



Molecular Breast Imaging for Screening in Dense Breasts: State of the Art and Future Directions

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OBJECTIVE. The purposes of this review are to discuss the motivation for supplemental screening, to address molecular breast imaging (MBI) radiation dose concerns, and to provide an updated guide to current MBI technology, clinical protocols, and screening performance. Future directions of MBI are also discussed.

CONCLUSION. MBI offers detection of mammographically occult cancers in women with dense breasts. Although MBI has been under investigation for nearly 15 years, it has yet to gain widespread adoption in breast screening.

Breast density notification legislation is intended to directly inform patients of the potential for dense breast tissue to mask cancers on mammography and to recommend discussion of supplemental screening options with their primary care provider [1]. This legislation was championed by advocates for patients who were diagnosed with advanced breast cancer after years of negative mammography examinations and who had never been informed of their own breast density or its impact on mammography [2, 3].

The breast imaging community, however, has long been aware that breast density influences mammographic performance, with early findings showing association of density with interval cancers, reader uncertainty, and delayed diagnosis [4–6]. Such findings led to inclusion of breast composition descriptors in the American College of Radiology BI-RADS lexicon that could be used to communicate predicted mammographic performance via the interpreting radiologist's report [7]. The original four composition patterns published in 1993 were as follows: The breast is almost entirely fat; there are scattered fibroglandular densities that could obscure a lesion on mammography; the breast tissue is heterogeneously dense, which may lower the sensitivity of mammography; and the breast tissue is extremely dense, which lowers the sensitivity of mammography.

Until recently, the degree to which density actually obscures lesions and lowers the sensitivity of mammography has been unclear.

Sensitivity describes the probability of detecting a cancer when it exists. A typical reference standard used to establish whether a cancer exists is the total number of invasive cancers or ductal carcinoma in situ ascertained by tissue diagnosis within 365 days of the screening test and before the next screening [8, 9], although reference standards can vary considerably across studies [10]. With this method, registry data from the Breast Cancer Surveillance Consortium show an overall sensitivity of digital mammography of 84%, with similar sensitivity in dense breasts (82–84%) [9]. However, in studies that include more sensitive supplemental screening tests, mammographically occult cancers are revealed that would not have otherwise manifested during the study interval, creating a more accurate reference standard. In such clinical trials performed primarily in women with dense breasts or elevated risk for breast cancer or both, the sensitivity of mammography was shown to be 25–50%, considerably lower than the sensitivity derived from trials relying on mammography as the sole imaging test [11–17].

Density has also been independently associated with breast cancer risk, even after accounting for masking of cancers [18]. Furthermore, density is highly prevalent, with between 35% and 50% of screening-aged women estimated to have dense breasts [19–21]. These factors taken together make a strong case for offering supplemental screening to women with dense breasts.

Currently there is no consensus on which modality, if any, should be recommended

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Fig. 1—Photograph shows Discovery NM 750b molecular breast imaging unit (GE Healthcare) with mounted biopsy accessory. Biopsy option is 510(k) pending at U.S. Food and Drug Administration. It is not for sale in United States and is not CE (European Conformity) marked. CZT = cadmium zinc telluride. (Courtesy of GE Healthcare)

for supplemental screening in women with dense breasts [22]. Digital breast tomosynthesis, which was initially considered a supplemental test, is now rapidly being adopted for primary screening [23]. The most widely offered supplemental test is whole-breast ultrasound, whereas MRI is recommended for higher-risk women [24]. Molecular breast imaging (MBI) is a nuclear medicine technique that uses dedicated gamma cameras to image the physiologic uptake of a radiopharmaceutical, typically ^{99m}Tc -sestamibi, in the breast. MBI is capable of detecting mammographically occult cancers, particularly in women with dense breasts [16, 17, 25–30]. Studies directly comparing MBI to other supplemental modalities in a screening setting are yet to be done, but a comparison of available data suggests that MBI could offer a favorable incremental cancer detection rate and false-positive rate at acceptable cost [31].

Molecular Breast Imaging Technology

A detailed description of the technical aspects of various dedicated nuclear breast imaging systems has been previously provided [32]. Currently, three vendors supply U.S. Food and Drug Administration (FDA)-approved dedicated gamma cameras for breast imaging.

The Dilon 6800 (Dilon Technologies) is referred to as a breast-specific gamma imaging (BSGI) system. BSGI uses a scintillating sodium iodide (NaI) detector as does a conventional gamma camera, but instead of one

large crystal, it uses an array of pixelated crystals coupled to specialized position-sensitive photomultiplier tubes. The compact design of BSGI (15 × 20 cm FOV) enables positioning of the breast directly on the detector, analogous to mammography. Early studies showed improved detection of small breast lesions with BSGI over conventional systems [33].

The latest generation of dedicated gamma cameras uses solid-state cadmium zinc telluride (CZT) detectors. These systems have adopted the term “molecular breast imaging (MBI)” or “direct-conversion MBI (DC-MBI).” The terms MBI and BSGI are sometimes used interchangeably despite important technologic differences. Two commercial MBI systems are available: the LumaGem (Gamma Medica) and the Discovery NM 750b (GE Healthcare). Both are dual-head cameras in which the breast is lightly compressed between two opposing CZT detectors. In a study that evaluated potential benefits of adding a second CZT detector head to an MBI camera, a dual-head system was shown to improve detection of small lesions over a single-head system [34]. With redesigned collimators specific to a dual-head design, the system was shown to simultaneously retain both high count sensitivity and high spatial resolution over the typical range of breast sizes [35].

MBI systems using CZT detectors confer advantages over BSGI systems with NaI crystals, including improved count sensitiv-

ity, energy resolution, spatial resolution, and lesion detection [36, 37]. Importantly, the use of dual-head CZT detectors has been shown to provide at least a 2.5-fold reduction in the necessary injected activity to perform MBI (from 20 to 30 mCi to < 8 mCi ^{99m}Tc -sestamibi) [38, 39]. Some data suggest that BSGI may not offer acceptable image quality at these reduced doses [37, 40], although a recent retrospective review of BSGI in the diagnostic setting suggests that similar sensitivity for breast cancer is obtained in patients with administered activities of 7–10 versus 15–30 mCi [41].

Because MBI and BSGI can identify lesions that cannot be visualized on mammography or targeted ultrasound, direct biopsy capability is desired. In a report of 1585 women presenting for screening MBI, 47 (3%) underwent biopsy of a lesion detected only on MBI; 35 of these 47 (74%) were biopsied with ultrasound guidance, but 12 of 47 (26% or 0.8% of the screening cohort) needed MRI to localize the lesion [31]. Currently, the only commercially available FDA-approved biopsy unit for gamma imaging is configured for the BSGI system (GammaLoc, Dilon Technologies). This biopsy system uses a set of angled collimators to perform stereotactic localization and has been previously described [42]. Biopsy capability for the LumaGem MBI system is currently in development. A biopsy unit for the Discovery NM 750b has been recently submitted to the FDA for 510(k) clearance. This unit is a self-contained accessory, mounted on the dual-head system after moving the upper detector head upward, that includes an angled pair of CZT detector modules for obtaining stereotactic views (Fig. 1).

Molecular Breast Imaging Procedure Low-Dose Imaging Protocol

An MBI examination requires IV injection of a single-photon emitting radiopharmaceutical, ^{99m}Tc -sestamibi, which emits 140-keV gamma rays and has a 6-hour physical half-life. First introduced in 1991 as a myocardial perfusion tracer, ^{99m}Tc -sestamibi has a long history of safe use, with few contraindications other than prior allergic reaction to sestamibi and pregnancy. Adverse reactions to ^{99m}Tc -sestamibi are rare (1–6 events per 100,000 injections) and are mild in severity (e.g., flushing, rash, metallic taste) [43, 44].

Nuclear medicine technologists who have received additional training in mammographic positioning techniques typically perform

the MBI examination. Assistance in positioning patients for a minimum number of 25 cases has been suggested [45]. It may be feasible to have mammography technologists acquire the images after the patient has received the injection from a nuclear medicine technologist.

Patient preparation is not required before MBI, although recent studies have shown that if patients are in a fasting, resting, and warm state at the time of injection, uptake of ^{99m}Tc -sestamibi in breast tissue is improved [46]. At our institution, MBI patients are asked to fast for 3 hours before injection and be well-hydrated to dilate veins and provide an easier needle stick.

With current CZT-based dual-head MBI, administered activities of 240–300 MBq (6.5–8 mCi) of ^{99m}Tc -sestamibi are routinely used [17, 25]. Recent studies of BSGI have reported using administered activities of between 260–500 MBq (7–13.5 mCi) [26, 41]. Because sestamibi can adhere to plastic syringes, residual activity remaining in the syringe after injection can be on average 20% of the dispensed activity and should be measured to accurately assess administered activity to patients [47]. The feasibility of using administered activities as low as 150 MBq (4 mCi) of ^{99m}Tc -sestamibi has been shown [38, 39], but further studies are needed to ensure that adequate image quality can be reliably achieved at this dose. Consistent patient

preparation and selection of low-residual syringes will likely help attain this goal.

Image acquisition can begin nearly immediately (within 5 minutes) after injection because ^{99m}Tc -sestamibi is rapidly circulated and taken up by breast tissue and the concentration in breast tissue remains generally constant over the course of the MBI examination [39]. Standard craniocaudal and mediolateral oblique projections of each breast are acquired with the breast under gentle compression, with acquisition time of 7–10 minutes for each of the four projections [17, 25]. The MBI examination is generally well-tolerated by patients; during acquisition, patients are seated, can breathe normally, and may watch a video or listen to music.

Molecular Breast Imaging Interpretation

MBI examinations are recommended to be interpreted by radiologists specializing in breast imaging because of the frequent need to correlate MBI findings with other breast imaging and to direct any further recommendations for workup and biopsy. Analysis of 173 patients with positive supplemental screening MBI examinations showed that 54 (31%) could be explained as benign by comparison with a recent mammography examination and review of clinical history (e.g., uptake in a previously biopsied fibroadenoma) [31].

To facilitate standardized interpretation of MBI examinations, a lexicon for MBI was

developed using a BI-RADS-like structure [48]. High interobserver agreement and diagnostic accuracy were obtained after radiologists completed a 2-hour training session [49]. On the basis of this work, a training module for MBI was recently developed and is now available for free use through the American College of Radiology. This online resource includes more than 100 MBI cases, including interactive cases with quizzes enabling the learner to assess MBI interpretation skills and didactic modules for both radiologists and technologists.

Although the MBI lexicon parallels the BI-RADS lexicon, further research is necessary to fully assess the predictive value of lesion descriptors and assessment codes. For example, a review of category 3 assessments on MBI showed a malignancy rate of 5% [31]. This is greater than the less than 2% chance of malignancy established in the mammography and ultrasound literature [50, 51] and highlights the necessity to determine the types of MBI uptake that necessitate biopsy rather than short-term follow-up imaging.

A consideration for radiologists seeking to integrate supplemental screening into their practice is the impact of an additional modality on their workflow. With only eight images to interpret (bilateral craniocaudal and mediolateral oblique views from two detector heads) that are displayed on a single

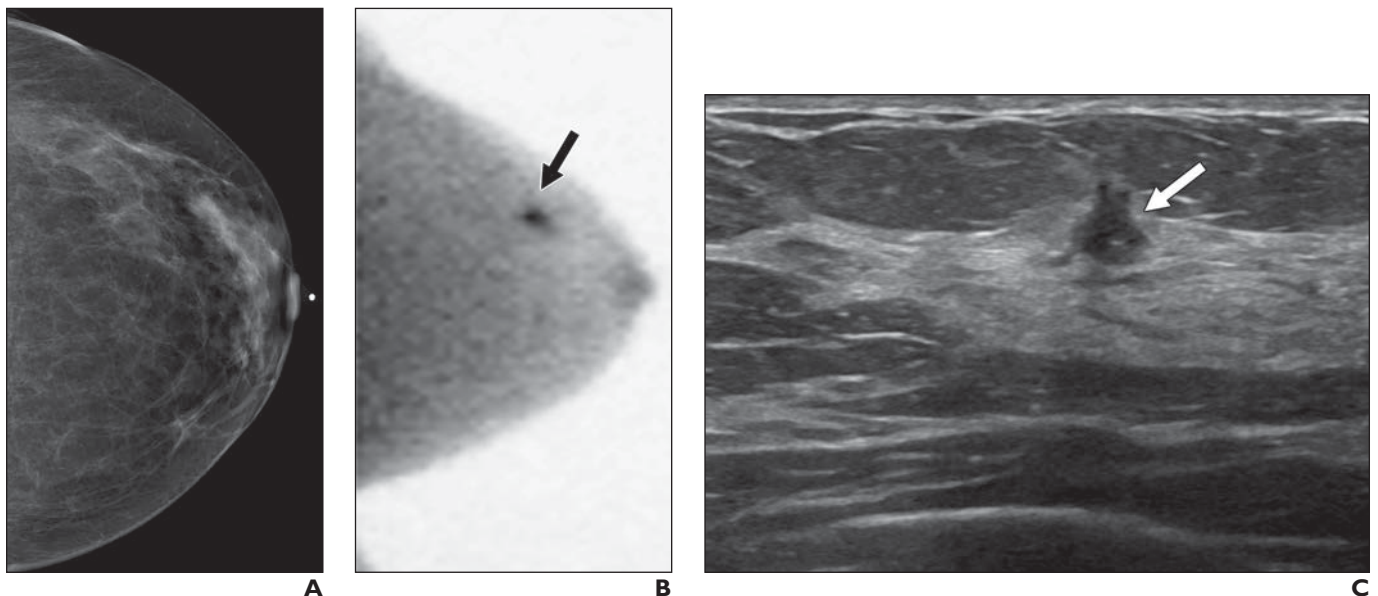


Fig. 2—Supplemental screening molecular breast imaging (MBI) examination detects mammographically occult cancer in 47-year-old woman with family history of mother with postmenopausal breast cancer. (Courtesy of Moch A, Capital Health Medical Center-Hopewell, Pennington, NJ)
A, Left craniocaudal projection from mammography study shows heterogeneously dense tissue and was interpreted as negative.
B, Left craniocaudal projection from MBI screening performed with 8 mCi of ^{99m}Tc -sestamibi and 10-minute acquisition shows intense uptake in 7-mm mass (arrow).
C, Targeted ultrasound image shows 7-mm solid hypoechoic irregularly margined mass (arrow). Biopsy was performed with ultrasound guidance, yielding invasive ductal carcinoma. Subsequent lumpectomy showed 6-mm invasive ductal carcinoma.

TABLE 1: Summary of Literature Examining Molecular Breast Imaging (MBI) and Breast-Specific Gamma Imaging (BSGI) as Supplemental Screening Techniques

Study	Participant Inclusion Criteria	Administered Activity of ^{99m} Tc Sestamibi	ICDR		Size of Cancers Detected Only by MBI or BSGI (Median, Range) (cm)	Additional Recall Rate ^a	PPV3 of MBI or BSGI Findings
			Invasive Cancer and DCIS	Invasive Cancer Only			
MBI, Rhodes 2011 [16]	Dense breasts; at least one additional breast cancer risk factor	740 MBq (20 mCi)	7.5	5.3	1.1, 0.4–5.1	5.9%	28%
MBI, Rhodes 2015 [17]	Dense breasts	300 MBq (8 mCi)	8.8	6.9	0.9, 0.5–4.1	6.6%	33%
MBI, Shermis 2016 [25]	Recent negative mammogram; dense breasts; primarily < 20% lifetime risk by Gail or Tyrer-Cuzick models	300 MBq (8 mCi)	7.7	6.5	1.0, 0.6–2.4	8.4%	19%
BSGI, Brem 2016 [26]	Recent negative mammogram; at least one breast cancer risk factor	590–1190 MBq (16–32 mCi) or 260–500 MBq (7–13.5 mCi)	16.5	7.1	2.5, 0.3–4.0	25%	14.4%
MBI, Hruska 2012 [53]	Receiving ^{99m} Tc-sestamibi injection for myocardial perfusion scanning	1850 MBq (50 mCi) ^b	13.1	9.8	0.6, 0.2–1.2	7.2%	44%

Note—ICDR = incremental cancer detection rate of MBI or BSGI relative to screening mammography in number of women diagnosed with cancer per 1000 women screened, DCIS = ductal carcinoma in situ, PPV3 = proportion of positive findings on MBI or BSGI that resulted in a diagnosis of malignancy.

^aRefers to proportion of patients recalled due to screening MBI or BSGI findings beyond the proportion of patients already recalled for screening mammography findings.

^bPatients received between 666–2035 MBq of ^{99m}Tc-sestamibi for myocardial perfusion imaging; the median administered dose was 1850 MBq. Images were acquired for 3 min/view.

screen, the interpretation of MBI is less complex and more rapid than screening tomosynthesis, automated whole-breast ultrasound, and MRI, each of which requires review of hundreds to thousands of images.

Molecular Breast Imaging Screening Evidence

Supplemental MBI screening of women with dense breasts has been incorporated into both academic and community-based clinical practices. Example cases from MBI use in practice are shown in Figures 2–4. A summary of studies evaluating the performance of screening MBI is provided in Table 1.

Two prospective single-center trials performed at an academic medical center have examined MBI as a supplement to mammography in women with dense breasts [16, 17]. In both of these trials, asymptomatic women presenting for screening mammography were offered supplemental MBI if they were known to have dense breasts on the basis of a prior mammography study. In the first trial of 936 women, MBI was performed using a conventional administered activity of 20 mCi of ^{99m}Tc-sestamibi [16]. After several modifications to the MBI system to enable use of reduced radiation doses [35, 38, 39], a second trial of similar design was performed in 1585 women, using 8 mCi of ^{99m}Tc-sestamibi ad-

ministered activity for MBI [17]. With this low-dose MBI protocol and a dual-head CZT gamma camera, the addition of low-dose MBI increased cancer detection by 8.8 per 1000 women screened.

In these two prospective trials, adding supplemental MBI to screening mammography resulted in a similar rate of additional recalls (5.9% and 6.6%) and similar rate of malignancy per biopsy for MBI findings (positive predictive value [PPV3], 28% and 33%). In an analysis that considered the costs of screening examinations, diagnostic imaging workup, and biopsies performed, the cost per cancer detected was lower for screening with mammography and MBI together relative to mammography alone [31].

Comparable results were reported from a retrospective review of a large community practice in which MBI was performed in 1696 patients who had negative findings on mammography, had dense breast tissue, and were not considered high risk (92% of patients were below 20% lifetime risk by Gail and Tyrer-Cuzick models) [25]. In this setting, an additional 8.4% of patients were recalled due to MBI findings, and MBI detected 7.7 cancers per 1000 women screened.

Another retrospective review reported the performance of BSGI in women with recent negative mammography findings and consid-

ered at increased risk due to one or more risk factors, primarily including personal or family history of breast cancer [26]. BSGI screening in these women resulted in an incremental cancer detection rate of 16.5 cancers per 1000 women screened. BSGI supplemental screening led to additional recalls in 25% of patients, considerably higher than the recall rate reported for MBI studies (5.9–8.4%). This difference may be partially explained by a known greater likelihood of radiologists to recall patients with multiple risk factors [52].

Additional screening evidence was provided from a study in which women undergoing myocardial perfusion imaging with ^{99m}Tc-sestamibi were offered MBI. In 306 screening patients (asymptomatic with negative prior mammography), 22 (7.2%) were recalled because of MBI findings, with four cancers detected, resulting in an incremental cancer detection rate of 13.1 cancers per 1000 women screened [53].

One important measure of supplemental screening effectiveness is the relative detection of clinically important cancers versus noninvasive cancers that may contribute to overdiagnosis. Of the reported 41 malignancies detected only by supplemental MBI screening, 31 (76%) were invasive and 10 (24%) had invasive lobular histology [16, 17, 25, 53]. The studies also revealed a wide range of tumor

sizes that were occult on mammography in dense breasts. Tumors detected only by MBI were as small as 2 mm but also as large as 5.1 cm. Eighteen of 41 (44%) mammographically occult tumors were at least 1 cm in maximal dimension. Although discussion of mortality reduction is beyond the scope of the published studies, the detection of clinically important disease with supplemental MBI is an important surrogate endpoint.

In contrast to the MBI studies, most of the cancers detected by BSGI screening were DCIS (8/14 [57%]). BSGI also detected benign high-risk lesions such as atypia at the same rate as cancers (16.5 per 1000 women screened). The detection of earlier-stage disease by BSGI may be attributable to the use of higher administered activity in 75% of the study population, which may have aided in detection of subtler findings.

Radiation Concerns

A persistent barrier to MBI acceptance is concern about its radiation risks from the injected radiopharmaceutical [54–56]. Because ionizing radiation can cause carcinogenic effects in humans, it is prudent to strive for ways to minimize radiation exposure and follow the ALARA (as low as reasonably achievable) principle. For tests used for screening of healthy individuals, minimizing radiation risks is even more important. In the range of

radiation doses typically used in medical imaging (effective doses < 25 mSv), however, the likelihood of causing carcinogenic effects is extremely low and possibly nonexistent. Attempts to calculate radiation risk from mammography and MBI have shown that the hypothetical risk of each is much less than the anticipated benefit [56, 57].

Examination of data from atomic bomb survivor studies has shown that with effective doses above of 100 mSv, there is a quantifiable increase in cancer risk [58]. Because of a lack of data at lower doses, this association of high doses and cancer induction is extrapolated down to calculate risk at lower doses. This is the basis of the linear no-threshold (LNT) model, which assumes there is no radiation dose below which risk does not exist. The use of LNT at low doses has been widely criticized [59]. Although it is reasonable to use LNT for the most conservative radiation safety purposes, it is unlikely to represent the true biologic relationship between radiation dose and cancer induction.

The lowest levels of radiation in our environment are from background radiation (excluding medical), which range from 2 mSv to more than 10 mSv per year in the United States [60]. At these dose levels, no carcinogenic effects have ever been shown, and in fact, some data tend to show a hormesis effect (i.e., those receiving the highest natural

background doses have lower overall cancer incidence) [61]. Between the range of 10–100 mSv, there is a lack of statistically reliable data to support either a hormesis effect or a carcinogenic effect, even in the largest epidemiologic studies [59, 62]. The American Association of Physicists in Medicine [63] offers the guidance that “doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent.” The Health Physics Society has issued similar guidance [64].

The effective dose (which takes into account relative sensitivities of all irradiated organs in the body) from MBI performed with 8 mCi of ^{99m}Tc-sestamibi is approximately 2.4 mSv, whereas the effective dose of mammography and tomosynthesis is typically between 0.5 and 1.2 mSv. Although the dose of MBI is technically a factor of two to fivefold that of the dose from mammography, the doses from both examinations are at least an order of magnitude smaller than doses at which consideration of risks from radiation are warranted (above 50–100 mSv). Hence, the notion of comparing low radiation doses of MBI and mammography in deciding which modality best serves the needs of the patient [56] has little merit. Better education on effects of ionizing radiation doses in the medical imaging range is a key aspect to ensuring that patients and providers do not discount valuable screening tools under the misguided impression that they carry a significant radiation risk [65, 66].

Future Directions

Clinical Trials

Studies to date have only examined the performance of MBI as a prevalence screen and as a supplement to mammography. More evidence is needed to determine the best screening interval for MBI (e.g., annually or biennially) and to determine whether MBI screening could be alternated with mammography rather than supplement mammography. Head-to-head evaluations of MBI with other supplemental screening technologies, in the same population of women, are needed to directly compare the strengths and weaknesses of each modality. Such trials are complex and costly to carry out.

Reported incremental cancer detection rates for supplemental screening of dense breasts are generally higher for functional techniques of MBI and MRI (8–10 addition-

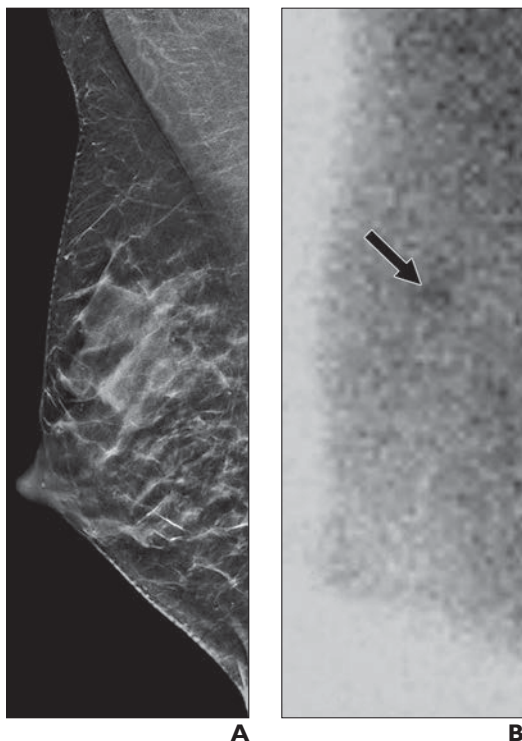


Fig. 3—Supplemental screening molecular breast imaging (MBI) examination detects cancer occult on tomosynthesis screening in 44-year-old woman. (Courtesy of Shermis R, ProMedica Breast Care, Toledo, OH)

A, Right mediolateral oblique C-view (Hologic) reconstruction from screening digital tomosynthesis. Examination was interpreted as negative, and heterogeneously dense breast tissue was noted.

B, Right mediolateral oblique projection from MBI screening performed with 8 mCi of ^{99m}Tc-sestamibi and 7-minute acquisition. Subtle finding in right upper outer quadrant (arrow) was noted. Targeted ultrasound identified hypoechoic mass that was biopsied, revealing invasive ductal carcinoma. Size at surgical pathology was 7 mm.

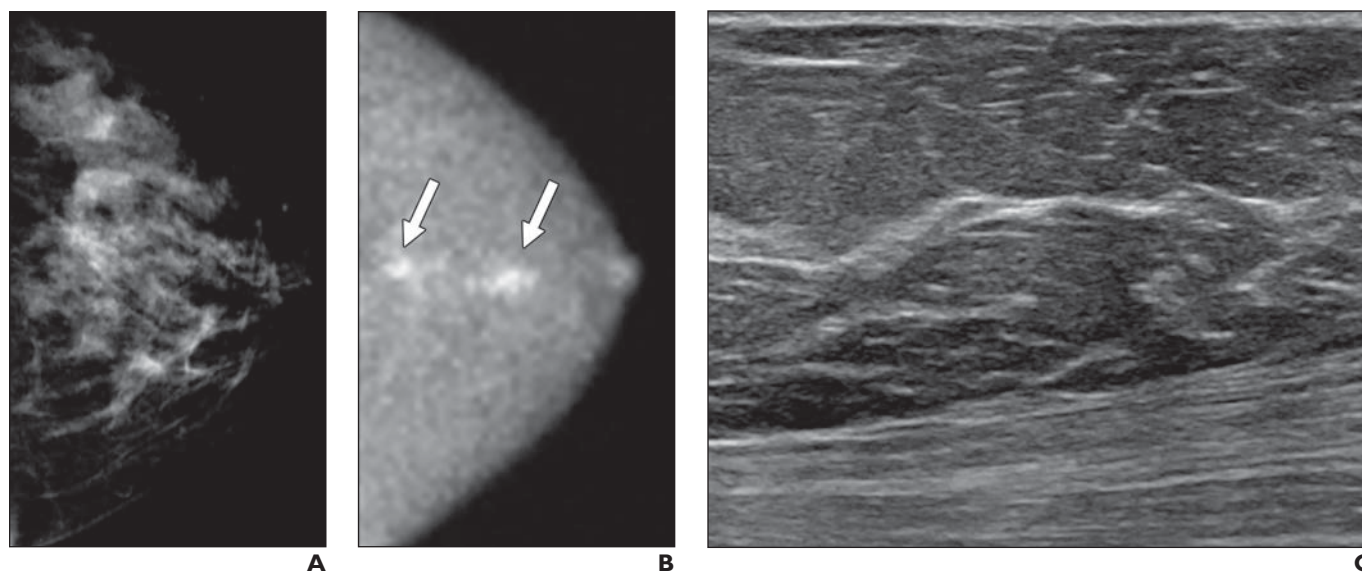


Fig. 4—Supplemental screening molecular breast imaging (MBI) examination detects multifocal breast cancer occult on both mammography and targeted ultrasound in 49-year-old woman with family history of breast cancer. (Courtesy of Schilling K, Lynn Women's Health and Wellness Institute, Boca Raton, FL)
A, Left craniocaudal projection from screening mammography shows heterogeneously dense tissue and was interpreted as negative.
B, Left craniocaudal projection from MBI screening performed with 8 mCi of ^{99m}Tc -sestamibi and 10-minute acquisition is shown. MBI detected two areas of focal uptake (arrows).
C, Targeted ultrasound of left breast was unremarkable so MRI was recommended for patient.
D, Maximum intensity projection from MR examination shows two lesions in left breast correlating with MBI findings (arrows). MRI-guided biopsies yielded invasive ductal carcinoma at both sites.

al cancers/1000 women screened) relative to rates reported for anatomic techniques of whole breast screening ultrasound (2–4 additional cancers/1000 women screened) and tomosynthesis (1–2 additional cancers/1000 women screened) [45]. Given the cost of breast MRI examinations and the complexity of interpretation, MBI offers functional imaging at a lower cost and simpler interpretation that may fill the current gap for women with dense breast tissue who do not qualify by risk for MRI.

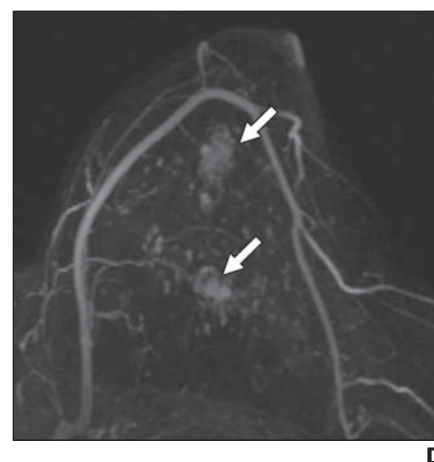
Also, more data are required to drive specific guidance on which patient groups are best served by screening MBI. In our practice, annual screening with digital tomosynthesis is available to all women. Supplemental MBI is offered to those who have dense breast tissue (BI-RADS categories C or D) and either cannot undergo or do not qualify for MRI screening. MRI qualification is determined by American Cancer Society guidelines, which recommend annual MRI for women with at least a 20% lifetime risk by appropriate familial risk models (Tyler-Cuzick, Claus) or other factors such as known mutation in the *BRCA1* or *BRCA2* gene [67]. One practice has implemented a similar workflow but uses software tools with built-in thresholds to determine which

patients are considered to have dense breasts and to triage patients considered at high risk to MRI screening and those considered at intermediate risk to MBI screening [25].

Importantly, high-quality trial data from prospective multicenter studies will be necessary to provide justification for more widespread reimbursement of MBI as a screening tool by insurers and Medicare. Currently MBI is often covered under the 78800 and 78801 Current Procedural Terminology codes for tumor imaging and the A9500 code for the imaging agent ^{99m}Tc -sestamibi, but coverage is dependent on local insurance carriers and varies substantially across the nation. Across our multisite practice, MBI for the indication of dense breast screening is routinely covered by insurers and is also offered as an out-of-pocket charge. Nationally, the average cost of MBI and BSGI examinations has been estimated as \$450. Coverage is a key issue to enable widespread adoption of MBI. Existing disparities in breast cancer outcomes for some minority groups may be further exacerbated if supplemental screening modalities require substantial out-of-pocket expense [68].

Next-Generation Molecular Breast Imaging

With several industry partners now manufacturing and selling MBI equipment, im-



provements in MBI detector design, gantry design, and direct biopsy techniques are anticipated over the next 5 years. Improvements to the CZT detector modules are forecasted to produce gains in count sensitivity, which in turn will enable shorter procedure times and further reductions in the necessary administered activity to patients.

The two commercial MBI systems (Discovery NM 750b and LumaGem) are currently designed with detectors mounted to a fixed gantry that typically requires a dedicated room for MBI examinations. One practice has recently incorporated an MBI system into a mobile semitrailer (personal communication, Kinsella J, Marshfield Clinic, Marshfield, WI). The BSGI system (Dilon 6800) is mounted on a portable cart, similar to the size of an ultrasound system, which allows the BSGI camera to be moved between rooms or facilities as needed. The compact design of CZT detectors permits their place-

ment on small mobile carts, similar to the BSGI system, but would require a redesign of the current MBI systems.

Other areas of nuclear medicine have embraced systems that combine functional and anatomic imaging, such as SPECT/CT and PET/CT because of the proven clinical value from registered images in identifying and ruling out disease. Future development of combined MBI-tomosynthesis or MBI-ultrasound technologies may enable similar benefits, including localization of MBI findings. One such system that combined a dedicated gamma camera into a tomosynthesis unit was previously investigated [69].

Radiotracer Development

Currently ^{99m}Tc -sestamibi is the radiopharmaceutical of choice for use with MBI. It is FDA-approved for diagnostic breast imaging, although it is acceptable to be used off-label for screening applications. It has an excellent safety record, is inexpensive, and is widely available in small shippable generators or in unit-dose format from central radiopharmacies. Given the substantial cost of bringing a new radiopharmaceutical through the FDA approval process, development of alternative radiopharmaceuticals is not likely to occur until there is an established market for MBI that would justify the cost. Several existing compounds, including ^{99m}Tc -tetrofosmin [70] and ^{99m}Tc -DMSA (dimercaptosuccinic acid) [71], are already FDA approved but not specifically for breast imaging and have only been studied on a limited scale in patients with breast disease. Other promising radiopharmaceuticals under study include ^{99m}Tc -maraciclatide [72], which is a marker of angiogenesis, and ^{123}I -labeled estradiol [73].

Conclusion

The implementation of screening with mammography over the past 50 years has contributed to an approximate reduction of 30% in breast cancer mortality. Although this reduction is important, the potential magnitude of benefit from screening is diluted by the differential performance of mammography in nondense versus dense breasts, with up to 75% of cancers in dense breasts being occult mammographically and detectable with functional imaging techniques of MBI or MRI [11–17]. Because close to half of screening-eligible women have dense breasts, compelling potential exists to improve the mortality benefit through targeted supplemental screening of the dense breast population to detect can-

cers that remain occult on mammography, often over multiple screenings.

Despite the promising results described, considerable barriers still exist to the widespread adoption of MBI. To overcome these barriers, the following are required: continued efforts to educate our medical and lay communities about the risk of radiation at low medical imaging doses, improved partnerships between experts in breast imaging and nuclear medicine to facilitate smooth incorporation of MBI into a breast practice, and multicenter trials and reports of clinical experience to further clarify the role of MBI in screening women with mammographically dense breasts.

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