



Breast Tomosynthesis

The Use of Breast Tomosynthesis in a Clinical Setting

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Andrew Smith, Ph.D., Vice President - Imaging Science, Hologic

Introduction

Since the U.S. Food and Drug Administration's (FDA) approval of the first commercial systems in 2000, digital mammography has become an accepted standard of care in breast cancer screening and diagnosis and has paved the way for the newest groundbreaking technology in this arena - breast tomosynthesis.

Breast tomosynthesis is a screening and diagnostic modality that acquires images of a breast at multiple angles during a short scan. The individual images are then reconstructed into a series of thin, high-resolution slices typically 1 mm thick, which can be displayed individually or in a dynamic ciné mode.

A tomosynthesis data set virtually eliminates detection challenges associated with overlapping structures in the breast, which is the primary drawback of conventional 2D analog and digital mammography. In addition, breast tomosynthesis offers other potential benefits including increased lesion and margin visibility, help in localizing structures in the breast, a reduction in recall rates, and increased cancer detection.

Breast tomosynthesis goes by a number of names in the radiology and general press. Digital breast tomosynthesis (DBT), 3D mammography, 3D breast tomosynthesis, 3D tomosynthesis, tomosynthesis, and tomo are all used. In this paper, we will refer to the new technology as tomosynthesis or tomo.

Tomosynthesis has been available in Europe and other countries recognizing the CE mark since 2008. In February 2011, Hologic's Selenia® Dimensions® breast tomosynthesis system was the first commercial system approved by the FDA. With the Hologic tomosynthesis system, an examination takes only seconds longer than a conventional two dimensional digital mammogram. The system was approved for use in the same clinical indications as 2D mammography, including breast cancer screening and diagnosis.

This white paper provides detailed information about Hologic's tomosynthesis clinical studies submitted to the FDA and how these study results correlate with other research findings for this technology. The paper also looks at the performance of tomosynthesis in different breast composition and lesion types and looks at ongoing works-in-progress advances for this modality.

Initial Hologic Clinical Trial Purpose and Methodology

Hologic conducted a large multi-center clinical trial comparing the performance of 2D digital mammography plus tomo imaging (combo-mode) to that of 2D mammography alone in support of its FDA tomosynthesis submission. Images were acquired from 5 clinical centers in the U.S. under an IRB-approved protocol and informed patient consent. All subjects had bilateral 2-view mammograms (mediolateral oblique (MLO) and cranio-caudal (CC) in both 2D and tomo imaging modes).

Hologic conducted two reader studies using images from the initial clinical trial data set. The reader study results were analyzed using Receiver Operating Characteristics (ROC) methodology, with the area under the curve measuring the ability of individual radiologists (readers) to correctly characterize the presence or absence of disease in subjects in a study population. The reader studies' results are summarized below and are available in the FDA's Summary of Safety and Effectiveness, which was issued following approval of Hologic's Selenia Dimensions breast tomosynthesis system.¹ Full details of the clinical trial and results have been submitted for publication.

Clinical Trial Results

Results from Hologic's first reader study was presented by Elizabeth Rafferty at the Radiological Society of North America (RSNA) annual conference in 2007, and both reader studies were presented at the FDA panel meeting in September 2010.^{1,2} In both studies, the performance of 2D mammography plus tomo was shown to be significantly superior to the performance of 2D alone, as demonstrated by an improved area under the ROC curve. In addition, both studies showed a reduced non-cancer recall rate. These results were consistent with those of an independent third reader study from University of Pittsburgh researchers who found a 7% improvement in the area under the ROC curve for 2D plus tomo compared to 2D alone.³ The FDA advisory panel considered all three reader studies in their unanimous vote that Hologic's application demonstrated both the effectiveness and safety of tomosynthesis.⁴

At the RSNA 2011 conference, Per Skaane also presented results on the use of tomosynthesis in screening.⁵ Taken together, the following results have been seen in the performance of tomosynthesis:

- 2D mammography plus tomo is superior to 2D alone
- The sensitivity of 2D mammography plus tomo is higher than 2D alone
- The screening recall rate of 2D mammography plus tomo is lower than that of 2D alone
- Performance using both tomo CC and MLO views was greater than tomo MLO alone

These results are discussed in greater detail below.

Improved Sensitivity

Radiologists reading in combo-mode (2D plus tomosynthesis) compared to 2D alone demonstrated improved sensitivity (the proportion of mammograms with cancer which were correctly diagnosed).

Because of the demonstrated improvement in the ROC area using 2D plus tomo imaging, researchers predicted that the expected sensitivity gain from using tomosynthesis in combo-mode would be considerable. The actual gain will likely vary by site based on individual radiologist's thresholds on detection and recall rate. The exact improvement in cancer detection will not be known until the technology is more widely implemented in screening practices.

Figure 1 shows a hypothetical example of ROC curves based on 2D plus tomo imaging. The diagonal arrow shows how an individual's cancer detection rate can be improved and their recall rate reduced using a technology that has a higher ROC curve.

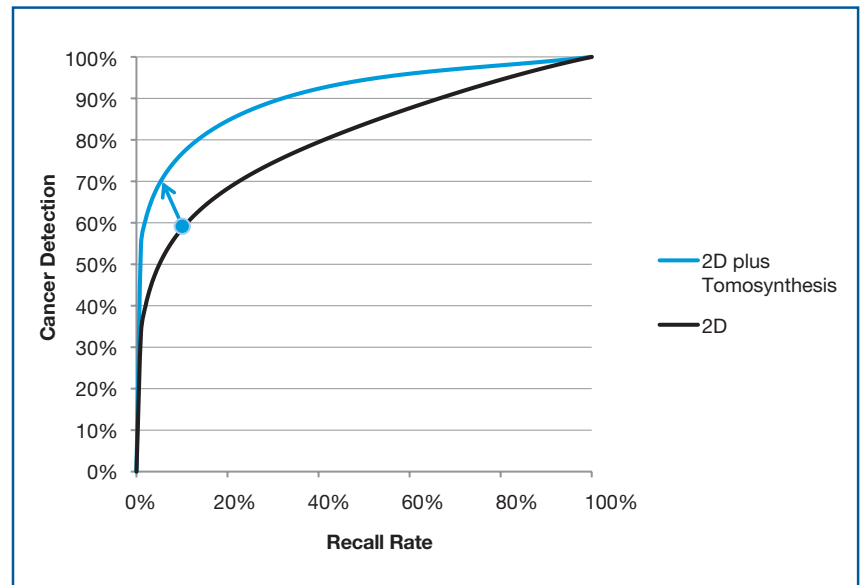
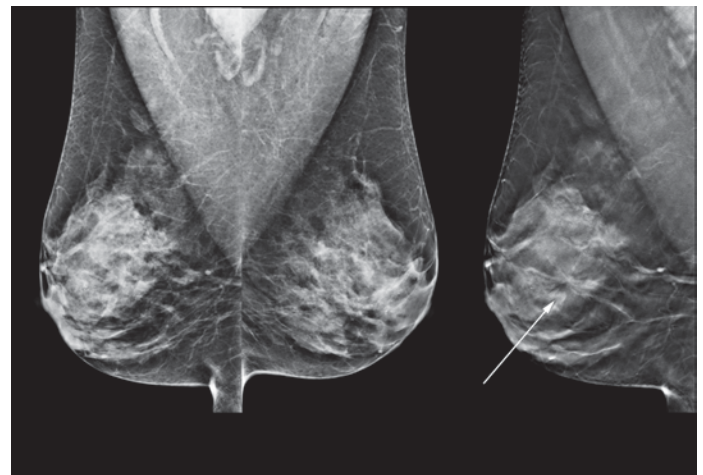


Figure 1. The use of 2D mammography plus tomosynthesis in breast cancer screening is expected to improve cancer detection and decrease recall rates.

The first results on the improved cancer detection seen when tomosynthesis is used in a screening environment were presented by Skaane at the RSNA 2011 conference.⁵ In an analysis of the first 3,500 patients entering a prospective trial of over 20,000 women, Skaane observed a relative increase of 47% in cancer detection using tomosynthesis compared to 2D mammography alone.



INCREASED CANCER DETECTION: The tomosynthesis reconstructed slice shown on the right reveals a definitive spiculated mass that is only faintly revealed in the 2D image shown on the left. (Diagnosis: Invasive Ductal Carcinoma)

Reduced Recall Rate

Radiologists reading in combo-mode compared to 2D alone demonstrated reduced recall rates.

A reduction in recall rates was reported for 2D plus tomosynthesis compared to 2D alone in all three reader studies. The reader study by Gur et.al. suggested that the use of tomosynthesis during baseline screening mammography may reduce the recall rate by 28%.⁶ Rafferty, in her 2007 RSNA presentation, estimated the recall reduction rate to be over 40%.² Subsequent studies have also found a significant reduction in recall rates with tomosynthesis.

Greater Performance Using Two-View Tomosynthesis

Two-view tomosynthesis (CC and MLO) was superior to one-view tomosynthesis (MLO) in combo-mode.

All three reader studies considered by the FDA used two-view mammography for both 2D and tomosynthesis imaging. One of the reader studies also investigated a 3rd arm: single-view tomosynthesis (MLO) imaging in combination with 2-view (CC and MLO) 2D imaging. In Hologic's reader study, the performance of 2D imaging plus tomo MLO showed that the tomo MLO-only arm performed better than 2D imaging alone, but not as well as 2D plus both tomo views.

These results are consistent with several other studies, illustrating that MLO-only tomosynthesis is likely to be inferior to two-view tomo. These study results are explored in greater detail in the discussion of one-view versus two-view tomosynthesis later in this paper.

Performance of Tomosynthesis in Different Breast Compositions and Lesion Types

The expanding library of clinical trial results on the use of tomosynthesis makes it possible to evaluate its performance in different breast compositions and lesion types such as calcifications, masses and distortions, invasive

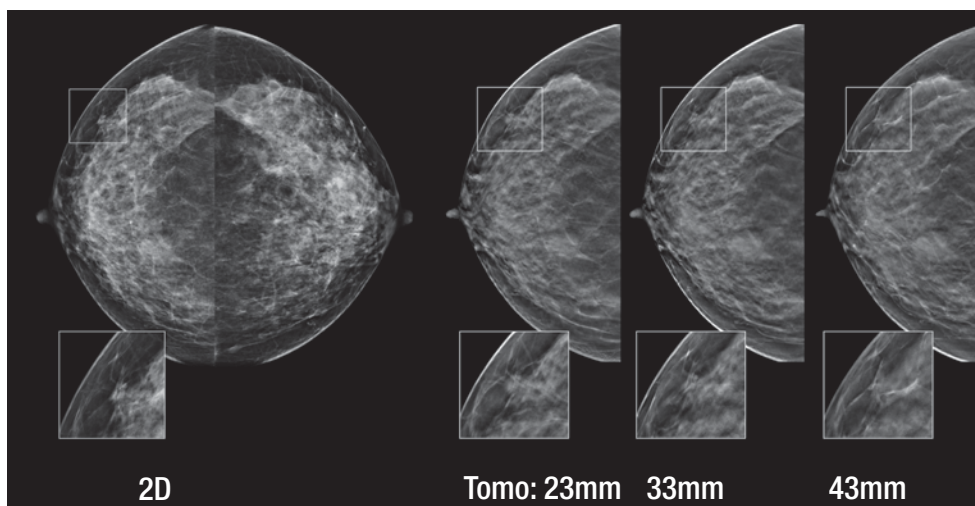
and noninvasive cancers, and fatty and dense breast tissue. There are also some early indicators of how the use of tomosynthesis may affect the management of symptomatic patients.

Performance in Calcifications, Masses and Distortions

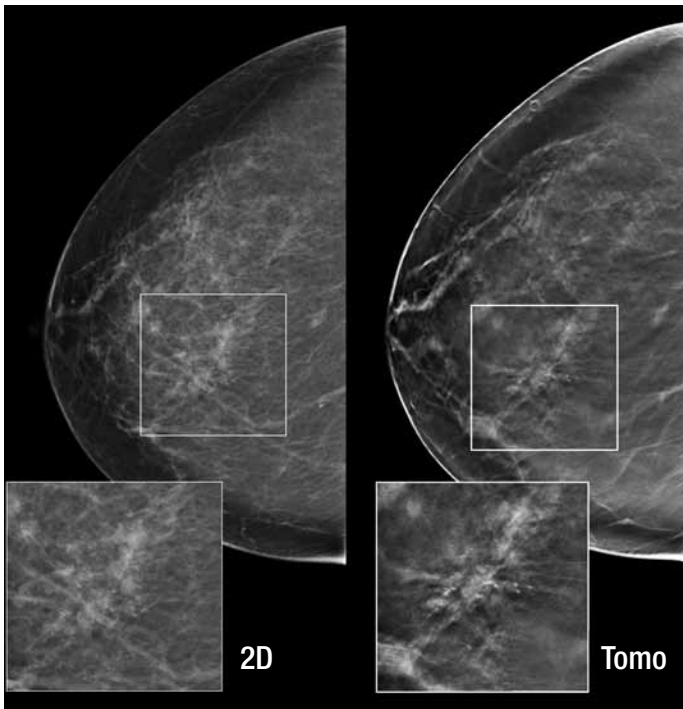
The clinical trial data presented as part of Hologic's FDA submission has been analyzed by separating the image sets into calcification and non-calcifications cases. Rafferty found that 2D plus tomo offered a very significant increase in performance relative to 2D imaging for cases involving masses and distortions.² For the imaging of cases involving microcalcifications there was a small, but not statistically significant, improvement in the ROC performance with the addition of tomosynthesis. It is important to note that the use of tomosynthesis was not associated with a poorer microcalcification ROC performance compared to 2D alone.

Other studies have looked at calcifications and their visibility with tomosynthesis. Early investigations found that digital mammography was often superior to tomosynthesis for calcification visualization.⁷ However, these early studies were done with systems that had long scan times (10-18 seconds) which can lead to patient motion and an associated negative impact on the conspicuity of microcalcifications.

Scan times have been reduced significantly in recent Hologic systems, and subsequent papers have found that tomosynthesis is useful in finding and characterizing microcalcifications, as well as masses and architectural distortions. For example, Kopans found that the characterization of calcifications in tomosynthesis was equal or superior to their characterization in conventional digital mammography in 92% of the cases studied.⁸ If exams include acquisition of 2D plus tomo images, it can be assured that calcifications will always appear optimal in at least one image set.



REDUCED RECALL RATES: The 2D mammogram reveals what appears to be a spiculated mass laterally in the right CC view. Tomosynthesis slices at 23, 33 and 43 mm above the breast platform show that this 2D finding was superimposed structures, resolved through the use of tomosynthesis imaging.



ADDED VALUE FOR CALCIFICATIONS: The 2D mammogram on the left shows right medial microcalcifications. The tomosynthesis reconstructed slice on the right illustrates the associated architectural distortion only revealed on the CC tomosynthesis image and not on the mammogram. (Diagnosis: Ductal Carcinoma In-situ/High Grade)

Performance in Invasive and Noninvasive Cancers

It is expected that the majority of additional cancers found by tomosynthesis will be mass lesions and not calcification-only cancers because of the much greater improvement in the ROC curve performance in the reader studies for non-calcifications than for cases involving calcifications. Thus, it is to be expected that the gain in sensitivity using tomosynthesis can be primarily attributable to invasive cancers. A cancer found on the tomo image and not seen in the 2D image during routine screening would not have been found until a successive screening round one or more years out or when the mass became palpable, had the tomo scan not been performed. This represents one of the key benefits of tomosynthesis; the potential for earlier-stage breast cancer detection.

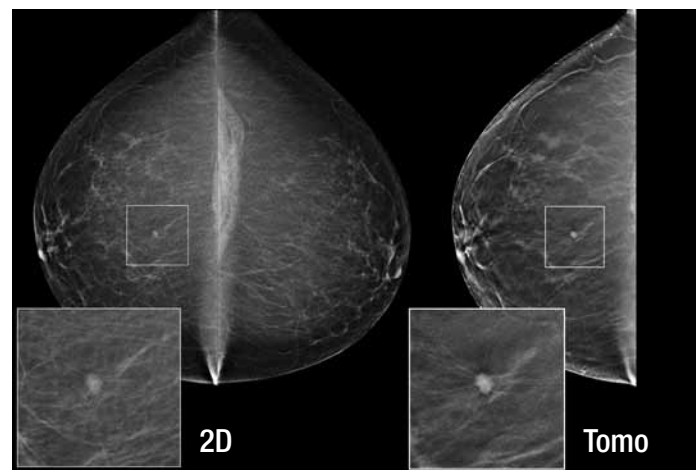
Performance in Fatty and Dense Breasts

Tomosynthesis has been shown to improve the performance of mammography in both fatty and dense breasts. Researchers have performed an analysis on cases following their grouping into fatty breast and dense breast sub-groups. For this analysis, fatty breasts were defined as BI-RADS density 1 and 2 and dense breasts were defined as BI-RADS density 3 and 4.

Rafferty studied the performance of tomosynthesis in women with dense breasts and found an increase in the recall for cancer cases and a reduction in the recall rate for non-cancer cases.⁹

These results are as expected. Fatty breasts often have sufficient parenchyma that tomosynthesis would be expected to offer some advantages. However, the even larger improvement in performance in denser breasts using tomosynthesis illustrates that tomosynthesis is doing what is expected from the physics principles – reducing superimposed parenchyma.

In a separate study, Rafferty found that 2D plus tomo was significantly better than 2D mammography alone in ROC performance for both fatty and dense breasts.¹⁰ While there was a gain in the area under the ROC curve in both breast density types, the gain was 2-3 times higher in dense breasts than it was in fatty breasts. Rafferty also reported large recall rate reductions in both fatty and dense breast types.



VALUE IN FATTY BREASTS: While the 2D mammogram reveals the 12:00 o'clock mass, tomosynthesis more accurately characterizes this mass as spiculated (Invasive Ductal Carcinoma).

Tomosynthesis Compared to Ultrasound

No studies have been published directly comparing the performance of tomosynthesis to ultrasound in breast cancer screening. Nonetheless, several observations may be made about this. Tomosynthesis, like ultrasound, has a superior performance in dense breasts relative to mammography. However, unlike ultrasound, where the recall rate of 2D and ultrasound was 4 times that of 2D mammography alone as was seen in the ACRIN 6666 trial, tomosynthesis improves sensitivity without increasing the recall rate.¹¹ Further clinical research will be needed to identify the respective roles of tomosynthesis and ultrasound, particularly in screening women with dense breasts.

Tomosynthesis Performance in the Evaluation of Symptomatic Patients

The use of tomosynthesis in diagnostic assessment offers the opportunity for both improved performance and a reduction in the number of x-ray images needed, with a resultant reduction in both dose and exam time.

Zuley et.al. found comparable sensitivity and specificity in the use of two-view tomo imaging in place of the additional diagnostic 2D views typically taken.¹² Because the number of diagnostic views in the evaluation of masses or focal asymmetries can average three or more¹³, there is a clear opportunity to reduce radiation exposure through the use of tomosynthesis in diagnostic evaluations.

Other researchers such as Svahn have also shown that the combined diagnostic performance of digital mammography and tomosynthesis is superior to either digital mammography or tomosynthesis alone.¹⁴

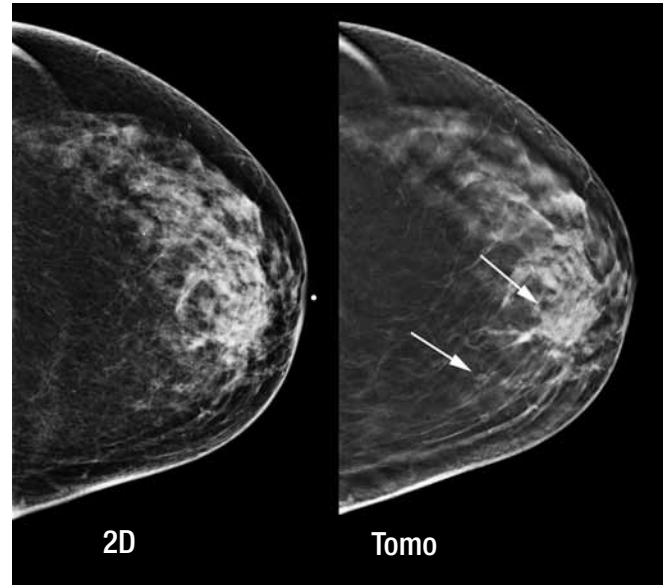
Several studies have shown that tomosynthesis is superior to 2D mammography in predicting tumor size, demonstrating margins, extents of lesions, and in staging.

Michell showed that tomosynthesis is superior to 2D mammography in predicting the histological tumor size because tomosynthesis demonstrates the margins and extents of the mammographic lesions more clearly. His study concluded that this modality provided critical information for prospective treatment planning by the multi-disciplinary team.¹⁵

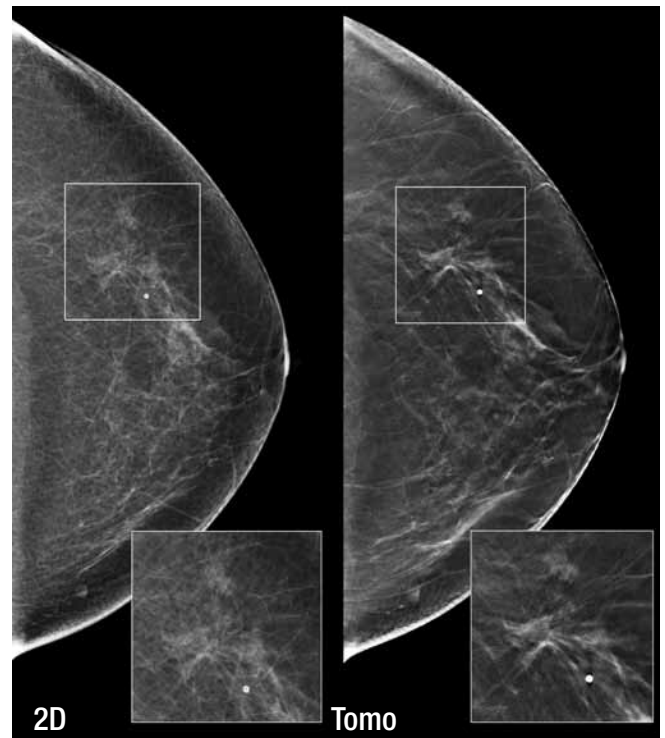
Fornvik found breast tomosynthesis superior to digital mammography in the assessment of breast tumor size and stage.¹⁶

Meacock found that tomosynthesis was more accurate than 2D in tumor size measurement.¹⁷

Tagliafico found that tomosynthesis could replace spot compression views, lowering both radiation dose and offering the potential to reduce biopsies on non-malignant lesions.¹⁸



GREATER PERCEPTION OF EXTENT OF DISEASE: In addition to the subtle area of architectural distortion best defined on the tomosynthesis reconstructed slice on the right (top arrow), a second spiculated mass is also revealed (bottom arrow) 21 mm posterior to the primary area of interest. (Diagnosis for both areas: Invasive Ductal Carcinoma)



REDUCED NEED FOR WORK-UP: Tomosynthesis demonstrates a definitive architectural distortion only subtly appreciated on the 2D digital mammogram, replacing the need for additional 2D diagnostic imaging.

Clinical Considerations in Implementing Tomosynthesis

Clinical research has shown the benefits of tomosynthesis in screening and diagnostic indications, as well as in a range of breast compositions and tissue types. However, there are a number of clinical considerations to be evaluated when determining how to introduce tomosynthesis to a clinical practice. What configuration of 2D and tomosynthesis views ensures the earliest possible detection of breast cancers and reduction of unnecessary recalls? What benefit will combo-mode imaging provide? How will these choices affect patient dose?

These considerations are discussed in more detail below.

One-view versus Two-View Tomosynthesis

The relative performance of one-view versus two-view 2D mammography is well understood.

Single view tomosynthesis (either CC or MLO) is a lower-dose procedure compared to two-view tomosynthesis, but it has been demonstrated to have poorer clinical performance. Screening using two views offers an increase in cancer detection and a reduction in recall rate compared to single-view mammography; the paper by Wald estimates the sensitivity gain is 24% and recall rate reduction is 15%.¹⁹

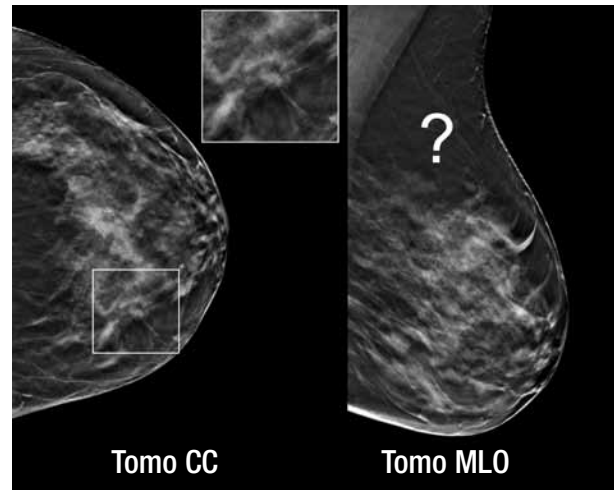
There is mounting evidence that two-view tomosynthesis has increased sensitivity relative to one-view tomosynthesis. This has been illustrated in the initial Hologic reader studies where the clinical performance of two-view 2D combined with a single (MLO) tomosynthesis view, as measured using ROC curve analysis, was inferior to the performance of two-view 2D combined with two-view tomo imaging.

Other data is consistent with this finding.

Rafferty found that 12% of lesions were better seen on the tomosynthesis MLO image, 15% better seen on tomo CC and 9% of lesions were visible only on tomo CC.²⁰

Similar results were reported by Baker, who found 8% of lesions were visible only on the tomosynthesis CC view and 1.4% only on the tomo MLO.²¹

These results are also consistent with evaluations where studies comparing the ROC performance of two tomosynthesis views demonstrate superior performance over two-view digital mammography (Michell), but studies comparing one tomo view to two-view digital mammography have poorer performance and do not show superiority (Gennaro, Wallis).^{22,23,24}



TWO VIEW TOMOSYNTHESIS OPTIMIZES CHANCE FOR CANCER DETECTION: A lesion can be seen in the tomosynthesis CC view but it is not apparent in any of the tomosynthesis MLO slices. (The central MLO slice is shown above.) A number of researchers have concluded that two-view tomosynthesis improves radiologist performance over single view tomosynthesis.

In addition to the likely loss of sensitivity that occurs if only one tomo view is taken, there are some clinical challenges that arise with single view tomosynthesis imaging. Neither the CC nor the MLO views capture all the breast tissue, so both views in some form are needed.

Mixing up technologies, such as combining a tomosynthesis MLO view and a 2D mammography CC image, might address the tissue coverage, but creates its own set of issues. It might be difficult, for example, to correlate a suspicious lesion seen in 2D CC with the same lesion in the tomo MLO, or vice versa.

An even more challenging situation is when the exam consists solely of a tomo MLO. It could be difficult to see asymmetries with only one view, and comparison to 2D prior images would also be challenging. The best clinical performance will likely be seen in protocols that acquire both a tomo CC and MLO image set.

Performing two views uses more radiation dose than one view. However, these doses are commonly accepted in conventional mammography, where two-view mammography is performed to optimize the cancer detection rate. Likewise, two-view tomosynthesis is associated with higher sensitivity along with reduction in recall rates, as compared to single view tomosynthesis, where sensitivity will suffer.

Given that there is an established dose limit for mammographic imaging in the U.S., it would seem reasonable to maximize the use of the dose budget. An alternative approach to acquiring two tomosynthesis views, given a fixed radiation dose budget, would be to acquire only one tomosynthesis view, but double the dose for that view. This certainly would lower noise and may result in a superior image due to the increased photon statistics. However, based on the above results, it is better for a fixed 2x dose budget to split the dose into two views. The Gennaro 2009 study confirmed that the use of single-view tomo at 2x dose achieved inferior performance, compared to digital mammography, than did Michell, who used two tomo views at approximately 1x dose each.^{22, 21}

Benefits of Combo-mode Imaging

There are several reasons why acquiring both a 2D mammography and tomosynthesis image together are useful, especially in screening. It is well known that comparison of current images with prior images is standard mammography practice and critical to perceive subtle changes which may be associated with a cancer. Obtaining a 2D exam along with the tomo exam allows direct comparison of current 2D images with prior 2D images.

The 2D exam is also useful for the rapid detection of calcifications and perception of their distribution. Segmental and clustered calcifications are more easily and quickly appreciated with 2D because they can traverse multiple tomosynthesis slices.

The tomosynthesis portion of the 2D plus tomo exam is also critical in optimizing performance. The tomo image reduces structure overlap, minimizing recalls for overlapped structures and better demonstrates masses and architectural distortions. Thus we see that 2D and tomo are complementary and acquired together offers an advantage in clinical use.

In summary, both the 2D and tomosynthesis images in an exam are valuable because:

- The 2D image is useful for comparison to priors
- The 2D image allows for quick reading of microcalcifications
- The tomo image reduces structure overlap and better demonstrates masses

There may be methods to eliminate the need to separately acquire the 2D exam through mathematical algorithms that generate a synthesized 2D image reconstructed from the tomo dataset. This approach is discussed in the following section of this paper.

Patient Dose and Risk/Benefit

The dose of a combined 2D and tomosynthesis exam are very small. Even taken together as a combo-mode acquisition, they are below the U.S. FDA/MQSA-determined safe level and are not far from historical screen-film mammography doses.²⁵

As discussed above, the clinical protocol of 2D CC and MLO plus tomo CC and MLO gives the best clinical accuracy for screening. In a diagnostic work-up, however, there are many methods of performing the 2D and the tomo exam, and the patient dose will vary depending upon how many exposures are made, i.e. what combinations of 2D CC and MLO and tomo images are taken.

The doses of a 2D and a tomo exam can be compared to the levels of background radiation that everyone receives from natural sources such as cosmic rays and the soil. These exposure levels are shown in Figure 2. A 2D, tomo, or combined 2D plus tomosynthesis study all have effective dose levels that are fractions of typical doses that people are exposed to annually. There are normal variations in these levels, and higher altitude cities have higher background radiation levels that can give a resident more radiation than on average, as seen in the background radiation in Colorado compared to the average in the U.S. Breast cancer mortality rates are lower in Colorado than on average in the U.S., which is an indication that radiation at these levels should not be a concern.²⁶

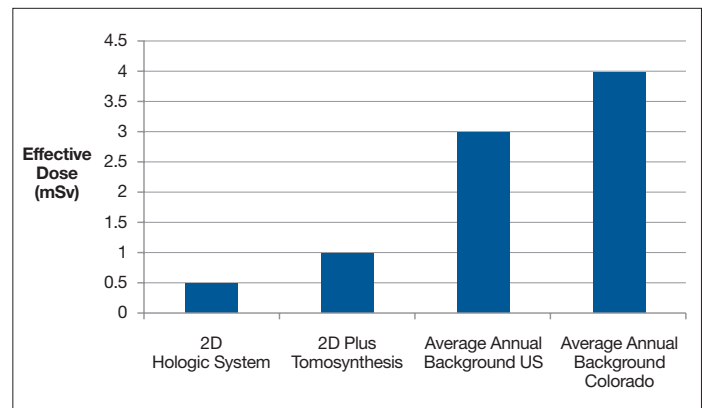


Figure 2. Dose levels of 2D and tomo exams compared to natural background radiation

The Health Physics Society issued a position statement on the very topic, stating that “Estimation of health risk associated with radiation doses that are of similar magnitude as those received from natural sources should be strictly qualitative and encompass a range of hypothetical health outcomes, including the possibility of no adverse health effects at such low levels.”²⁷

It is important to keep a perspective on the actual risks from the very low radiation doses delivered by modern mammography and tomosynthesis systems. Doses at current levels are low and risks are hypothetical.²⁸ The benefits of screening mammography and early detection of cancer, on the contrary, are not hypothetical – they are proven. Tomosynthesis will be an improvement over conventional mammography in improving sensitivity and avoiding unnecessary workup of women without disease.

When establishing initial protocols for the use of tomosynthesis, users should carefully evaluate clinical evidence and regulatory guidelines and apply that information to their particular patient populations, practice-specific needs and regional standards of care. In addition, to ensure effective accommodation of all patient care needs, it will be important that the tomosynthesis system provides adequate flexibility to efficiently allow acquisition of any combination of views and imaging modalities (2D, tomo and combo-mode imaging).

Future Advances in Tomosynthesis

The growing adoption of tomosynthesis in clinical use creates an opportunity for technological evolutions that may be useful in streamlining workflow, reducing dose, improving diagnostic accuracy and expanding clinical applications. Some of the early efforts in these areas are discussed in the following sections.

Synthesized 2D Images

One area in which extensive research and development efforts have been focused is the creation of a 2D image synthesized from a tomosynthesis data set. In November 2011, Hologic announced the commercial release of its C-View™ synthesized 2D image reconstruction algorithm that eliminates the need for a conventional 2D mammogram as a component of a tomosynthesis screening procedure. The C-View software was introduced for sale throughout the European Economic Area and in other countries recognizing the CE Mark.²⁹

This approach would provide the advantage of reducing the number of exposures, leading to slightly shorter exam times and reduced patient dose. The dose would be approximately half the dose of a 2D plus tomo exam, and approximately the same as a 2D exam alone. This could be an important evolution of this technology, especially in dose-sensitive regions.

The algorithms to create such a synthesized image that approximate the necessary components of the true 2D involve smart summing of the individual slices that make up the tomosynthesis image set. In clinical use, the synthesized 2D image will be reviewed together with the tomosynthesis image set.

There are technical challenges to creating a synthesized 2D image that is close in quality to that of a true 2D image, however much progress has been made in this area. Gur has studied the performance of an early version of synthesized 2D in a pilot study.³⁰ He concluded that a minor improvement in the quality of a synthesized 2D image could lead to an acceptable diagnostic quality and eliminate the need for acquiring both a 2D and tomo dataset during tomosynthesis based screening. This is certainly promising and offers the possibility of providing the improved performance gain of two-view breast tomosynthesis with doses comparable to current 2D mammography levels.



While still being improved, the quality of the Hologic synthesized 2D is very good and offers the potential for eliminating the need for an additional exposure to acquire a 2D image.

Tomosynthesis Computer-Aided Detection (CAD)

Just as in conventional 2D digital mammography, CAD may help find suspicious objects in a tomosynthesis dataset. However, there are differences in the use for CAD in tomosynthesis. Conventional 2D CAD helps find both masses and microcalcifications. In tomosynthesis, there may be less of a need for a mass-detection algorithm, because often the masses and distortions are found very quickly and easily by the human observer.

The situation is different in the case of microcalcifications. It can be time consuming to have to carefully search a large number of slices, and there is the potential for the reviewer to overlook some subtle microcalcifications. An efficient and sensitive calcification CAD algorithm could help speed up the search. For example, CAD could identify suspicious calcification clusters on a scout image and rapidly navigate to the

appropriate slices of interest. Figure 4 shows an example of a CAD algorithm marking potentially suspicious microcalcifications on a single slice from a tomo study.

Hologic has developed an extension to its ImageChecker® CAD product line for identification of potential calcifications in tomosynthesis slices. ImageChecker 3D Calc CAD is available in Canada and throughout the European Economic Area and in other countries recognizing the CE Mark.

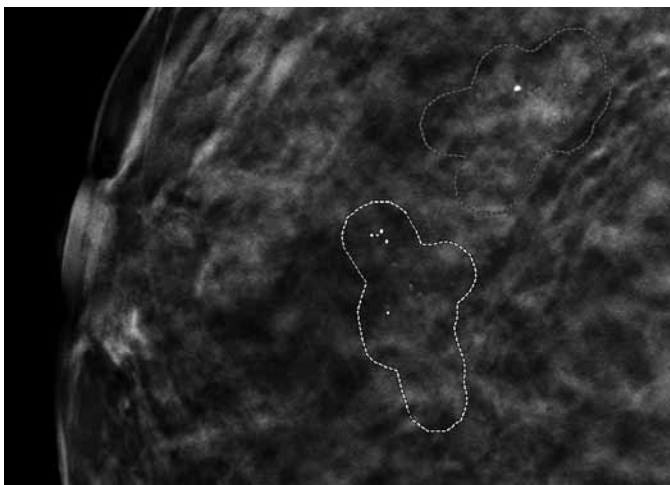
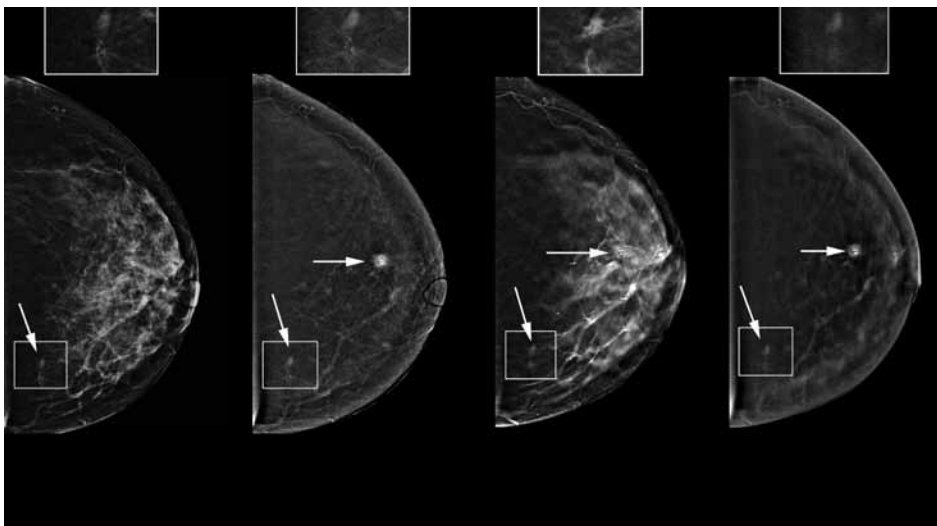


Figure 4. CAD marks identify areas of interest on a single tomosynthesis slice

Contrast Enhanced Breast Imaging

Contrast enhanced breast imaging is a procedure that images the distribution of an iodinated contrast agent using either 2D or tomosynthesis x-ray imaging technologies. This technology is in its early evaluation stage but may offer some advantages relative to contrast breast MRI in terms of reduced cost, comparable care to patients for whom MRI is contraindicated, and access to patients in areas where MRI systems are not available. Contrast enhanced breast imaging combines functional information from the distribution of the contrast agent and morphological information from the x-ray images. Hologic is investigating this technology using a dual modality system, capable of imaging the functional 2D contrast uptake and the morphological tomosynthesis image in rapid sequence, and combining these two image sets into a single fused study. In the fused study, the 2D or tomo contrast image can identify potential lesions based on their physiological state which causes increased contrast agent uptake. The standard tomo image can then be overlaid and provide morphological information on the lesion, such as improved visibility of associated spiculations.



CONTRAST IMAGING: This study of 2D and tomosynthesis iodine contrast mammography was acquired under a single compression. The proven cancer in the subareolar breast (horizontal arrow) is not visible on the enhanced 2D mammogram except for the clips placed at biopsy but is easily seen on the 2D and tomosynthesis dual energy contrast images. Contrast imaging led to the detection of an additional cancer in the far medial breast (downward arrow.) The tomosynthesis image shows the irregular shape of the lesion, making it highly likely that the lesion is malignant.

Conclusions

Tomosynthesis is an exciting new technology that will likely revolutionize mammography. It offers the potential for improvements in both screening and diagnostic evaluations. The improvements in clinical performance, compared to 2D mammography, are significant. Hologic's clinical study results demonstrate that 2D mammography plus tomo can offer either improved cancer detection rate, or reduced recall rate, or both, compared to 2D alone. These are certainly very positive results, and are much stronger than the ACRIN DMIST study results which compared the performance of digital to screen-film mammography, and found no average difference in performance between the two technologies.³²

Reader studies considered by the FDA advisory panel using the Hologic breast tomosynthesis system demonstrated superior performance in the detection of masses and architectural distortions and equivalent or slightly better performance in the detection of microcalcifications in using 2D plus tomo imaging compared to 2D alone. Acquisition of both the CC and MLO views in 2D and tomo provided statistically

significant superior performance compared to 2D alone; however, use of only the MLO tomo with both the 2D CC and MLO views also provided better performance compared to 2D alone – just not as good as acquiring both CC and MLO Tomo. Finally, it was demonstrated that the addition of tomosynthesis to 2D imaging provides improved performance in both fatty and dense breasts, compared to 2D alone, with the performance gain in dense breasts higher than in fatty breasts.

There is a growing body of evidence that tomosynthesis has the potential to reduce the number of exposures needed for diagnostic imaging and provide other diagnostic benefits including enhanced performance in assessing tumor size and stage and more clearly demonstrating margins and extent of lesions.

Future advances in tomosynthesis include CAD algorithms to facilitate the rapid identification of suspicious clusters of calcifications, development of a synthesized 2D image to reduce the number of exposures in an exam while still providing a 2D-equivalent image for ease of review, and contrast enhanced imaging for patients where access to breast MRI is limited or contraindicated.

Glossary

2D	Conventional digital mammography
BI-RADS	Breast Imaging - Reporting and Diagnosis System
Breast tomosynthesis	A technology involving limited angle tomography acquisition and reconstruction. Also referred to as digital breast tomosynthesis, 3D mammography, 3D tomosynthesis, tomosynthesis and tomo.
CAD	Computer-aided Detection
Forced BI-RADS	A rating method where only BI-RADS scores from 1 to 5 are allowed.
IRB	Institutional Review Board
MQSA	Mammography Quality Standards Act
Recall rate	The percentage of women recalled from screening for further assessment. In mammography screening, the majority of recalled cases are false positives.
ROC	Receiver Operating Characteristics
Sensitivity	The measure of how many cancers are detected.
Synthesized 2D	A method of creating an enhanced 2D image from a reconstruction of a tomosynthesis dataset.
Specificity	The measure of how many non-cancers are correctly identified.

References

- ¹ http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080003b.pdf
- ² Rafferty E, Niklason L, Halpern E, et. al. Assessing radiologist performance using combined full-field digital mammography and breast tomosynthesis versus full-field digital mammography alone: results of a multi-center multi-reader trial. Radiological Society of North America annual meeting. Chicago, IL, 2007.
- ³ Gur D, Bandos AI, Rockette HE, et. al. Is an ROC-type response truly always better than a binary response in observer performance studies? *Acad Radiol.* (17)5:639-645, 2010.
- ⁴ One advisory panel member abstained from voting.
- ⁵ Skaane P, Gullien R, Eben EB, et. al. Reading time of FFDM and tomosynthesis in a population-based screening program. Radiological Society of North America annual meeting. Chicago, IL, 2011.
- ⁶ Gur D, Sumkin J, Zuley R, et. al. Recall rate reduction with tomosynthesis during baseline examinations – preliminary assessment from a prospective screening trial. Radiological Society of North America annual meeting. Chicago, IL, 2011.
- ⁷ Poplack SP, Tosteson TD, Kogel CA, et. al. Digital breast tomosynthesis initial experience in 98 women with abnormal digital screening mammography. *Am J Roentgenol.* 189:616-623 (2007).
- ⁸ Kopans D, Moore R. Calcifications in digital breast tomosynthesis (DBT). Radiological Society of North America annual meeting. Chicago, IL, 2008.
- ⁹ Rafferty EA, Niklason L. FFDM versus FFDM with tomosynthesis for women with radiologically dense breasts: an enriched retrospective reader study. Radiological Society of North America annual meeting. Chicago, IL, 2011.
- ¹⁰ Rafferty EA, Niklason L, Smith A. Comparison of FFDM with breast tomosynthesis to FFDM alone: performance in fatty and dense breasts. Tomosynthesis Imaging Symposium, Duke University, 2009.
- ¹¹ Berg WA, Blume JD, Cormack JB, et. al. Combined screening with ultrasound and mammography vs. mammography alone in women with elevated risk of breast cancer. *JAMA* May 14; 299(18):2151-63, 2008.
- ¹² Zuley M, Sumkin J, Ganott M, et. al. Digital breast tomosynthesis vs. supplemental diagnostic mammography images for the evaluation of non-calcified breast lesions. Radiological Society of North America annual meeting. Chicago, IL, 2011.
- ¹³ Harvey JA, Nicholson BT, Cohen MA. Finding early invasive breast cancers: a practical approach. *Radiology*, July 2008; 248:61-76.
- ¹⁴ Savhn T, Andersson I, Chakraborty D, et. al. The diagnostic accuracy of dual-view digital mammography, single-view tomosynthesis and a dual-view combination of breast tomosynthesis and digital mammography in a free-response observer performance study. *Radiat Prot Dosimetry.* 139(1-3): 113-117(2010).
- ¹⁵ Michell M, Iqbal A, Wasan R, et. al. A comparison of the accuracy of digital breast tomosynthesis with two dimension digital mammography in measurement of breast tumour size. Radiological Society of North America annual meeting. Chicago, IL, 2010.
- ¹⁶ Fornvik D, Zackrisson S, Ljunberg O, et. al. Breast Tomosynthesis: Accuracy of tumor measurement compared with digital mammography and ultrasonography. *Acta Radiol* 3; 240-247, 2010.
- ¹⁷ Meacock LM, et. al. The accuracy of breast cancer size measurement: Digital breast tomosynthesis (DBT) vs. 2D digital mammography (DM). European College of Radiology annual meeting. Vienna, Austria, 2010.
- ¹⁸ Tagliafico A, Astengo D, Cavagnetto F, et. al. One-to-one comparison between digital spot compression view and digital breast tomosynthesis. *Eur Radiol.* 2011 Oct 11 [Epub ahead of print].
- ¹⁹ Wald NJ, Murphy P, Major P, et. al. UKCCCR multicentre randomized controlled trial of one and two view mammography in breast cancer screening. *BMJ* 311:1189-93, 1995.
- ²⁰ Rafferty E, Niklason L, Jameson-Meehan L. Breast tomosynthesis: one view or two? Radiological Society of North America annual meeting. Chicago, IL, 2006.
- ²¹ Baker JA, Lo JY. Breast tomosynthesis: state-of-the-art and review of the literature. *Academic Radiology* 18:10. 1298-1310 (2011).
- ²² Michell MJ, Iqbal A, Wasan R, et. al. Phase I trial to determine the performance of digital breast tomosynthesis versus two dimension digital and film-screen mammography. Radiological Society of North America annual meeting. Chicago, IL, 2010.
- ²³ Gennaro G, Toledano A, di Maggio C, et. al. Digital breast tomosynthesis versus digital mammography: a clinical performance study. *Eur Radiol* 20:1545-1553 (2009).
- ²⁴ Wallis MG, Moa E, Zanca F, et. al. Two-view and single-view tomosynthesis versus full-field digital mammography: high-resolution x-ray imaging observer study. Published online before print. *Radiology*, Jan 24, 2012.
- ²⁵ See, for example, Updated trends in mammography dose and image quality. <http://www.fda.gov/Radiation-EmittingProducts/MammographyQualityStandardsActandProgram/FacilityScorecard/ucm113352.htm>
- ²⁶ <http://www.cdc.gov/cancer/breast/statistics/state.htm>
- ²⁷ Health Physics Society Position Statement – Radiation Risk in Perspective. 2004.
- ²⁸ Feig SA, Hendrick RE. *J Natl Cancer Inst Monogr.* 22:119-124, 1997.
- ²⁹ http://www.hologic.com/en/news-releases/view/173-year.2011_173-id.234881907.html
- ³⁰ Gur D, Zuley ML, Lu A, et. al. A two-fold dose reduction in breast screening with tomosynthesis (DBT) through the use of reconstructed 2D images from the DBT dataset. Radiological Society of North America annual meeting. Chicago, IL, 2011.
- ³¹ ftp://medical.nema.org/medical/dicom/final/sup125_ft.pdf
- ³² Pisano ED, Gatsonis C, Hendrick E, et. al. Diagnostic performance of digital versus film mammography for breast cancer screening. *N Engl J Med* 2005; 353: 1773-1783.

Hologic, Inc.

35 Crosby Drive
Bedford, MA 01730 USA
T: 781.999.7300

www.hologic.com
womenshealth@hologic.com