Dual-Modality Breast Tomosynthesis¹

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Purpose:

To evaluate the clinical performance of a hybrid scanner that uses dual-modality tomosynthesis (DMT) and technetium 99m sestamibi to provide coregistered anatomic and functional breast images in three dimensions.

Materials and Methods:

A prospective pilot evaluation of the scanner was performed in women scheduled to undergo breast biopsy after institutional review board approval and informed consent were obtained. All subject data were handled in compliance with the rules and regulations concerning the privacy and security of protected health information under HIPAA. The study included 17 women (mean age, 53 years; age range, 44–67 years) and 21 biopsy-sampled lesions. Results of DMT scanning were compared with histopathologic results for the 21 lesions.

Results:

Of the 21 lesions, seven were malignant, and 14 were benign. Among the 13 subjects with one lesion each, three had positive biopsy results, and 10 had negative biopsy results. Among the four subjects with two lesions, the biopsy results were as follows: bilateral in one, both negative; bilateral in one, both positive; unilateral in two, one positive and one negative. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of DMT scanning were 86%, 100%, 100%, 93%, and 95%, respectively.

Conclusion:

Pilot clinical evaluation of the DMT scanner suggests that it is a feasible and accurate method with which to detect and diagnose breast cancer. Systems such as the DMT scanner that are designed specifically for three-dimensional multimodality breast imaging could make possible some of the advances in tumor detection, localization, and characterization of breast cancer that are now being observed with whole-body three-dimensional hybrid systems, such as positron emission tomography/computed tomography (CT) or single photon emission computed tomography/CT.

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The sensitivity of x-ray mammography is 71%–96% when averaged across all breast types (1), but it is reduced in women with radiographically dense breasts (2,3). In addition, the rate of false-positive results obtained with mammography and ultrasonography (US) is high. When averaged across the 44 participating sites in a recent multicenter study, the positive predictive value (PPV) of mammography and US (defined as the proportion of screenings that were associated with a breast cancer diagnosis within the 1-year follow-up period among those with a Breast Imaging Reporting and Data System classification of 0, 4, or 5) was 4.1%. Furthermore, just 38.8% of patients with mammograms classified as Breast Imaging Reporting and Data System 4 or 5 that resulted in a recommendation for biopsy, surgical consultation, or fine-needle aspiration were associated with a breast cancer diagnosis during follow-up (4). These low numbers motivate the development of technologies that would enable better depiction of early lesions in the radiographically dense breast and/or adjunct modalities that provide additional information beyond that provided by x-ray mammography and US.

Digital x-ray breast tomosynthesis has been developed actively both academically and commercially during the past decade (5–8). In x-ray tomosynthesis, multiple projections (views) are imaged across a restricted range of view-

ing angles to produce a series of section images in which there is a substantial reduction in the amount of superimposed breast tissue present in each tomosynthesis section, thereby improving lesion conspicuity compared with that of two-dimensional digital mammography while providing comparable in-section spatial resolution. There is also evidence that by using tomosynthesis, the compressive force on the breast can be reduced substantially, thereby improving subject comfort during the examination (5). Within the past decade, the availability of large-area, high-spatial-resolution, digital x-ray detectors capable of rapid readout has prompted a number of major mammography equipment manufacturers to develop digital breast tomosynthesis systems, and several are currently in the process of obtaining data for approval by the Food and Drug Administration. X-ray tomosynthesis is likely to improve sensitivity for small lesions when compared with planar digital mammography; however, it still will provide only anatomic information. Therefore, additional imaging modalities that return complementary functional information are desirable.

Nuclear medicine imaging of the breast with an intravenously injected

tracer emitting single gamma rays and one or more imaging gamma cameras is referred to as scintimammography, breast scintigraphy, molecular breast imaging (MBI), or breast-specific gamma imaging. Nearly all studies to date have used 20–30-mCi (740–1100-MBq) injections of the tracer technetium 99m (^{99m}Tc) sestamibi (hexakis-2-methoxyisobutyl-isonitrile). Sestamibi is approved by the Food and Drug Administration for breast cancer imaging, accumulating preferentially in breast cancers rather than in surrounding healthy tissues (6). It is also a substrate for P-glycoprotein, which is associated with multidrug resistance (7–10), so its washout rate may be predictive of chemotherapeutic effectiveness. Results from early scintimammography studies demonstrated that breast imaging with ^{99m}Tc sestamibi provides useful diagnostic information complementary to that of x-ray mammography (11–14); however, sensitivity for lesions smaller than 1 cm in diameter in early studies was low because of geometric imaging limitations when bulky conventional gamma cameras were used. Relatively recently, the use of compact dedicated breast gamma cameras and mild breast compression has permitted camera placement adjacent to the chest wall

Advances in Knowledge

- Integrated x-ray tomosynthesis and gamma emission tomosynthesis breast scanning with an upright mammographic gantry is feasible.
- Comparison with histopathologic results among 21 biopsy-sampled lesions demonstrates that dual-modality tomosynthesis with technetium 99m sestamibi has sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 86%, 100%, 100%, 93%, and 95%, respectively.

Implications for Patient Care

- Dedicated hybrid breast imaging systems may improve detection and characterization of breast lesions through precise coregistration of anatomic and functional image data obtained with a single pain-free compression of the breast; this system is likely to be particularly advantageous for women with radiographically dense breasts.
- Coupled with the current movement in the mammography community toward x-ray tomosynthesis, hybrid systems such as the one described could become available to a large number of breast care clinics in the near future because of their relatively low cost and compatibility with current breast imaging rooms.

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Abbreviations:

DMT = dual-modality tomosynthesis

MBI = molecular breast imaging

PPV = positive predictive value

SNR = signal-to-noise ratio

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Guarantor of integrity of entire study, M.B.W.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, M.B.W.; clinical studies, M.B.W., P.G.J., S.G.; statistical analysis, P.G.J.; and manuscript editing, all authors

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and in contact with the breast, thereby permitting the entire breast to be imaged with high spatial resolution and resulting in reliable detection of tumors smaller than 1 cm in diameter (15–17). Several groups have developed such dedicated breast gamma cameras (18–23).

Like magnetic resonance (MR) imaging, MBI with dedicated cameras is particularly useful in women with radiographically dense breasts because the relatively high-energy (140-keV) gamma rays emitted by ^{99m}Tc sestamibi are much less attenuated by fibroglandular tissue than are the lower-energy (20–30-keV) x-rays used in mammography. Brem et al (24,25) compared the performance of MBI with that of contrast material-enhanced MR imaging as adjuncts to x-ray mammography and reported comparable sensitivity but greater specificity for MBI relative to MR imaging. Investigators at the Mayo Clinic showed that sensitivity for small lesions can be increased even further by using a two-headed MBI system (17,26). MBI with dedicated cameras also has shown promise in presurgical planning for women known to have breast cancer. In a study of 138 patients with newly diagnosed breast cancer, Zhou et al (27) reported that the PPV for MBI was 92.9% and that MBI depicted additional malignancy or more extensive malignancy in the same breast or the contralateral breast 10.9% of the time.

One difficulty with current MBI techniques is the lack of an accurate way to correlate MBI findings with anatomic information from mammography, US, or MR imaging. Inevitable differences in the direction and magnitude of breast compression make accurate spatial correlation of findings within the breast difficult. Hybrid imaging systems combining anatomic and functional imaging modalities are a means to obtain accurate localization correlation between modalities.

In recent years, our group at the University of Virginia, Charlottesville, has investigated limited-angle, dual-modality tomosynthesis (DMT) breast imaging (28,29), and we have built two upright DMT scanners. The scanners

evolved from previous planar hybrid breast scanners (30–32). The second DMT scanner was built in collaboration (Dexela, London, England; Jefferson Laboratory, Newport News, Va). It combines x-ray tomosynthesis and MBI tomosynthesis in a single integrated upright mammography-style gantry. Digital x-ray tomosynthesis and digital MBI tomosynthesis are performed in rapid succession by using the same mild breast compression, permitting the structural and functional volumetric images to be exactly correlated and automatically fused. The purpose of this study was to evaluate the clinical performance of a hybrid scanner that uses DMT and ^{99m}Tc sestamibi to provide coregistered anatomic and functional breast images in three dimensions.

Materials and Methods

The gantry and x-ray source for this study, including the associated x-ray tomosynthesis acquisition software, was supplied by Dexela. The gamma camera and its readout electronics and acquisition software were provided by Jefferson Laboratory. The x-ray detector and gamma camera positioning mechanisms were supplied by the University of Virginia. Nonindustry investigators (M.B.W., P.G.J.) maintained control of the image data and all other information that might present a real or apparent conflict of interest for industrial collaborators.

DMT Scanner Description

The DMT scanner uses full isocentric motion, in which both the tube and the detector rotate around a common axis (33), with the breast support and compression mechanism independent of the gantry arm, and the breast near the axis of rotation of the gantry arm (Fig 1) (28). The gantry uses a servomotor coupled via a worm gear to the gantry arm. The x-ray component of the scanner includes a high-output, oil-cooled, tungsten-target, x-ray tube (RAD 70; Varian Medical Systems, Palo Alto, Calif) and a charge-coupled device-based x-ray detector with a field of view of 20×30 cm that was developed

with National Cancer Institute funding (34). The detector was designed for single-view digital mammography and was not optimized for short readout time. With 2×2 on-chip binning, the readout time is approximately 2 seconds. A 50- μm -thick rhodium filter provides external filtration. Typically, 13 views are imaged across an angular range of between $\pm 12^\circ$ and $\pm 20^\circ$ away from the direction of breast compression by using nonuniform angular spacing between views. For tomosynthesis reconstruction, statistically based iterative algorithms that prevent overfitting of the noise in the data are used.

The gamma camera has a field of view of 15×20 cm. It consists of a 3×4 array of flat-panel, position-sensitive photomultiplier tubes (H8500; Hamamatsu Photonics, Hamamatsu City, Japan) that are optically coupled to a thallium-doped sodium iodide crystal array. The array has a crystal size of 2.0 mm, pitch of 2.2 mm, and thickness of 6 mm. The camera is equipped with a parallel-hole lead-foil collimator and has an overall efficiency (the combined efficiency of the detector and collimator) of 2.0×10^{-4} (sensitivity of 450 counts/MBq/min). The gamma camera is mounted on the gantry arm between the x-ray tube and the breast support by means of a pair of parallel, motorized linear translation stages to allow the camera to be moved parallel to the long axis of the gantry arm, which permits the distance between the collimator surface and the axis of rotation to be varied continuously. Minimizing the distance between the axis of rotation and the gamma camera for each view maximizes the signal-to-noise ratio (SNR) in the reconstructed image because of improved spatial resolution and higher lesion contrast (28). The chest-anterior position of the camera is adjusted by sliding it manually along two slider rails, the ends of which are mounted on the parallel linear translation stages. During x-ray imaging, the camera is positioned close to the gantry arm out of the beam. It is then repositioned in the posterior direction for gamma imaging so that the chest wall edge of the collimator is aligned with the

Figure 1: DMT breast scanner. A dedicated high-spatial-resolution gamma camera is mounted on a translation stage attached to the gantry arm. The configuration during gamma imaging is shown here. The camera is positioned anteriorly out of the x-ray beam during x-ray imaging.

chest wall edge of the compression paddle. Gamma imaging can be performed in list mode to permit postacquisition scatter correction (35) and/or extraction of information about tracer dynamics, if desired. MBI tomosynthesis reconstruction is performed by using an expectation maximization algorithm. The known collimator-axis of rotation separation for each view is used along with the empirically determined separation-dependent camera point spread function for spatial resolution recovery during reconstruction. The measured root mean square colocalization errors between the two modalities of the DMT scanner are 0.25, 0.51, and 0.63 mm in the x, y, and z (parallel to the direction of breast compression) dimensions, respectively.

Pilot Human Study

A prospective pilot evaluation of the DMT scanner was performed between April 2008 and May 2009. Eligible participants were scheduled for breast biopsy and were not pregnant. The study was performed with institutional review board approval from the University of Virginia Human Investigations Committee, and all participants provided informed consent. All subject data were handled in compliance with the rules and regulations concerning the privacy and security of protected health information under the Health Insurance Portability and Accountability Act. Candidates for the study were identified on the basis of information from the clinical biopsy schedule. Although that schedule was not always avail-

able to the investigators in this study, all known eligible candidates were invited to participate. The study included 17 women (mean age, 53 years; age range, 44–67 years) and 21 lesions sampled at biopsy.

Volunteers received 30 mCi (1110 MBq) of ^{99m}Tc sestamibi intravenously (Miraluma; Bristol-Myers Squibb, North Billerica, Mass). The resulting absorbed radiation dose to the breast is approximately 2 mGy, and the whole-body dose is approximately 4.8 mGy (36). Mild breast compression is used to minimize breast motion while permitting 12-minute x-ray imaging and MBI to be performed comfortably. Volunteers are seated during both x-ray and gamma ray imaging. X-ray tomosynthesis imaging is performed first, followed by MBI tomosynthesis. X-ray imaging was performed by using the manual mode, with parameters (kilovolt peak and milliamperes-second settings) chosen to result in a total mean glandular dose to the breast that is less than or equal to that of the most recent clinical two-view mammographic examination (typically approximately 3–4 mGy). The kilovolt peak was selected on the basis of a technique chart that treats the volunteer's compressed thickness and radiographic density, as determined from the volunteer's mammogram, as input parameters. The chart was generated to maximize the ratio of the square of the image SNR to the mean glandular dose when imaging breast-equivalent phantoms that represented a variety of breast thicknesses and compositions (37). Thirteen views were imaged within an angular range of $\pm 12^\circ$ away from the direction of breast compression. The radiation dose was divided approximately evenly among all views, and the total scanning time was approximately 30 seconds. MBI tomosynthesis was performed by using five evenly spaced views across an angular range of 40° . In each view, the radial distance of the camera from the axis of rotation was minimized. Image acquisition time was 2 minutes per view, for a total MBI tomosynthesis scanning time of 11 minutes per breast, including camera movement time. These choices

represent a practical compromise between improved image quality and reasonably short overall acquisition time.

All images were read by a board-certified mammography radiologist with 5 years of experience. The interval between prior care and DMT image reading was at least 4 months to minimize the effects of recall bias. The reader was blinded to biopsy results, as well as to all clinical mammographic, US, and MR images. First, the x-ray tomosynthesis images alone were presented in a random sequence. Next, the MBI tomosynthesis images alone were presented in a different random sequence. Finally, the matched DMT data sets were presented. In all three reading sessions, all findings were rated by using a five-point scale: 1, definitely benign; 2, probably benign; 3, indeterminate; 4, suggestive of malignancy; and 5, highly suggestive of malignancy. In subsequent analysis of the reading results, reader scores were classified as either positive or negative on the basis of one of two operating thresholds: (a) all scores greater than 3 are considered positive and (b) all scores greater than 4 are considered positive. Only findings coinciding with the location of a lesion were analyzed.

Results

Of the 21 lesions, seven were malignant, and 14 were benign. Among the 13 subjects with one lesion each, three had positive biopsy results, and 10 had negative biopsy results. Among the four subjects with two lesions, the biopsy results were as follows: bilateral in one, both negative; bilateral in one, both positive; unilateral in two, one positive and one negative.

Table 1 shows the histologic and imaging results for the 21 lesions. Table 2 shows the resulting sensitivity, specificity, PPV, negative predictive value, and accuracy for each modality and for the two combined modalities. Results are presented for each of the two operating thresholds. The data indicate that for either operating threshold, adding MBI tomosynthesis notably improves specificity and PPV compared with the specificity and PPV of x-ray tomosynthesis alone.

Table 1

Histologic and Imaging Results for the 21 Lesions Sampled at Biopsy

Tumor Status and Type	No. of Lesions	DMT Result*
Benign		
Lobular carcinoma in situ	1	0/1
Atypical ductal hyperplasia	1	0/1
Fibroadenoma	2	0/2
Fibrocystic changes	7	0/7
Papilloma	2	0/2
Radial scar	1	0/1
Malignant		
Ductal carcinoma in situ	2	1/2
Infiltrating ductal carcinoma	3	3/3
Poorly differentiated carcinoma	2	2/2

* For each lesion type, we have listed the fraction of times that DMT was negative for benign lesions and positive for malignant lesions.

Table 2

Performance Metrics for Each Modality Alone and for the Two Modalities Combined

Metric	Score >3 Was Positive			Score >4 Was Positive		
	X-ray Only	MBI Only	Dual Modality	X-ray Only	MBI Only	Dual Modality
Sensitivity	86 (6/7)	86 (6/7)	86 (6/7)	57 (4/7)	71 (5/7)	71 (5/7)
Specificity	57 (8/14)	100 (14/14)	100 (14/14)	86 (12/14)	100 (14/14)	100 (14/14)
PPV	50 (6/12)	100 (6/6)	100 (6/6)	67 (4/6)	100 (5/5)	100 (5/5)
NPV	89 (8/9)	93 (14/15)	93 (14/15)	80 (12/15)	88 (14/16)	88 (14/16)
Accuracy	67 (14/21)	95 (20/21)	95 (20/21)	76 (16/21)	90 (19/21)	90 (19/21)

Note.—Metric values are percentages; data in parentheses are numbers of lesions. NPV = negative predictive value.

Figure 2 shows example images obtained in a patient in whom cancer was not detected at the clinical examination but was detected by means of DMT scanning. On the basis of microcalcifications visible on her screening mammogram, the patient was scheduled for biopsy of a region at the 9 o'clock position in her right breast. Before the biopsy, she underwent DMT scanning. Although the biopsy result was negative (as were the DMT results in that region of the breast), the DMT scan showed an area of focal uptake in a radiographically dense region of the right breast at the 10 o'clock position. Figures 2a and 2b are x-ray tomosynthesis and MBI tomosynthesis sections, respectively, located at the same depth within the breast, and Figure 2c shows the two sections fused. The region of focal tracer uptake is evident on the MBI tomosynthesis section and the fused image. On

the basis of the DMT scan, further clinical evaluation was performed, and a second biopsy in the region of focal uptake was performed with US guidance. The result was high-grade ductal carcinoma in situ with comedonecrosis.

Discussion

Pilot clinical evaluation of this DMT system suggests that it is a feasible and accurate method with which to detect and diagnose breast cancer and that specificity and PPV can be improved by adding MBI tomosynthesis to x-ray tomosynthesis. Hybrid systems permit unambiguous correlations to be made between the structural and functional image data. Systems such as the DMT scanner that are designed specifically for three-dimensional multimodality breast imaging could, in the context of breast cancer, make

Figure 2

Figure 2: (a) X-ray tomosynthesis section from the DMT scan in a 52-year-old woman who was scheduled to undergo breast biopsy because of suspicious-looking microcalcifications visible on her screening mammogram. (The microcalcifications lay at a different depth in the breast than the section shown.) The section was 1 mm thick. Mediolateral oblique breast compression was used. The overall compressed breast thickness was 6.6 cm. (b) Gamma ray tomosynthesis section located at the same depth within the breast as the section shown in a. The region of focal uptake corresponds to the location of high-grade ductal carcinoma in situ comedonecrosis. This cancer was not detected at clinical examination. Note that its location coincides with that of the radiographically dense parenchyma in a. (c) Merged sections from a and b show the location of ductal carcinoma in situ (arrow). The circle indicates the region in which biopsy was performed on the basis of the clinical examination results. Results of that biopsy were negative.

possible some of the advances in tumor detection, localization, and characterization that are now being observed in whole-body three-dimensional hybrid systems, such as positron emission tomography (PET)/computed tomography (CT) and single photon emission computed tomography (SPECT)/CT. The strength of the DMT approach is that the MBI tomosynthesis scan depicted a clinically occult lesion in a region of radiographically dense fibroglandular tissue, and the fused x-ray tomosynthesis images yielded an anatomic reference with which to identify exactly which region of the breast contained the lesion, thereby permitting subsequent localization and biopsy by means of US.

Integrated imaging systems may be especially important in multimodal breast imaging, since the malleable na-

ture of the breast results in changes in shape with changing gravitational or compression direction, thereby making unambiguous correlation between features in the two image sets obtained with separate scanners difficult or impossible. In x-ray tomosynthesis, three-dimensional imaging inherently improves the contrast between breast lesions and normal tissue by reducing superposition of fibroglandular breast tissue in the section images. Although it has not been quantified in this study, MBI tomosynthesis might, in a similar fashion, result in a reduction in the superposition of heterogeneous radiotracer background from uptake in normal breast tissue compared with planar MBI.

Results of phantom studies performed at the University of Virginia to assess the value of multiple-view MBI

relative to single-view planar MBI show that in a mildly compressed breast, imaging geometry limited-angle tomography improves the contrast and detectability of deep-seated lesions by reducing the negative effect of tracer uptake in the overlying tissue (28). The dependence of contrast and SNR on the angular range is a function of the location of the lesion inside the breast. For angular ranges less than 90°, the contrast and SNR are substantially better in all multiple-view images than in a single-view image. Lesion contrast increases substantially as the number of views is increased from one to 10, with more modest increases beyond 10 views. For a fixed number of views, both the image contrast and the SNR in the reconstructed sections decrease with increasing angular range. The reduction

in contrast and SNR at higher angular range is much greater for deeper lesions and for a fewer number of views. Predictably, the spatial resolution in the direction of compression is degraded as the angular range is decreased.

Integrated, multimodal, three-dimensional breast imaging systems are being developed by other investigators. Crotty et al (38) and Brzymialkiewicz et al (39) are developing a hybrid SPECT/CT scanner for use in dedicated breast imaging. In their system, the patient lies in the prone position, and the noncompressed breast is pendant through a hole in the table, with the x-ray and gamma subsystems below. The gamma camera is mounted on a goniometer that makes complex three-dimensional camera orbits possible.

Researchers at the University of California-Davis recently described early human tests of a prototype dedicated prone breast PET/CT scanner. The scanner uses two opposing planar PET detectors that provide a transaxial field of view of 11.9 cm and an acquisition time of approximately 10 minutes per breast. For CT scanning, 500 views across 360° are imaged across 16.6 seconds. Among the four subjects with five biopsy-proved cancers who underwent scanning, both modalities yielded true-positive results in two of five lesions, with false-negative results in two of five lesions for CT and one of five lesions for PET (40).

Investigators at the University of Michigan have developed an integrated system that permits x-ray tomosynthesis and three-dimensional US images to be obtained with the breast in the same geometry. Software then permits volumes of interest drawn in the volumetric image of one modality to automatically generate the corresponding volumes of interest in image obtained with the other modality (41).

X-ray tomosynthesis scanners will become commercially available soon and are likely to replace an increasing fraction of existing planar digital mammography units over the next decade. An adjunct compact gamma camera capable of MBI could be mounted on an upright x-ray tomosynthesis scanner

relatively inexpensively and could be made available either as an accessory at the time of scanner installation or as an optional add-on at a later date. Planar breast scintigraphy with dedicated cameras already has been approved by the Food and Drug Administration, so the type of DMT breast scanning described here could move quickly to the clinical setting. The design of this system, which is based on an upright gantry configuration, is compatible with most existing breast imaging facilities in terms of floor space requirements and room layout.

Although the results of this pilot study are encouraging, it is a small study, and more experience with DMT breast scanning will be necessary to optimize subject positioning and acquisition protocol, as well as to assess more precisely the incremental benefit of DMT relative to x-ray tomosynthesis alone. A possible limitation of this study is recall bias, since the study reader was involved in patient care for some of the enrolled subjects. However, the effect is thought to be minimal because (a) reading took place more than 4 months after patient care and (b) it has been shown that even if a study includes mammograms that radiologists have previously read, they do not remember most mammograms showing cancer that they have interpreted, either correctly or incorrectly, after they are mixed with mammograms showing cancer that were interpreted by other radiologists (42). Furthermore, in this study, the radiologist was blinded to the mammograms during the reader study and viewed only the DMT images.

Potential improvements to the DMT scanner itself include shorter x-ray scanning time and larger mutual field of view. The x-ray tomosynthesis scanning time now is determined primarily by the readout time of the detector, which was developed for single-shot digital mammography. At the present time, the mutual field of view is limited by that of the gamma camera, which is somewhat smaller than that of the x-ray component. This limitation could present difficulties in imaging large breasts with a single compression. In addition,

both detectors are thicker than optimal, resulting in difficulty in positioning for a small fraction of women with short body habitus and/or limited ability to turn their head to the side. Thus, future improvements include increasing the x-ray detector readout rate, increasing the gamma camera active area, and decreasing the thickness of both detectors.

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