only once in every 2,200 exams – already comparable to a human reader.

QVCAD has been developed over six years by a group of AI experts with over 100 years of combined experience in breast cancer screening. The current deep-learning algorithm is very robust and has been trained on over 20,000 ABUS cases, 3,000 of which are biopsy-proven ABUS cancer cases. For comparison, a typical practicing breast radiologist will see fewer than 500 cancers in his/her entire professional career, illustrating the depth and expertise of the QVCAD system. Over 30 sites around the world, including those of many key opinion leaders, have used QVCAD on over 100,000 patients under IRB approval. Recall rates amongst the users of QVCAD/ABUS is comparable to screening with mammography.

SECTION I – FUNCTIONAL OVERVIEW OF QVCAD

The QVCAD algorithm is based on a combination of machine vision and deep learning neural network technologies. It analyzes the 3D volumetric ABUS images and identifies suspicious areas of interest that the user should review in detail. The CAD-generated output from the QVCAD system is presented in two forms:

i) A QVCAD CAD Navigator image is a CAD enhanced minimum intensity projection of an ABUS volume. 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 green circles around areas of interest and displayed within the CAD Navigator image and within the corresponding original ABUS images. CAD marks are intended to highlight potentially malignant lesions.

The user is instructed to use both the CAD Navigator image and the CAD marks in support of their review of the ABUS case. The CAD Navigator image is a static roadmap displayed concurrently with the original ABUS images (transverse, sagittal, 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 at the area of interest.

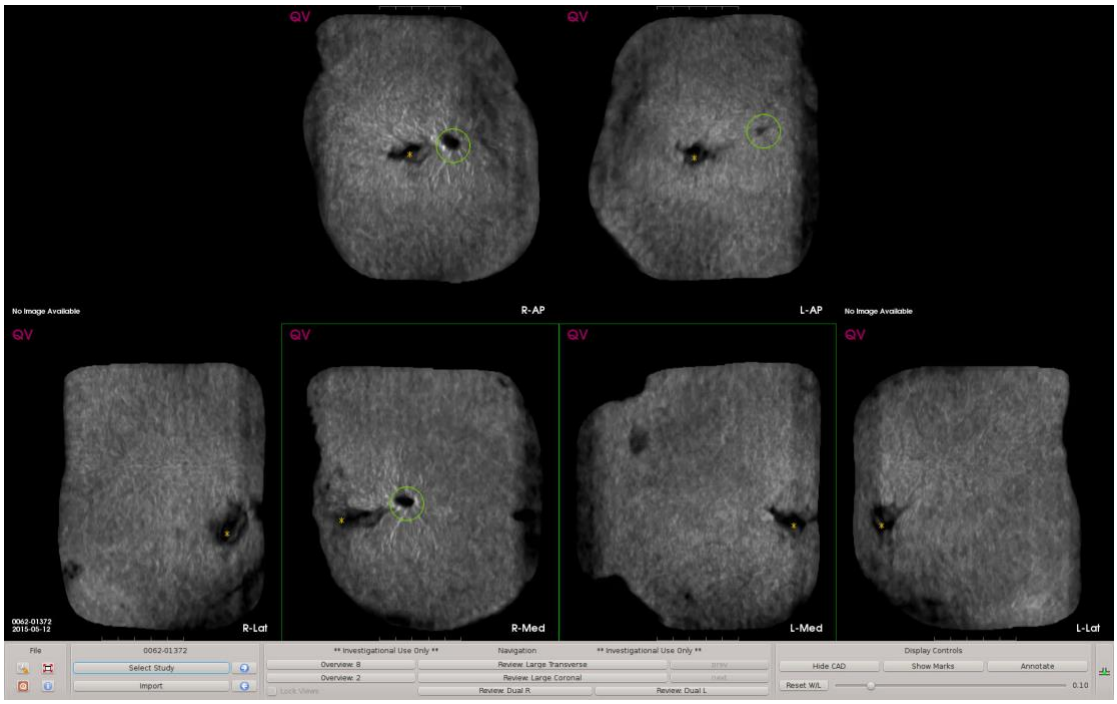


Figure 1: QVCAD startup screen gives an overview of the entire case with CAD Navigator images and CAD marks.

In the QVCAD overview screen (as shown in Figure 1), which contains a QVCAD Navigator image for each view in the study, 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.

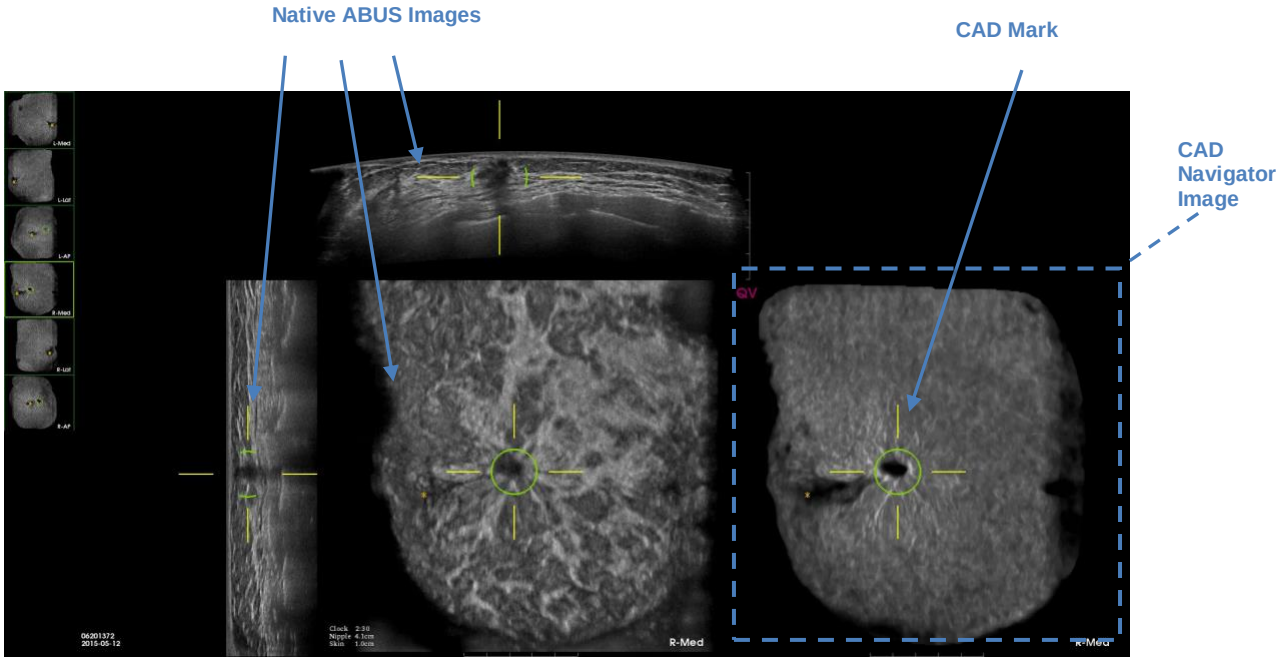


Figure 2: single view screen with CAD Navigator image and CAD mark presented within the original ABUS images

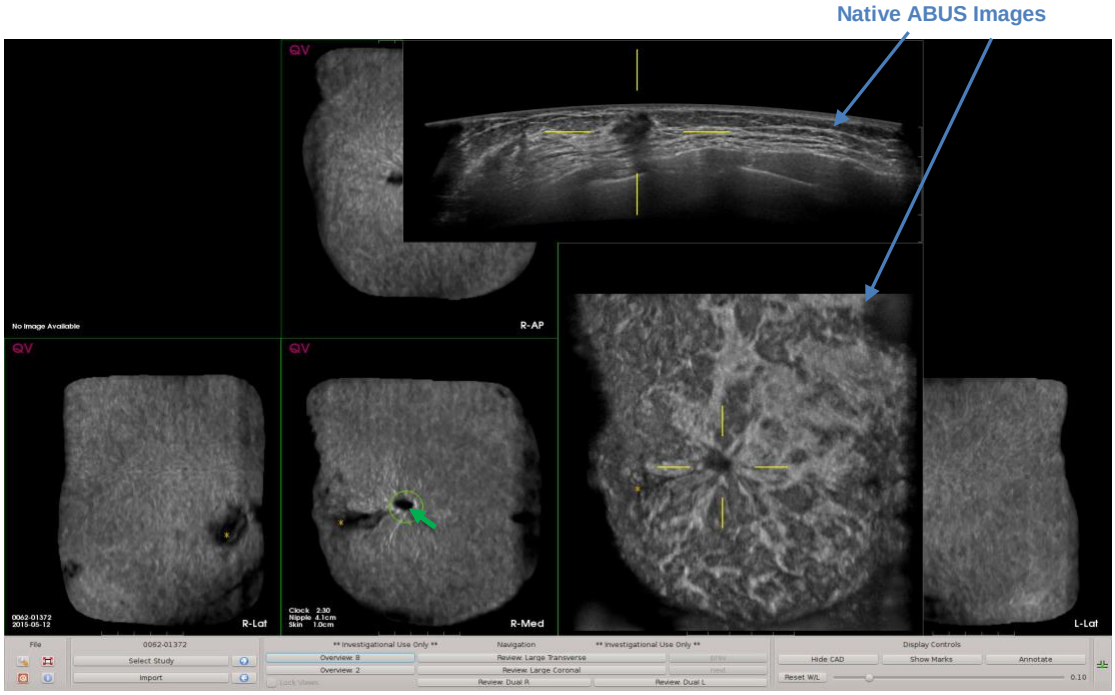
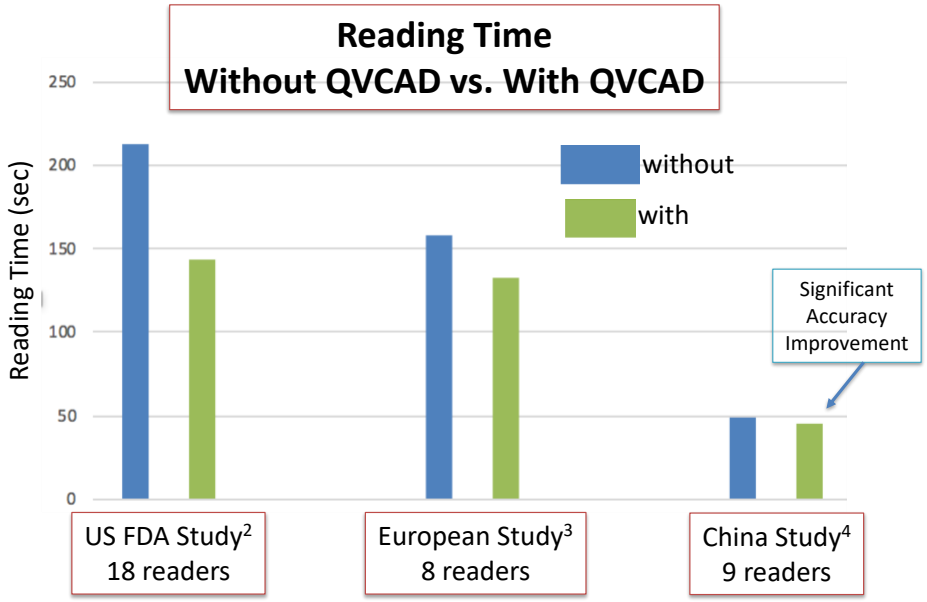


Figure 3: QVCAD "Hover" function. User hovers the cursor (green arrow shown in the R-Med view) in the CAD Navigator image. The native ABUS images pop-up to show the lesion in detail marked by crosshair cursors. This allows user to survey all views quickly from a single

Section II – CLINICAL BENEFITS OF QVCAD

(A) REDUCE ABUS READ TIME WITHOUT ANY COMPROMISE IN ACCURACY OR PERFORMANCE

Three recently published studies (a U.S. FDA study[5a], a study in Europe[5b], and a study in China[5c]) are summarized in the following chart, demonstrating that using QVCAD, ABUS images can be read in less time, with improved confidence and without compromise in performance or with improved performance.

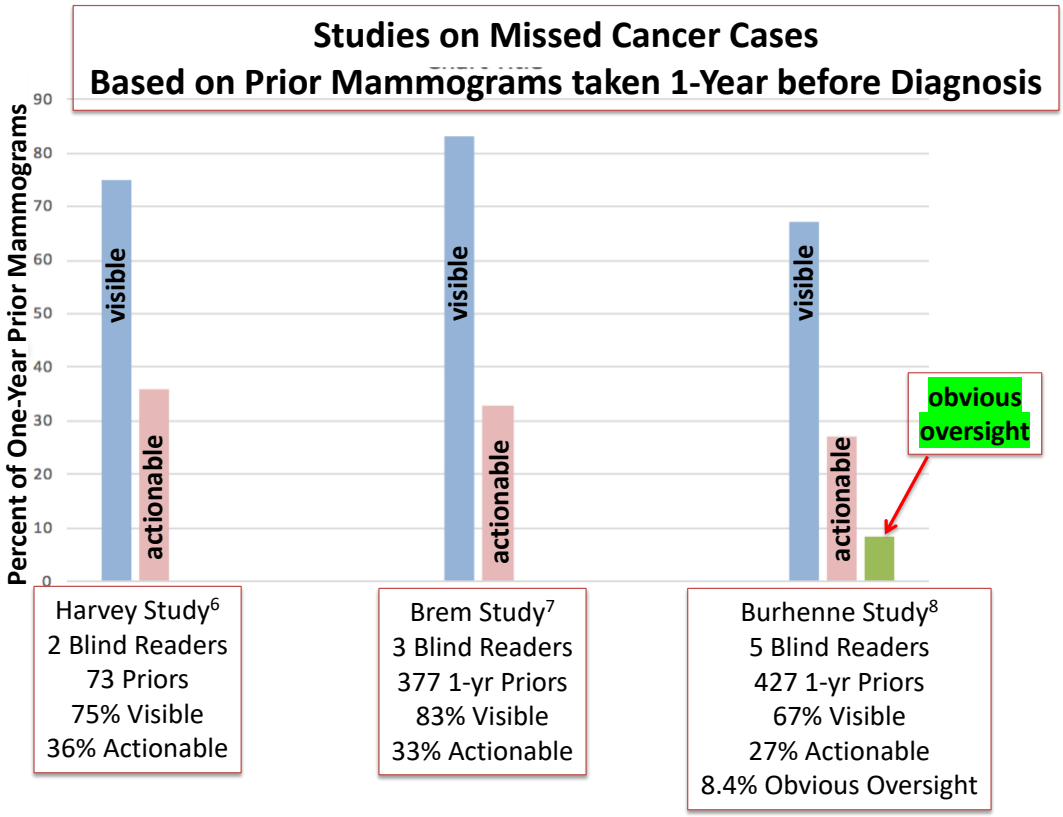


Note 1: the reading time differences between the FDA study and the others are partially due to the number of views per patient. All the cases in the FDA study were bilateral 6 views per patient, while the European study were unilateral 3 views. The China study were a mix of unilateral and bilateral, 2, 4 and 6 views per patient.

Note 2: the FDA and European studies showed that the reader ROCs (Receiver Operating Characteristics) were the same with and without the aid of QVCAD, while the China study showed statistically significant improvement with the aid of QVCAD.

(B) POTENTIAL TO REDUCE "ACTIONABLE CANCERS"

The core reason and justification for QVCAD and CAD in general is based on the three studies[4] on prior cancer mammograms taken one-year before diagnosis. These studies are summarized in the chart below. Knowing where to look, 67% to 83% of the cancers on these 1-year prior mammograms are visible retrospectively. On blind-review of these prior mammograms, 27% to 36% of the cancers on these prior mammograms are found by the blinded readers, without any prompting aid, and are considered to be "actionable cancers" missed by the attending radiologists. More seriously, in the Burhenne[4b] study, 5 out of 5 blinded readers all caught the same 36 "obvious oversight" cancers from 427 1-year prior mammograms, without any prompting aid. These "obvious oversights", which could raise medico-legal issues, occur at a rate of 8.4%. How can this happen? Could it be fatigue, inattention, or distraction? An analogy to help understanding this obvious oversight phenomenon is as follows: one misses seeing a bottle of ketchup in a refrigerator door. Consider that if only one ketchup bottle appears in every 300 refrigerator doors, then this will occur once after inspecting 4,000 refrigerator doors. In future studies, it is anticipated that QVCAD would reduce the occurrence of "actionable cancers" and "obvious oversights" in reading ABUS cases. Each ABUS case generates 500 times more images to read than 2D mammography, we should expect similar or worse "actionable" and "obvious oversight" numbers from 1-year prior cases, if QVCAD were not used.

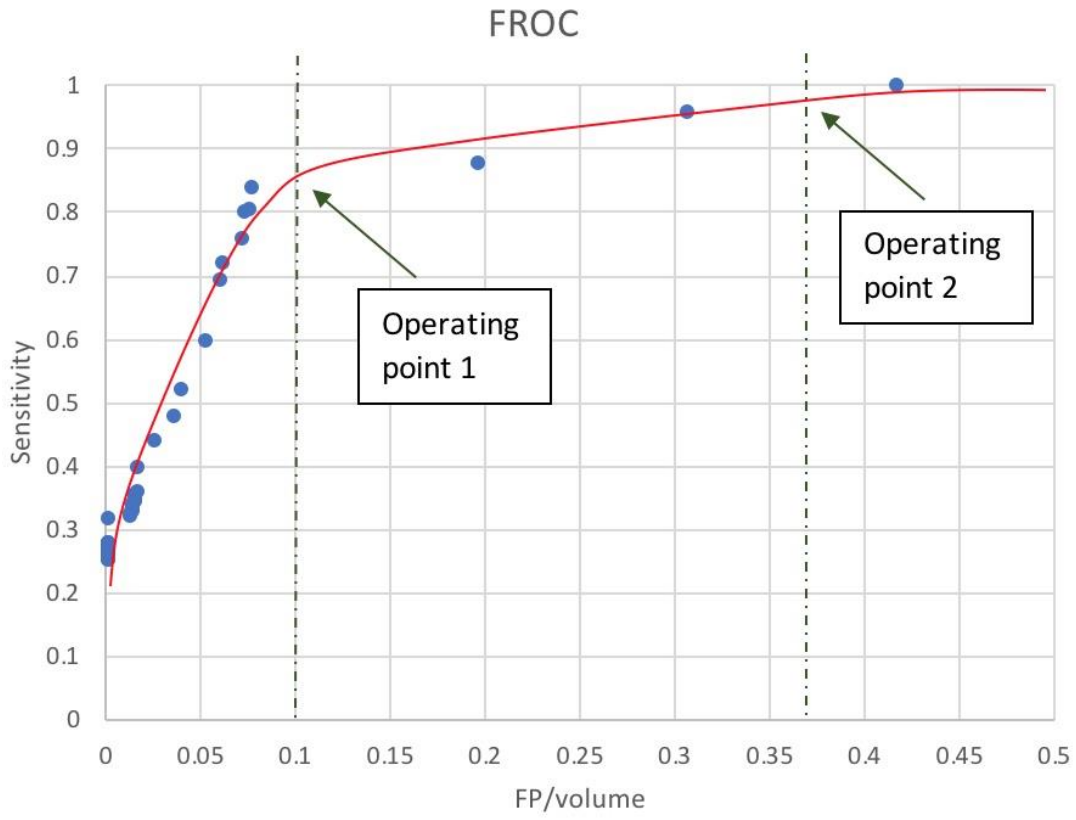


(C) QVCAD HAS HIGH SENSITIVITY AND HIGH SPECIFICITY

Based on the FDA PMA study, standalone QVCAD has high sensitivity as shown in the FROC (Free-Response Receiver Operating Characteristic) chart below. In this study, the "Green Circle CAD Marks", which are intended to mark lesions that are highly suspicious of malignancy, are generated by the condition set at "Operating point 1", where the sensitivity is 85% at a false positive rate of 0.1 FP per volume. The "Enhanced Dark Areas" in the Navigator image, which are intended to highlight both malignant and benign lesions, are generated by the condition set at "Operating point 2", where the sensitivity is 98% at a false positive rate of 0.37 per volume. In this FDA PMA study, 55% of the normal cases have no Green Circle CAD Marks.

Some users found this information useful in accelerating their ABUS usage learning curve as well as training their less experienced staff because, in comparison, the FDA PMA study shows the average standalone physician sensitivity without QVCAD to be 65%.

QVCAD is most commonly used in a concurrent reading mode. However, based on the high sensitivity performance, users not reading their ABUS images concurrently with QVCAD find it useful to check with QVCAD at the end of their read to help ensure no "obvious oversights" had been made.

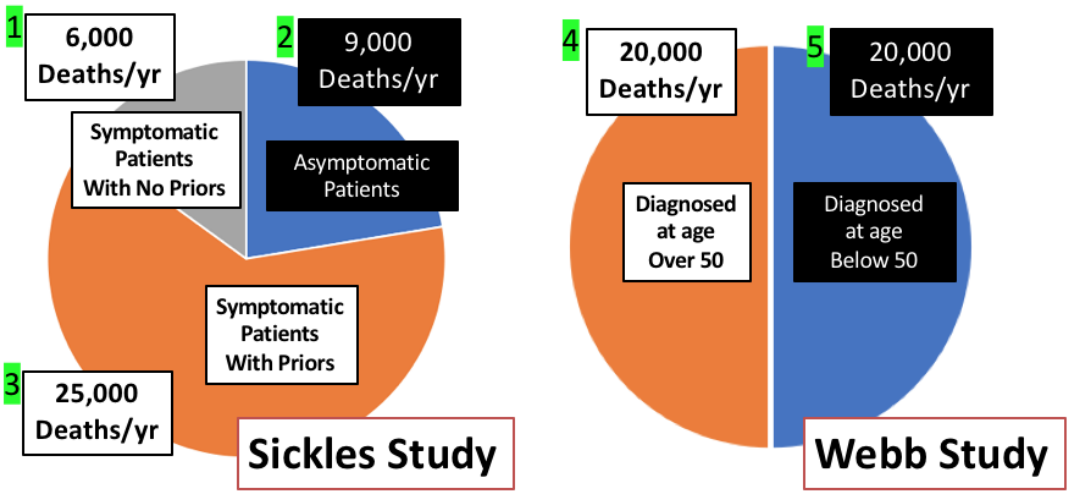


SECTION III – FUTURE OF QVCAD

(A) PROBABLE CAUSES OF BREAST CANCER DEATHS IN U.S.

Sickles[2] Study. A large study on diagnostic mammography was conducted by Sickles et al on a study population of 11.8 million, which is comparable in profile to that of the U.S. population. In this study, details of 8,411 diagnostic cancers are reported, of which 2,774 cancers are in late-stage (Stages II+III+IV). Of these 2,774 late-stage cancers, 622 (22%) are found in asymptomatic patients, 1,737 (63%) are found in symptomatic patients with prior mammograms, 415 (15%) are found in symptomatic patients without prior mammograms. The same ratios also hold for Stage III + Stage IV cancers. Since death is directly proportional to stage-stage cancers and the similarity in profiles for Sickles and U.S. populations, these ratios could be used, as a first approximation, to extrapolate into probable causes of breast cancer deaths in the U.S., namely 6,000 deaths/yr from symptomatic patients with no prior screenings, 25,000 deaths/yr from symptomatic patients with prior mammograms, and 9,000 deaths/yr from Asymptomatic patients. See summary chart below.

Webb[3] Study. A study by Webb et al (Kopans is a co-author) on the 609 confirmed breast cancer deaths, reports that half of these deaths are from young women with an initial diagnosis below the age of 50 (median age 49), most of these young women were never screened. See summary chart below and a proposed screening solution in the next section.



(B) PROPOSED SOLUTIONS

I totally agree with the recent papers by Tabar[6] and Kopans[7] urging the continuation of breast cancer screening, including to younger women in the face of new recommendations to raise the screening age by USPSTF and by the American Cancer Society, and also of reports questioning the effectiveness of mammography screening and the recommendations by the Swiss Medical Board to abolish mammography screening altogether. I would go even further to suggest: (1) increased screening of women in the age range of 25 to 50; and (2) broad and aggressive deployment of supplemental use of breast ultrasound. I believe (1)+(2) would increase U.S. screening population by another 20 to 30 million and would save most of the 40,000 lives per year while saving billions of dollars to the U.S. healthcare system each year.

More specifically aimed at the above discussed probable causes of breast cancer deaths, the proposed solutions are as follows.

[1] For the 6,000 deaths/yr from Symptomatic patients with no priors – From the Sickles study, most of these 6,000 deaths may be from young women below the recommended screening age. This problem could be solved by screening young women in age range of 25 to 50 with breast ultrasound in the form of QVCAD/ABUS which avoids ionizing radiation for these younger women. See more discussions below in section [5] below.

[2] For the 9,000 deaths/yr from Asymptomatic patients – From the Sickles study and Actionable Priors studies, the problem may be due to the delayed detection of the mammographically visible cancers. Digital Breast Tomosynthesis (DBT, or 3D Mammo) used with 2D and 3D mammography CAD should be able to solve this problem.

[3] For the 25,000 deaths/yr from Symptomatic patients that have prior mammograms – The problem may be from cancers not mammographically visible due to dense breast tissues. Many Breast Density Notification Law activists, including movement leader, Nancy Cappello, are examples of such symptomatic patients in late-stage with recent prior screening mammograms. As found by these activists after their own traumatic experience, breast density is the major factor for missing such cancers. Thus, we should be focusing on saving 25,000 lives/yr instead of quibbling over Breast Density Notification Law (only 36 states passed in 10 years) and other minor issues. DBT may be a fair stop-gap solution, and breast MRI may be better. However, breast ultrasound is the correct solution – it is superior to DBT (see APPENDIX-B) and is much less expensive and much more widely available than MRI. It is therefore far superior from a screening perspective. QVCAD/ABUS eliminates the challenges of time-consuming and operator dependent hand-held ultrasound which make it unaffordable and impractical for screening. QVCAD/ABUS is the first such PMA approved commercially available system which could be broadly deployed as a supplemental screening modality with the high likelihood of making a significant impact on reducing mortality.

[4] From the Webb study, for the 20,000 deaths/yr from young women with initial diagnose over age 50 – The sources of problems to this population should be the same as that for the population in Sickles study. The suggested solutions, shown above, should apply.

[5] From the Webb study, for the 20,000 deaths/yr from young women with initial diagnose below age 50 – Since most of these young women would have mammographically dense breasts, and because of the increased radiation risk to younger women (see APPENDIX-C) if mammography were used, we recommend screening these younger women in the age range of 25 to 50 with breast ultrasound in the form of QVCAD/ABUS. This may increase the screening population by 20 million. Due to the low screening yield in younger women, we clearly need to find a low-cost approach. This low-cost approach is in the use of QVCAD as the first reader (without a human reader) described below. A first order estimate of cost for using QVCAD/ABUS as a first reader, we should be able to approach $50,000 per QALY. (Please note that some of the young women in [5] could be a part of the symptomatic patients with priors in [3], such that [5]+[3] does not exceed 40,000/yr).

(C) POTENTIAL USE OF QVCAD AS THE FIRST READER

QView AI technology, QVCAD, used in combination with ABUS, already has good standalone performance as the first reader. QVCAD's neural network algorithm has been trained on over 20,000 ABUS cases, of which 3,000 are cancer cases. In comparison, typical practicing breast radiologists will see fewer than 500 cancers in their entire professional career. The performance of ABUS, already in its third generation, will continue to improve with time, and QVCAD's AI will also improve by training with more and better ABUS images. QVCAD is anticipated to be able to remove perhaps 80% to 90% of the benign cases in a screening program to substantially reduce screening costs. This would further accelerate the growth of the ABUS market. This projection is based on the massive amount of information available from ABUS images and the increasing ability for QVCAD to effectively utilize this information. A typical ABUS, much like CT but without the damaging radiation, generates 2,000 sectional 2D images such that a typical lesion would be covered by over 20 sectional images (slices) to depict its fine features. This capability of QVCAD/ABUS is unique due to the massive amount of volumetric information available for AI Deep-Learning analysis. No other X-ray based modality can match it. Currently, based on U.S. FDA studies on QVCAD, already 55% of the normal cases show no QVCAD marks. If these QVCAD negative cases were ignored, it would miss a cancer only once in every 2,200 exams – already comparable to a human reader.

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In the past 40+ years, Bob Wang advanced clinical practice and expanded the breast imaging market through the companies he founded, and the products he developed.

Companies Wang Founded	Products Developed	Derivative Products & Market Impact
Int'l Medical Tech, Inc. (Acquired by 3M, Licensed to Kodak)	**Low-Dose Rare-Earth Screens** 100-fold lower Mammo Dose	**Kodak Min-R Mammo Screens** *Initiated Mammo Screening, Became standard of care*
Diagnostic Information, Inc. (Acquired by Xonics, then by Picker)	**First Digital Tomosynthesis** U.S. Pat. 4,598,369, Co-Inventor: Russell Morgan	**Digital Breast Tomosynthesis** by Hologic, GE & Siemens *Became standard of care*
R2 Technology, Inc. (Acquired by Hologic)	**Computer-Aided Detection For Mammo, and for Lung CT**	**Many Mammo CAD, and Lung CT CAD** *Current practice in breast and lung cancer screening*
U-Systems, Inc. (Acquired by GE, Licensed to Siemens)	**Automated Breast Ultrasound System (ABUS)**	**Invenia by GE, and ABVS by Siemens** *Emerging screening standard for dense breast*
Qview Medical, Inc.	**First AI Deep-Learning Algorithm (QVCAD) for 3D Breast Ultrasound (ABUS)**	**Expected:** *Critical AI assistance for radiologists using ABUS;*

APPENDIX A - CAD IS FREQUENTLY MIS-UNDERSTOOD

Three separate studies on prior mammograms taken 1 year before the diagnosis of cancer show that not only 67% to 83% of the cancers are visible on 1-year prior mammograms, but 27% to 36% of the cancers on 1-year priors are considered "actionable" by blind readers. That is, these 27% to 36% of the cancers should have been detected by attending radiologists a year ago. In Burhenne study, 5 out 5 blind readers all caught the same 36 cancers from 427 1-year priors and these cancers are considered "obvious oversights". Twenty years ago, even the first-generation mammography CAD from R2 could catch 77% of these actionable cancers and 92% of the obvious oversights. It is beyond comprehension that prompting from CAD would not substantially reduce actionable cancers or obvious oversights from being missed. Future CAD studies should be conducted to compare prior mammograms from sites using CAD vs. sites not using CAD. Unfortunately, recent researchers have been looking for CAD's benefit in all the wrong places. Typical studies try to find the incremental increase in cancer yield from facilities using CAD compared to facilities not using CAD over a period of several years. However, CAD, like many other new screening modalities such as MRI, only detects cancers earlier – those cancers would have otherwise been detected a year or more later. When applied to the same screening population, an increase in the number of those CAD detected cancers would only occur in the first year, perhaps 4 to 5 or more cancers per 1,000 exams. In subsequent years, the number would be expected to fall back to 3 per 1,000 exams. No significant incremental increase in yield could be observed over several years. Consider an analogy like "mowing the lawn" as an illustration. If 10 pounds of grass is the average yield per week, you may get 12 pounds of grass the first week when the mower's blade is set lower. But in the following weeks, the yield will return to 10 pounds per week. That is the growth rate of the lawn grass. The only difference is that now the lawn grass is shorter. In the case of CAD, we should look for an incremental decrease in late-stage cancers from both the screening population and symptomatic patients.

The value of CAD is also misunderstood and underestimated in the use of "reader studies" to evaluate it. These studies tend to diminish the true benefit of CAD through the use of very low normal to cancer (N2C) ratios. The lower the N2C ratio, the lower the apparent benefit of CAD. In some studies, with a N2C ratio of 2 (vs. 300 in the real world), it is not surprising that CAD is found to be useless. The analogy is if you stock one ketchup bottle per 2 refrigerator doors, you would not commit obvious oversights. The real-world performance of CAD is demonstrated in the Burhenne study on 427 prior mammograms taken just one year before cancer detection: radiologists missed 27% of the "actionable" cancers and 8.4% of the "obvious oversight" cancers. It doesn't take much imagination to see that if the radiologists were prompted by CAD, these figures would be significantly reduced. This Burhenne study also shows that there is no increase in recall rate from reading with CAD.

APPENDIX B - ULTRASOUND (HHUS & ABUS) VS. DBT (3D Mammo)

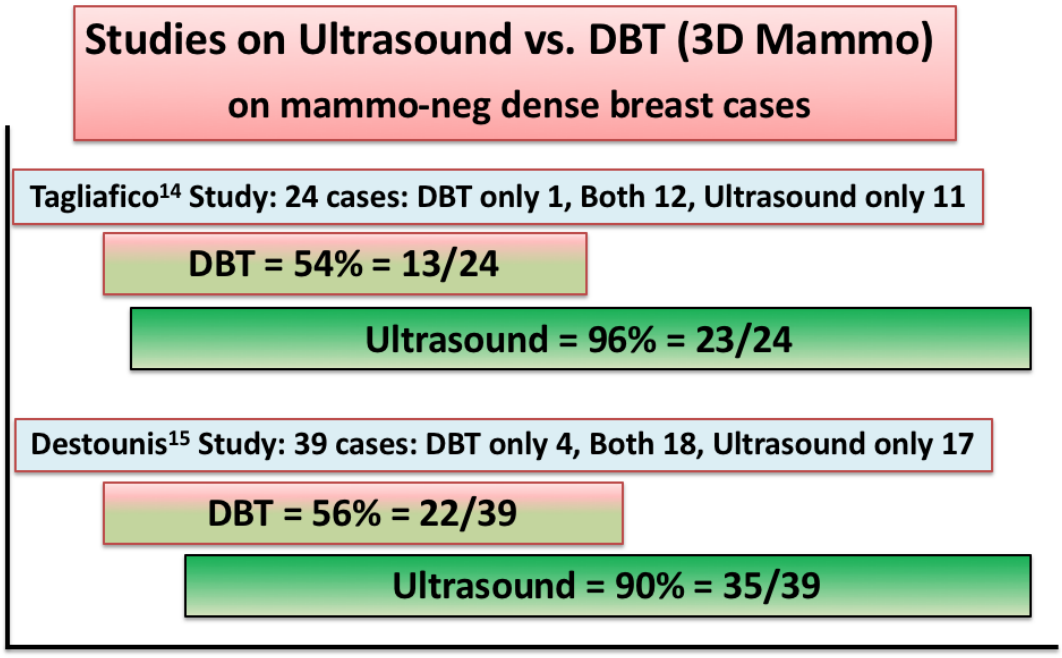
Breast ultrasound has long been shown by multiple studies to be a promising and more appropriate supplemental screening modality with a detection rate of 3.5 cancers per 1,000 mammo-negative patients[1].

Table 1 Summary of Published Studies on SWBUS **(Screening Whole Breast Ultrasound)**

Year Published	Author	# US Examinations	# US Only Detected Cancers	# Invasive Cancers	Mean Size, mm	SWBUS CDR
1995	Gordon	12,706	44	44	11	3.4 (per 1000)
2000	Buchberger	8103	32	32	9.1	3.9
2001	Kaplan	1862	6	5	9	3.2
2002	Kolb	13,547	37	36	9.9	2.7
2003	Crystal	1517	7	7	9.6	4.6
2008	Corsetti	9157	37	36	See note	4
2012	Berg	7473	32	30	10	4.2
2012	Hooley	935	3	2	6	3.2

Ref: Geisel et al, Semin Ultrasound CT MRI (2018) 39:25-34

Several studies[1,15] show that for detecting cancers in mammography-negative dense breasts, hand-held ultrasound (HHUS) is 90% to 96% effective, while DBT (digital breast tomosynthesis or 3D mammography) is 54% to 56% effective. These results are summarized in chart below.



Several studies[13,14] further show that automated breast ultrasound systems (ABUS) is equal in accuracy as hand-held ultrasound (HHUS). However, QVCAD/ABUS is superior to HHUS in the detection and visualization of lesions with spiculations. Spiculations are only visible in the reconstructed coronal images, or in the plane perpendicular to the compression, and are generally not visible in 2D HHUS images.

APPENDIX C – MAMMOGRAPHY RADIATION RISKS

Mammography radiation risks have been known for many years. Due to the high radiation level, mammography was initially employed for diagnostic purposes only. After the introduction of the low-dose rare-earth screen-film system in late 1970s, which reduced radiation level by 100-fold[10a], the concerns raised by Bailar[10b] disappeared. Even with 100-fold reduction in radiation exposure, current 2D and 3D mammography still operate at a level equivalent to the level less than 2 miles from Hiroshima A-bomb ground zero. Breast cancer screening with mammography in U.S. grew, in the past 40 years, from 0.5 million exams per year to 40 million exams per year or about 100 million exams per year worldwide. Several studies by Feig and Hendrick[11] and others[17, 18] analyzed mammography radiation risks and arrived at similar conclusions: screening with mammography saves 20 to 50 lives at the cost of one death caused by mammography radiation, depending on mammography mortality reduction rate, screening interval, and the screening commencement age of the patient. This benefit/risk ratio appears to be acceptable for women age 45 or above. However, with the emergence of screening modalities using no ionizing radiation, such as breast ultrasound, we need to review whether this benefit/risk ratio is still acceptable, especially for younger women (where radiation would cause more damage than older women).

Table 11.3. Breast cancer deaths averted per death caused by a single screening at age 45 years, with a dose of 2.5 mGy (0.25 rad) from a two-view per breast mammogram

	Mortality reduction		
	20%	40%	60%
Assuming no further screening	30	60	90
Assuming subsequent screening	37.5	100	225

Risk estimate based on BEIR V Report, National Research Council (1990)

Ref.: Feig and Hendrick (1997)