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Screening Algorithms in Dense Breasts: AJR Expert Panel Narrative Review

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Abstract

Screening mammography reduces breast cancer mortality; however, performance and resulting benefits are reduced in dense breasts. Increased breast density also represents an independent risk factor for breast cancer. Digital breast tomosynthesis (DBT), ultrasound (US), MRI, molecular breast imaging (MBI) and contrast-enhanced mammography (CEM) each have demonstrated improved cancer detection in dense breasts compared to 2D-digital mammography (DM). Producing simultaneous reduction of recalls, DBT is the preferred mammographic technique. US further increases cancer detection after DM or DBT and reduces interval cancers, but results in substantial additional false positive findings. MBI improves cancer detection with effective radiation dose about four-fold that of DM or DBT, but still within accepted limits. MRI provides the greatest increase in cancer detection and decreases interval cancers and late-stage disease; abbreviated techniques will reduce cost and improve availability. CEM appears to offer performance similar to MRI, but further validation is needed. Dense breast notification will soon be the national standard: understanding performance of mammography and supplemental modalities is necessary to optimize screening for women with dense breasts.

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Mammography and Breast Density

Mammography is the only imaging modality proven to reduce breast cancer deaths as demonstrated across both randomized controlled trials and observational studies [1, 2]. In the United States, women at average risk for developing breast cancer are advised to commence mammographic screening between ages 40 and 50 and continue annually or biennially through age 70 or as long as the woman is in good health [3-5]. Greatest benefit is observed with annual mammography beginning at age 40 [6]. With peak incidence at younger age, in the 40s [7], it is particularly important to begin annual screening by age 40 for Hispanic and black women.

However, not all women benefit equally from mammography. Mammographic performance is dependent on breast density. Breast density refers to the amount of fibroglandular tissue relative to fat and is determined mammographically, either visually or quantitatively. The Breast Imaging and Reporting Data Systems (BIRADS) 5th edition details four categories of breast density (from least to most fibroglandular tissue): BIRADS category A (fatty), B (scattered), C (heterogeneously dense), and D (extremely dense) [8] (**Figure 1)**. Categories C and D are considered “dense”. While malignant calcifications remain well seen, noncalcified cancers (representing about 45% of invasive cancers [9]) can be masked by dense tissue. Mammographic sensitivities range from 81-93% in fatty breasts, 84-90% with scattered fibroglandular density, 69-81% for heterogeneously dense breasts, to 57-71% for extremely dense breasts [10]**.**

Dense breasts are common. Approximately 36% of women over age 40 have heterogeneously dense breasts and 7% have extremely dense breasts [11]. To date, dense breast notification laws have been enacted in 38 states and the District of Columbia to alert patients to the possibility of a false negative mammogram due to masking by dense breast tissue; specific information and recommendations provided (if any) vary from state to state. National standardized reporting criteria are currently in development by the Food and Drug Administration [12].

Knowledge of a woman’s breast density is critical, as mammographic performance and resultant screening outcomes are significantly impacted. Both an increase in false

positives [10, 13] and a reduction in cancer detection are seen in women with dense breasts [14]. Women with dense breasts demonstrate lower reductions in breast cancer mortality [15, 16] and develop more interval cancers [17] than women with non-dense breasts.

Interval cancers are cancers detected in between recommended screenings, typically in patients presenting symptomatically. Interval cancer rates vary, ranging from 0.8/1000 in annual screening regimens to 2.11/1000 in biennial screening programs [18, 19]. Some interval cancers reflect more aggressive biology (triple negative or human epidermal growth factor 2 (HER2) receptor positive) with rapid growth. Other interval cancers, however, are histologically similar to screen-detected cancers and likely masked in dense breast tissue, going undetected on screening [20, 21]. Interval cancers are 13-18 times more common in women with extremely dense versus fatty breasts [22, 23]. Tracking long-term outcomes from screening, Webb et al [24] reported 609 breast cancer deaths in a cohort screened over 10 years with 60/609 (9.9%) attributable to interval cancers. More effective screening should reduce interval cancers.

In addition to masking cancers, dense parenchyma is one of the strongest and most prevalent risk factors for developing breast cancer [25]. Compared to women with fatty breasts, women with extremely dense breasts are at 4- to 6-fold greater risk [26]. Depending on age and hormonal status, women with heterogeneously dense and extremely dense tissue are 1.4-1.6 and 1.5-2.1 times more likely to develop breast cancer respectively compared to women with scattered fibroglandular density [27].

Data regarding histologic type, aggressiveness, size, and nodal status of breast cancers in dense breasts are sparse. A pooled analysis found younger women (<55 years old) with dense breasts are more likely to have estrogen receptor negative (ER-) tumors compared to older women [28]; increasing tumor size and positive lymph node status correlated with increasing breast density.

Lymph node status remains the most important prognostic factor in breast cancer outcomes. Indeed, across the randomized trials of mammography, only those that increased detection of node-negative invasive cancers produced mortality reduction

[29]. Similarly, reducing late-stage disease contributes significantly to decreased mortality from breast cancer [30].

Although mammography has proven value in reducing breast cancer mortality, the negative impact of breast density on mammographic performance highlights need for more effective screening strategies. Digital breast tomosynthesis (DBT), ultrasound (US), MRI, molecular breast imaging (MBI) and contrast-enhanced mammography (CEM) each have demonstrated value in improving breast cancer detection for women with dense breasts. Metrics associated with improved outcomes [increased incremental cancer detection rate (ICDR), especially of node-negative invasive cancers; reduced interval cancers; and reduced late stage disease] as well as recall rates will be examined for each modality. This comparative analysis of modality performance, in conjunction with information regarding availability and cost, can guide screening strategies in women with dense breasts.

Digital Breast Tomosynthesis

Digital breast tomosynthesis (DBT) is a digital mammographic technique that acquires multiple angled low-dose projection images and reconstructs them into thin (typically 1-mm) slices [31]. By minimizing impact of superimposed structures, tomosynthesis enhances lesion visibility and reduces unnecessary recalls from summation artifacts [32]. Introduction of synthetic reconstructed 2D mammography has allowed radiation dose to remain comparable to conventional 2D-digital mammography (DM) [33] and for DBT with synthetic reconstructions to replace DM.

DBT is proven effective in screening. Multi-institutional retrospective analysis revealed ICDR of 1.2/1000 (95%CI 0.8, 1.6, $p<0.001$) with DBT added to DM [34]. Two prospective European screening trials [35, 36] showed gains of 2.3 and 2.7 cancers/1000 respectively for women screened with DBT. Notably, improved CDR is attributable to additional invasive tumors rather than ductal carcinoma in situ (DCIS), lessening potential for overdiagnosis. Limited data available regarding biologic subtypes of invasive cancers detected only with DBT suggest a trend toward detection of smaller (<2 cm) tumors with luminal A-like characteristics [37, 38]. Using TMIST criteria

[metastatic (including nodal metastasis); ≥ 1 cm and either HER2-positive or ER/PR-negative or both; size ≥ 2 cm], Conant et al [39] reported greater detection of poor-prognosis cancers with DBT than DM, though differences were not significant. Doubling detection of invasive lobular carcinoma has been observed [34], likely due to increased conspicuity of tumor spiculation and architectural distortion.

An ongoing criticism of screening mammography is generation of false positive recalls, which prompt unnecessary additional evaluation and intervention [4]. DBT reduces false positive screening recalls due to summation artifact [32], and also because multiplicity and bilaterality of circumscribed masses is better depicted (allowing benign assessment [40]). In conjunction with gains in cancer detection, simultaneous absolute reduction in recall rate of 2% (relative reduction 15-17%) is achieved with DBT [34-36]. Importantly, Conant et al [39] demonstrated these gains were sustained over multiple rounds of DBT screening. However, interval cancer rates were not significantly impacted by DBT [39], a finding also reported by Bahl et al [41].

Given the inverse relationship between mammographic sensitivity and increasing density, stratification of DBT performance by breast density is of particular interest. **Table 1** summarizes four studies [13, 35, 42, 43] evaluating screening outcomes in women undergoing (DBT plus DM) vs. DM alone, stratified by breast density. DBT consistently increased cancer detection and decreased recalls in both “dense” and “non-dense” tissue. Rafferty et al [43] observed greatest gain in cancer detection and reduction in recalls in women with heterogeneously dense breasts (**Figure 2**). Women with extremely dense breasts experienced no improvement in cancer detection (**Figure 3**), although false-positive recalls were reduced [43]. Osteras et al [42] saw a trend toward improved CDR in women with extremely dense breasts with no reduction in recalls (Table 1). Lowry et al [44] observed reduced recalls and improved CDR on incidence screening DBT (compared to DM) in women with heterogeneously dense breasts but not those with extremely dense breasts.

DBT’s improved cancer detection and reduced recalls compared to DM are expected to produce improved health care outcomes at equivalent or reduced cost [45-47]. There is

now coverage by most major insurance carriers; at least 17 states and the District of Columbia mandate insurance coverage for screening DBT [48]. Despite addition of DBT, limitations in cancer detection persist, particularly in extremely dense breasts. These women would most benefit from supplemental screening strategies.

Screening Ultrasound: Technique

Unlike other methods of supplemental screening, screening US requires neither ionizing radiation nor intravenous contrast. There are several methods of performing whole-breast ultrasound (WBUS), including physician-performed (usually radiologist) handheld US (HHUS), technologist-performed HHUS, and automated ultrasound (AUS). Training is necessary; for HHUS, a minimum experience of 500 breast US examinations was required of American College of Radiology Imaging Network (ACRIN) 6666 investigators [49]. Billing is currently a “limited” breast US, current procedural terminology (CPT) code 76642, or “complete” breast US, CPT code 76641, which does not specify “screening” or “diagnostic” use, with a charge for each breast (right or left modifier). ICD-10 diagnosis code of R92.2, incomplete examination due to dense breasts, is used together with V76.19 “other screening”. Insurance will typically cover screening US when ordered by a healthcare provider, though deductibles/copays apply in most states.

Handheld methods should use a high-frequency linear array transducer, at least 12 MHz and ideally 17-18 MHz. Surveying is most efficient in transverse and sagittal planes; the axilla can be electively included. For a negative examination, documentation should include at least one image from each quadrant and the retroareolar region, as was validated in the ACRIN 6666 protocol [49]. For simple cysts, a single image is sufficient, and documentation is encouraged to reduce recalls from mammography/DBT (ACRIN protocol required only the largest simple cyst in each quadrant to be documented). For lesions other than simple cysts, orthogonal images should be taken without and with calipers in a manner that captures its longest diameter (often radial, like a clock-hand, along the duct system), with horizontal and anteroposterior diameters documented on that image and horizontal diameter on the orthogonal view. Power

Doppler can be used to document slow flow. Harmonics can help clear artifactual internal echoes in small cysts or clustered microcysts. Elastography can be applied to assess lesion stiffness. A cine loop can be obtained for later review when doing batch reading and can be helpful when technologists performing HHUS are uncertain about vague findings.

Uncommonly, a “technical recall” is needed to distinguish artifactual shadowing at the interface of fat lobules, or intraductal debris, from a true mass. An isolated circumscribed oval hypoechoic or isoechoic mass seen only on US can be assessed as BI-RADS 3, probably benign, but follow-up at the time of annual screening US is reasonable [50]. Failure to document a mass being followed can also prompt a technical recall (at no additional charge).

The most common method of AUS uses a wide (15-cm) curved transducer to acquire transverse images with coronal and sagittal reconstructions. A minimum of 3, and sometimes 5-6, acquisitions are needed to cover the breast. A semi-automated approach uses an automated arm and a standard transducer [51]. A final assessment typically can be rendered with HHUS, including BI-RADS 4 or 5 with biopsy recommendation (and contacting the patient and physician), whereas additional targeted US is needed for the vast majority of AUS recalls; Doppler and elastography are not available during AUS.

Outcomes from Screening US

In women with dense breasts, incremental CDR averages 2.0 to 2.7 per 1000 using either HHUS or AUS technique and 88% of cancers detected only on screening US are invasive [52] (**Figure 4**). With physician-performed HHUS, where detailed, 497/554 (89.7%) of invasive cancers detected were node negative as were 102/123 (82.9%) detected by technologist-performed HHUS and 63/69 (92%) invasive cancers found on AUS [52]. Mean size of invasive cancers ranged from 7-14 mm in nearly every series and invasive lobular cancers represent 15-20% of those detected only by screening US.

On average, about 3% of women will be recommended for biopsy on the prevalence round of screening US [52], with a wide range of 2 to 30% malignancy rates for suspicious findings seen only on ultrasound. Net added recalls from screening US average 7.5% of women with HHUS and 10.6% with AUS [52] and, as with all modalities, are lower with incidence than prevalence screens.

Adding screening US to mammography reduces interval cancer rates in women with dense breasts. The Japanese Strategic Anti-Cancer Randomized Trial (J-START) randomized women aged 40-49 with all breast densities to mammography alone or mammography plus HHUS and showed increased node-negative invasive cancer detection in women receiving screening US and half the interval cancer rate at 0.5 per 1000 [53]. In ACRIN 6666, the interval cancer rate was low at 9/111 (8%) of all cancers across 7473 screening examinations (1.2 per 1000) [54]. Corsetti et al [55] saw an interval cancer rate of 1.1 per 1000 for women with dense breasts when adding screening US, comparable to the 1.0 per 1000 rate for women with fatty breasts using mammography alone. Screening ultrasound has not been proven to reduce late-stage disease.

A few studies have evaluated US after DBT in women with dense breasts, with expected ICDR of 0.9-2.6 invasive cancers per 1000 women screened with HHUS [56-58]. One series reported similar results with AUS after DBT [59].

Barriers to implementing screening US include high prevalence of benign cystic lesions [60], shortage of trained personnel (HHUS), and large numbers of images (AUS). Artificial intelligence may facilitate interpretation of both HHUS and AUS (reviewed in [52]). In women who have screening MRI, there is no added benefit from screening US [61].

Molecular Breast Imaging (MBI)

Molecular breast imaging (MBI) is a nuclear medicine technique (subject to state licensing requirements) that uses a dedicated gamma camera to depict preferential uptake of Tc-99m sestamibi in mitotically-active breast tissue. Commercial MBI

technology includes single-head dedicated NaI cameras (formerly known as breast specific gamma imaging [BSGI]) or cadmium zinc telluride detectors in a dual-head configuration.

The MBI examination entails intravenous administration of Tc-99m sestamibi, typically 8 mCi, with imaging commencing immediately after injection. Patient preparation may include fasting for 3 hours before injection and peripheral blanket warming to increase breast uptake [62]. Bilateral craniocaudal and mediolateral oblique views are acquired for 7 to 10 minutes each (i.e. total time for routine four-view exam 28-40 minutes), with the patient seated and light compression applied to limit motion [62, 63].

Because MBI exploits functional behavior rather than x-ray attenuation, it can detect cancers masked by dense breast tissue [64]. In a single-center prospective trial of 1585 women with dense breasts [65], addition of MBI increased sensitivity to 90% (19/21) relative to 24% (5/21) with mammography alone ($p<0.001$), but decreased specificity, from 89% for mammography, to 83% for mammography plus MBI ($p<0.001$), and led to additional biopsies in 47/1585 (3.0%) women. ICDR from MBI was 6.9/1000 invasive cancers; 8.8/1000 with inclusion of DCIS. Interval cancer rate was 1.3/1000. Shermis et al [66] reported similar results on retrospective review of 1696 women undergoing supplemental screening MBI in clinical practice: after negative DM, MBI yielded an invasive ICDR of 6.5/1000 and overall ICDR 7.7/1000. Across five studies of screening MBI performance encompassing 63 breast cancers, 52 (83%) were detected only by supplemental MBI, of which 37/52 (71%) were invasive; 26/30 (87%) invasive cancers with reported node status were node negative (**Figure 5**) [64]. Cancers undetected by MBI (n=6) included three DCIS, two grade 1 invasive lobular cancers (0.6 cm and 0.7 cm), and one grade 2 invasive ductal cancer (0.3 cm) [64].

The ongoing prospective multicenter Density MATTERS trial compares MBI screening in dense breasts to DBT. Inclusion of two annual screening rounds will provide data currently lacking on MBI's impact on rates of interval cancer and advanced breast cancer (i.e. ≥ 2 cm or node positive).

MBI is an alternative for women who cannot undergo MRI [63]. Billing averages $450 and reimbursement about $300; coverage can require preauthorization. Benefit-to-risk ratios calculated for MBI screening in dense breasts overlap those for mammography [67]; however, concerns regarding radiation risk from MBI persist.

Barriers to use of MBI include the minimum 40-minute exam time and systemic whole-body radiation exposure. Dosimetry models show an effective dose of approximately 2 mSv for MBI versus 0.5 for DM or DBT with synthetic reconstructions; 2 mSv is below annual background radiation (averaging 3.1 mSv) and therefore considered low risk for harmful effects. Work is underway to validate processing algorithms to allow further reductions in administered activity or acquisition time for MBI [68] that may reduce barriers to adoption. Direct biopsy capability is available from one vendor (GE Healthcare, Chicago, IL) and in development for another (CMR Naviscan, Carlsbad, CA) [64].

MRI

Contrast-enhanced MRI is highly sensitive to breast cancer not limited by breast density and without ionizing radiation. Reported sensitivity of breast MRI alone is generally greater than 80%. Specificity ranges from 83 to over 98% and, on incident rounds, typically exceeds 90% [69]. Cancer detection depends on differential vascularity/enhancement and therefore requires use of gadolinium-based contrast. Low rates of adverse events of 0.17% (95%CI 0.15, 0.19) [70] are observed, including cumulative intracranial gadolinium deposition and nephrogenic systemic fibrosis [71]. To date, gadolinium deposition has no clear adverse effects, and is reduced with macrocyclic chelates [71].

Most literature on screening MRI involves high-risk women for whom breast MRI markedly reduces interval cancers and late-stage disease. Across 1592 screens in 501 women, Sardanelli et al [72] reported 16 additional cancers detected by MRI after mammography plus US (ICDR of MRI 10/1000), with 3 interval cancers (1.9/1000).

Vreemann et al [73] reported on 2773 women undergoing 9571 mammogram and MRI examinations. Of 129 screen-detected cancers, 118 were seen on MRI (91.5% sensitivity). Forty-one interval cancers were reported: 16 with symptoms (1.7/1000 exams, the majority in women with pathogenic *BRCA1* mutations) and 25 diagnosed at prophylactic mastectomy. Warner et al [74] observed a 70% reduction in stage II-IV breast cancers in 445 women with pathogenic *BRCA* mutations undergoing screening MRI with one interval cancer in MRI group and 38 in matched comparison group. Average size of invasive cancers in MRI cohort was 0.9 cm vs. 1.8 cm for comparison group ($p<0.001$). Based on 1275 high-risk screening MRI examinations diagnosing 114 cancers [with 10 interval cancers (8.1%)], Heijnsdijk et al [75] predicted mortality reduction of 48-61% with MRI alone. Although MRI has been primarily studied for supplemental screening, there is increasing evidence that mammography provides little additional benefit in some high-risk populations, particularly women with pathogenic *BRCA1* mutations under age 40 [75-77].

Current American Cancer Society [78] and National Comprehensive Cancer Network [79] guidelines recommend screening MRI for women at high risk of breast cancer, to begin at age 25 and to include mammography by age 30 in those with known or suspected pathogenic *BRCA1* or *-2* mutations and that MRI be considered in women with lobular carcinoma in situ or atypical hyperplasia. Screening MRI should stop by age 75 [79]. American College of Radiology guidelines also endorse screening MRI in women with personal history of breast cancer diagnosed by age 50 or dense breasts [80].

There is increasing support for MRI screening for women with dense breasts even without additional risk factors. The MRI substudy from ACRIN 6666 showed an ICDR of 14.7/1000 with MRI after mammography plus US (**Table 2**) [54]. Kuhl et al [81] evaluated supplemental MRI in women with <15% lifetime risk for breast cancer; for the 60% (1282/2120) of women with dense breasts, ICDR was at least 26/1282 (20.3/1000) and 11/1282 (8.6/1000) for prevalence and incidence screens respectively.

The Dutch DENSE trial invited women aged 50 to 75 years with normal screening mammograms and extremely dense breasts to undergo biennial screening with MRI and mammography versus mammography alone [82] with a 59% acceptance rate (similar to the 58% rate in ACRIN 6666 [83]). The first screening round yielded an ICDR from MRI of 79/4783 (16.5/1000), including 64 invasive and 15 DCIS (for an invasive ICDR of 13.4/1000); 55/64 (86%) of invasive cancers were node negative [82]. Use of MRI reduced interval cancer rate from 4.9/1000 to 0.8/1000. Preliminary results from the second MRI screening round demonstrated substantial reduction in both ICDR (5.9 per 1000 overall, 4.1/1000 invasive) and false positive recalls (21/1000 vs. 80/1000) [84]. Barriers to screening MRI include claustrophobia, fear/intolerance of contrast injection, inconvenience, and fear of false positives [83, 85].

Currently, accredited breast MRI protocols require pre-contrast, at least two post-contrast, and a T2-weighted series, resulting in typical scan times of 15 to 30 minutes. To reduce cost and increase availability, Kuhl et al [86] introduced an “abbreviated MRI” (Ab-MRI) using a single pre- and post-contrast T1-weighted sequence with subtraction and maximum intensity projections (**Figure 6**).

Comstock et al [87], in the Eastern Cooperative Oncology Group (ECOG)-ACRIN 1141 multicenter trial, compared prevalent screening Ab-MRI (including T2-weighted images) with incident DBT. Ab-MRI had superior sensitivity (96% vs. 39%) but reduced specificity (87% vs. 97%) among 1444 women with 26 cancers. Ab-MRI alone detected all 17 invasive cancers (16/17, 94% node negative) and 5/6 (83%) DCIS (missing one 7-cm high-grade DCIS seen on DBT); DBT detected 7/17 (41%) invasive cancers and 2/6 (33%) DCIS yielding an ICDR for Ab-MRI of 14/1444 (9.7/1000) and an invasive ICDR of 10/1444 (6.9/1000, p=.002) (Table 2). Additional imaging (recall or short-term follow-up) was 7.5% (108/1444) for Ab-MRI and 10.1% (146 women) for DBT (p=.02). Biopsy rate of Ab-MRI was nearly four-fold DBT (107 vs. 29, representing 7.4% and 2.0% of women respectively) with lower PPV_3 of biopsies (19% vs. 35.5%, p=.08).

While MRI clearly depicts additional cancers, concern regarding overdiagnosis remains. Importantly, MRI depicts relatively more invasive cancers than DCIS [88]. Although MRI

is more sensitive than mammography (89-92% vs. 55-46%) for depicting DCIS [89, 90], it appears relatively insensitive for low- and intermediate-grade DCIS [90, 91], potentially mitigating its contribution to overdiagnosis.

A few states and the District of Columbia require insurance coverage for screening MRI for women with dense breasts, and/or women at high risk; in New Jersey and Pennsylvania, insurance is required to cover screening MRI for extremely dense breasts without other risk factors [48]. Insofar as there is no CPT code for Ab-MRI insurance billing, facilities typically bill patients directly, charging $250-500 [92]. Non-contrast MRI using DWI holds promise [93].

Contrast-Enhanced Mammography

Contrast-enhanced digital mammography (CEDM or CEM), also known as contrast-enhanced spectral mammography, capitalizes on vascular enhancement from injected iodinated contrast to depict cancers on mammography. Craniocaudal and mediolateral oblique views of each breast are obtained at low energy (24-30 kVp) and high energy (typically 40-45 kVp); the latter exploit abrupt increase in x-ray absorption at the k-edge of iodine (~33keV). Two images per view result: the low-energy image mimics standard 2D mammography and a subtracted image shows only areas of enhancement (**Figs. 7, 8**). Overall radiation exposure is approximately twice standard mammography but well within accepted limits. Most data on CEM performance are from patients with newly diagnosed cancer in comparison to MRI. In a meta-analysis of 13 such studies, Xiang et al [94] found overall sensitivity of CEM mirrored MRI at 97%, but specificity was higher with CEM (0.66; 95%CI 0.59**,** 0.71) than with MRI (0.52; 95%CI 0.46, 0.58).

Sorin et al [95] reported results from 611 women undergoing screening CEM, of whom 568 (93%) had dense breasts and 295 (48.3%) had family or personal history of breast cancer. Of 21 malignancies, 11 were seen on mammography and 19 on CEM (ICDR of CEDM 8/611; 13.1/1000; 95%CI 6.2, 21.1). Of eight malignancies seen only with CEM, seven were invasive and two of four with node staging had metastases. Sung et al [96]

reported on 904 women undergoing CEM, 700 of whom had dense breasts (including the 307 women reported in [97]), with 15 (1.7%) women experiencing contrast reactions: one moderate (dyspnea, requiring diphenhydramine), the remainder mild (e.g. nausea or hives). Sixteen cancers were found; 14 (88%) on CEM and two interval cancers (2.2/1000), one seen on MRI and one on screening US 10 months later. Cancer was detected in 12 women with dense breasts, 6 (50%) on low-energy images, and 10 (83%) on CEM. Six of the 12 cancers in dense breasts were seen only on CEM (ICDR of 6/700, 8.6/1000); four invasive, with median size 0.8 cm, all node negative. Overall specificity for CEM was 93.7% with PPV_3 of 15/51 (29.4%). These promising results have prompted initiation of a multicenter trial [98] that will compare performance of CEM to (DBT plus US) in women with dense breasts at average to intermediate risk.

There remain several barriers to CEM adoption. Across 84 publications encompassing results from 14,012 women undergoing CEM, Zanardo et al [99] reported the pooled rate of adverse reactions was 0.82% (95%CI 0.64, 1.05), and staff should be trained in contrast reactions. CEM currently lacks widespread direct biopsy capability for findings not visible on mammography or US, uncommonly resulting in need for MRI-guided biopsy. Most centers utilize the CPT code for 2D mammography for billing CEM; billing and reimbursement for the contrast component is variable.

Consensus Opinions

1) Increased risk for cancer and masking of noncalcified cancers reduce the potential benefit of mammographic screening in women with dense breasts: supplemental screening should be discussed, considering patient tolerance and preferences. **Table 3** summarizes performance characteristics and extent of validation across the modalities discussed. **Figure 9** diagrams current approaches to supplemental screening in the context of other risk factors in addition to breast density.

2) Screening DBT with synthetic reconstructions improves cancer detection, reduces recalls, and is achieved with radiation dose comparable to DM; it is therefore the preferred mammographic technique for women with heterogeneously dense breasts. The sensitivity of mammography in extremely dense breasts, however, as measured by

clinically detected false negatives, is as low as 57% and not appreciably improved by DBT: supplemental screening should be performed

3) While there is a relatively small additional cancer yield from US after mammography or DBT, interval cancer rates are reduced by screening US.

4) MBI improves cancer detection in women with dense breasts, and assessment of impact on interval cancer rates after DBT is in progress, but this approach currently requires a 40-minute exam time and incurs whole body radiation exposure.

5) The most validated approach producing the greatest improvement in cancer detection is contrast-enhanced MRI, even after DBT. Interval cancer rates are decreased by MRI, as is late-stage disease (the latter proven only in high-risk women). Ab-MRI will reduce cost and improve availability, but claustrophobia and other patient tolerance issues must be considered. MRI should stop by age 75 even for high-risk women.

6) Contrast-enhanced mammography appears to have performance characteristics similar to MRI, but further validation is necessary as is improved availability of direct biopsy capability.

Summary

Dense breast notification will soon be the national standard: understanding performance of mammography and supplemental screening options is now incumbent on all physicians to optimize screening for women with dense breasts. Out-of-pocket costs and technology availability influence implementation. In national databases, data directly attributing recalls and cancers detected to each modality used in screening would facilitate both audits and outcomes analyses.

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Table 1. Summary of Incremental Increase in Cancer Detection and Decrease in Recall Rates with Addition of Digital Breast Tomosynthesis (DBT) to 2D-Digital Mammography (DM) in Dense and NonDense Breasts

	Ciatto et al 2013 [35][a]	Rafferty et al 2016 [43][b]	Osteras et al 2019 [42][a,c]	Conant et al 2019 [13][b]
Cancer Detection Rate per 1000				
Nondense				
DM+DBT	8.4 (51/6079)	5.1 (455/89,171)	7.7 (122/15,785)	5.6 (87/15612)
DM	5.6 (34/6079)	4.2 (610/146,910)	6.0 (94/15,785)	4.5 (301/66,664)
Difference (p-value)	2.8 (<0.0001)	0.95 (<0.001)	1.8 (<0.001)	1.1 (0.091)
Dense				
DM+DBT	6.6 (8/1215)	5.8 (495/84,243)	12.5 (106/8466)	7.8 (73/9321)
DM	4.1 (5/1215)	4.5 (597/131,996)	9.7 (82/8466)	5.4 (192/35,309)
Difference (p-value)	2.5 (0.25)	1.4 (<0.001)	2.8 (<0.001)	2.4 (<0.0001)
Heterogeneously Dense				
DM+DBT	NR	6.1 (450/72,481)	12.5 (83/6645)	NR
DM	NR	4.5 (528/113,290)	9.6 (64/6645)	NR
Difference (p-value)		1.6 (<0.001)	2.9 (<0.001)	
Extremely Dense				
DM+DBT	NR	3.9 (45/11,762)	12.7 (23/1821)	NR
DM	NR	3.8 (69/18,706)	9.9 (18/1821)	NR
Difference (p-value)		0.1 (0.88)	2.8 (0.06)	
Recall Rate per 1000				
Nondense				
DM+DBT	39 (233/6028)	79 (6955/89,171)	79 (1246/15,785)	76 (2334/30,839)
DM	45 (273/6028)	90 (12845/146,910)	96 (1515/15,785)	100 (8549/85,275)
Difference (p-value)	-6 (0.0035)	-12 (<0.001)	-17 (<0.001)	-24 (<0.001)
Dense				
DM+DBT	66 (80/1207)	109 (9030/84243)	125 (1061/8466)	105 (2109/20070)
2D	73 (88/1207)	127 (16582/131996)	133 (1126/8466)	135 (5931/44094)
Difference (p-value)	-7 (0.35)	-18 (<0.001)	-8 (<0.001)	-30 (<0.0001)

Heterogeneously Dense				
DM+DBT	NR	110 (7852/72,481)	120 (804/6645)	NR
DM	NR	128 (14,484/113,290)	132 (879/6645)	NR
Difference (p-value)		-18 (<0.001)	-12 (<0.001)	
Extremely Dense				
DM+DBT	NR	98 (1178/11,762)	141 (257/1821)	NR
DM	NR	114 (2098/18,706)	136 (247/1821)	NR
Difference (p-value)		-16 (<0.001)	5 (0.82)	

Abbreviations: DM = two-dimensional full-field digital mammography; DBT = digital breast tomosynthesis; nondense = fatty or scattered fibroglandular density; dense = heterogeneously dense or extremely dense; NR = not reported.

[a] Each patient had both standard DM and DBT exams and served as her own control.

[b] Historical controls for DM results.

[c] Results are reported at the breast level and inferred at the participant level; one woman had bilateral breast cancer.

Table 2. Summary of Results Using Supplemental Breast MRI to Screen Women with Dense Breasts

	ACRIN 6666 Trial [54]	Kuhl et al 2017 [81]	DENSE Trial [82]	ECOG-ACRIN 1141 Trial [87]	
Breast Density	Density C or D[a]	All densities; 60.5% density C or D	Density D	Density C or D	
Risk	≥ 2.5% 5-year risk Claus or Gail or ≥ 1.7% 5-yr risk and extremely dense, or PHBC	Average risk (< 15% lifetime risk by Gail model)	Risk level not specified	5-year risk (BCSC score) determined Median (range) 1.6 (0.3-7.8)	
Type of Conventional Imaging	Film or digital 2D plus US	2D mammography; 1335 (63%) had screening US	2D digital mammography	Tomosynthesis	
Total # patients and MRIs (# women with PHBC)	612 (273 women with PHBC)	2120 (0 women with PHBC)	4783 women and exams (PHBC not reported)	1444 women and exams (8 women with PHBC)	
Modality	Full protocol MRI	Full protocol MRI	Full protocol MRI	Ab-MRI	DBT
Incremental CDR per 1000	14.7 (9/612)	Overall: 15.5 (60/3861) Prevalence screen: 22.6 (48/2120); Incidence screens: 6.9 (12/1741); Prevalence screen in dense breasts only: 20.3 (26/1282)	16.5 (79/4783)	9.7 (14/1444)[b]	0.7 (1/1444)[b]
Incremental Invasive CDR	13.1 (8/612)	14.2 (30/2120 prevalence); 5.7 (10/1741 incidence)	13.4 (64/4783)	6.9 (10/1444)	0
Median size of invasive cancer (mm)	8.5	8	9.5	10.5	Not reported
Percent invasive cancers staged and node negative	100% (7/7)	90% (37/41)	85.9% (55/64)	94.0% (16/17)	Not reported
Recall Rate (Abnormal Interpretation Rate)	25.9% (159/612)	16.3% (346/2120)	9.5% (454/4783)	15.0% (215/1444)	10.1% (146/14444)
PPV_3	23.1% (12/52)	35.7% (61/174)	26.3% (79/300)	19.6% (21/107)	31.0% (9/29)

Sensitivity	87.5% (14/16)	100% (61/61)	95.2% (79/83)	95.7% (22/23)	39.1% (9/23)
Specificity	75.7% (451/596)	95.8% (1986/2072, prevalence) 98.4% (1701/1728, incidence)	92.1% (4329/4700)[c]	86.7% (1220/1407)	97.4% (1371/1407)
Interval Cancer Rate per 1000	NR	0	0.8 (4/4783)	0	NA

Abbreviations used: BCSC = Breast Cancer Surveillance Consortium; PHBC = personal history of breast cancer; DBT = digital breast tomosynthesis; CDR = cancer detection rate; Ab-MRI = abbreviated MRI; NR = not reported; NA = not applicable

[a] BI-RADS breast density categories C = heterogeneously dense; D = extremely dense

[b] Of 17 invasive cancers, 10 were seen only on Ab-MRI and of 6 DCIS, four were seen only on Ab-MRI, one only on DBT and one on both.

[c] Study reports 92.0%; however, it appears that 4 interval cancers were erroneously included in the denominator in the publication

Table 3. Summary of Comparative Impact of Supplemental Screening Beyond 2D Mammography in Women with Dense Breasts and Surrogate Endpoint Validation

Screening Modality	Total N	Incremental CDR per 1000	Incremental Invasive CDR per 1000	% Node Negative	Incremental Recall Rate per 1000	Reduced Interval Cancers	Reduced Late-Stage Disease
Tomosynthesis (DBT)	103,245[a]	1.7[a]	1.4[b]	Not evaluated	-20[a]	No	Not evaluated
Ultrasound (US)	452,743[c]	2.0 to 2.7[c]	1.8 to 2.3[c]	88.6 (635/717)	76 to 106	Yes	Not evaluated
Molecular Breast Imaging (MBI)[d]	4,277	8.1	6.2	85 (23/27)	67	Not yet evaluated	Not yet evaluated
MRI	9,256[e]	16.0	12.1	88 (99/112)	104	Yes	Yes[f]
MRI after DBT	1,444[g]	9.7	6.9	94 (16/17)	215	Not yet evaluated	
Contrast-Enhanced Mammography (CEM)	1,311[h]	10.7	8.4	75 (6/8)	150[h]	Not yet evaluated	Not yet evaluated

Abbreviations used: CDR = cancer detection rate

[a] Detailed in Table 1; CDR of DBT = 682/103,245 (6.61/1000) across four studies [13, 35, 42, 43], vs. 876/176,986 (4.95/1000) for 2D mammography, difference of 1.7/1000; recalls from DBT = 12,280/113,986 (10.77%) vs. 23,727/185,763 (12.77%) for 2D, a difference of 2.0% or 20/1000.

[b] From [43]; not reported in the other studies.

[c] As summarized in [52], results are from 361,562 physician-performed US, 64,018 technologist-performed US, and 27,163 automated screening US examinations, with ICDR averaging: 2 per 1000 for physician-performed handheld US (88% invasive); 2.7 per 1000 for technologist-performed US (86% invasive); and 2.5 per 1000 for automated US (91% invasive) [52].

[d] Across three series [65, 66, 100] limited to women with dense breasts on prior or current mammogram.

[e] Across three series [54, 81, 82] summarized in Table 2. In Kuhl et al [81], ICDR for prevalence screening was 22.6/1000 vs. 6.9/1000 for incidence screens. Other results are for prevalence screens.

[f] Reduced late stage disease has only been demonstrated for women with known pathogenic *BRCA1* or *-2* mutations screened with MRI [74].

[g] Prevalent screening with abbreviated MRI compared to tomosynthesis [87], detailed in Table 2.

[h] Across two series [95, 96]. Cancer results are shown for the 700 women with dense breasts in the series of Sung et al [96], while recall rates include false positive and true positive recalls across all 904 women as results were not distinguished for the subset with dense breasts.

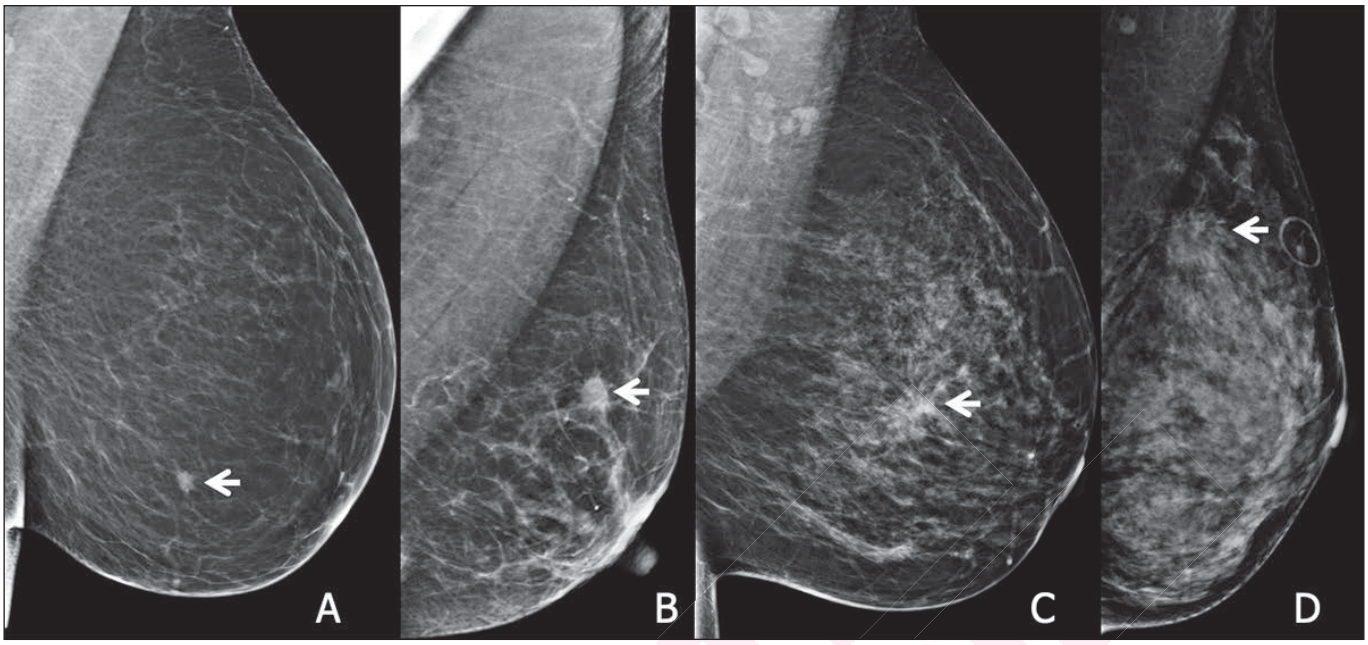


Figure 1. Cancer demonstrated on left mediolateral oblique (MLO) digital mammography in each of the four BI-RADS breast density categories. A) This 61-year-old woman with pathogenic BRCA1 mutation has fatty breasts and a spiculated mass (arrow) on screening. This proved to be a 0.9 cm grade 3 invasive ductal carcinoma (IDC), estrogen-receptor (ER) negative, progesterone-receptor (PR) negative, human epidermal growth factor 2 (HER2/neu) negative, Ki-67 proliferation index high at 90%, with associated ductal carcinoma in situ (DCIS) and three negative sentinel nodes. B) Screening mammogram in this 65-year-old woman shows scattered fibroglandular density and a spiculated mass (arrow) which proved to be a 1.1 cm grade 2 IDC with extensive DCIS, ER/PR positive, HER2/neu negative, Ki-67 high at 30%, with metastatic sentinel node and focal extracapsular extension. C) Baseline screening in a 40-year-old woman shows heterogeneously dense parenchyma, which may obscure small masses. Irregular mass with distortion is seen in the central left breast (arrow). Core biopsy showed 1.2 cm IDC, ER/PR positive, HER2 negative, Ki-67 moderate at 15%. The patient went elsewhere for treatment. D) Baseline screening in this 43-year-old woman shows extremely dense parenchyma which lowers the sensitivity of mammography. A spiculated mass with associated distortion is seen in the upper posterior left breast (arrow). This proved to be a T2 (> 2 cm) grade 2 IDC-DCIS, ER/PR positive, HER2 negative, Ki-67 low at 10% with negative sentinel node biopsy.

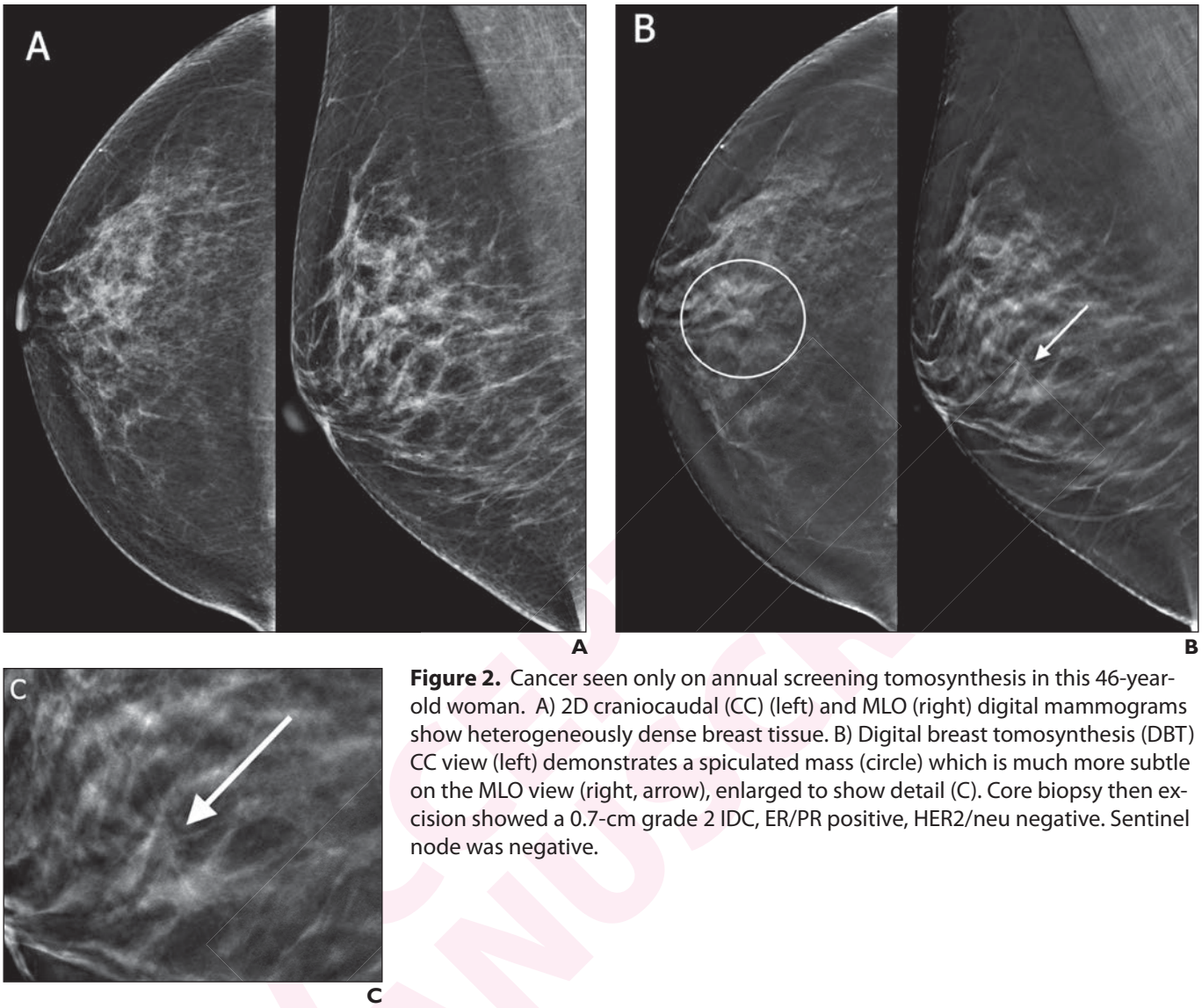


Figure 2. Cancer seen only on annual screening tomosynthesis in this 46-year-old woman. A) 2D craniocaudal (CC) (left) and MLO (right) digital mammograms show heterogeneously dense breast tissue. B) Digital breast tomosynthesis (DBT) CC view (left) demonstrates a spiculated mass (circle) which is much more subtle on the MLO view (right, arrow), enlarged to show detail (C). Core biopsy then excision showed a 0.7-cm grade 2 IDC, ER/PR positive, HER2/neu negative. Sentinel node was negative.

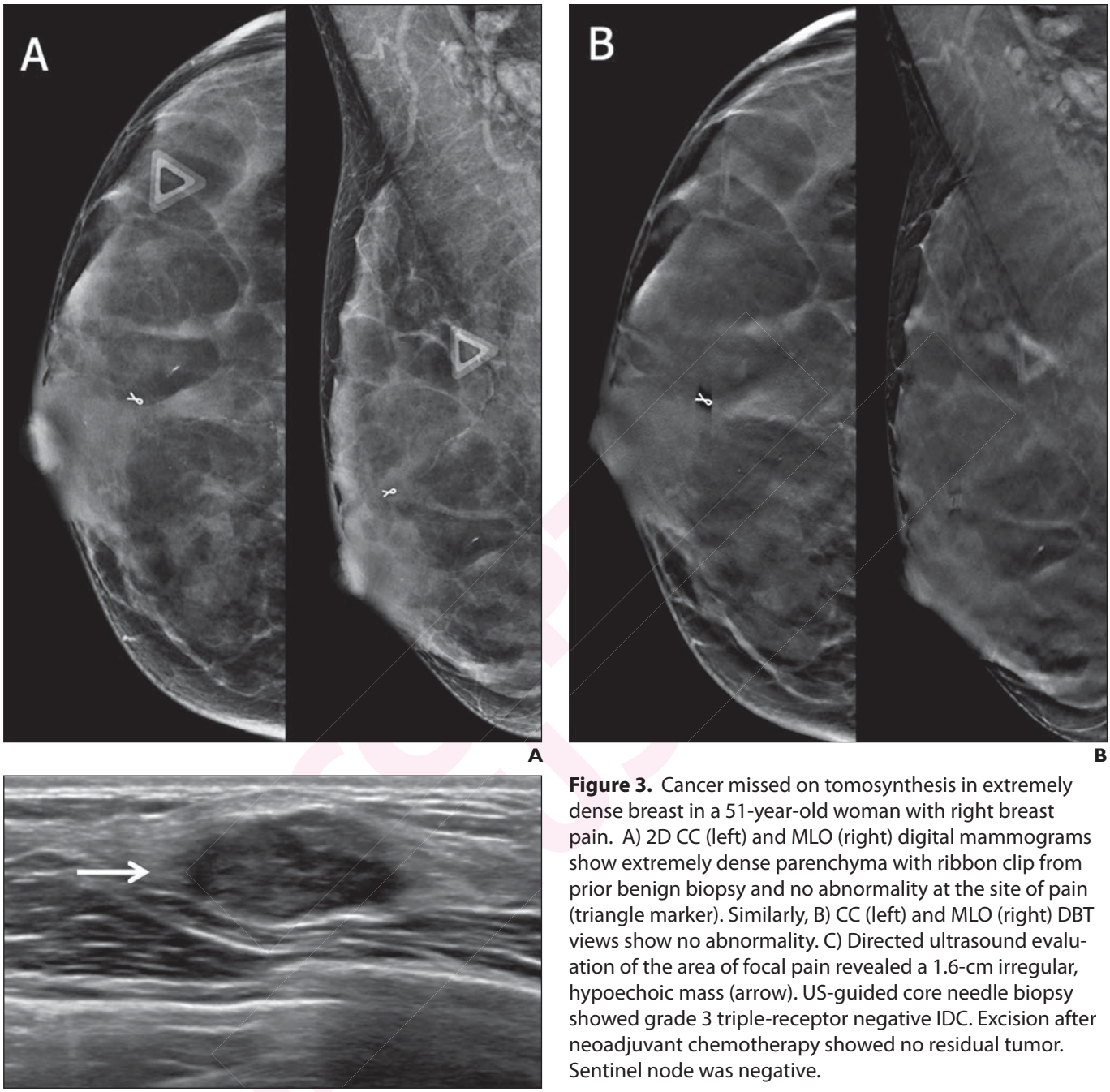


Figure 3. Cancer missed on tomosynthesis in extremely dense breast in a 51-year-old woman with right breast pain. A) 2D CC (left) and MLO (right) digital mammograms show extremely dense parenchyma with ribbon clip from prior benign biopsy and no abnormality at the site of pain (triangle marker). Similarly, B) CC (left) and MLO (right) DBT views show no abnormality. C) Directed ultrasound evaluation of the area of focal pain revealed a 1.6-cm irregular, hypoechoic mass (arrow). US-guided core needle biopsy showed grade 3 triple-receptor negative IDC. Excision after neoadjuvant chemotherapy showed no residual tumor. Sentinel node was negative.

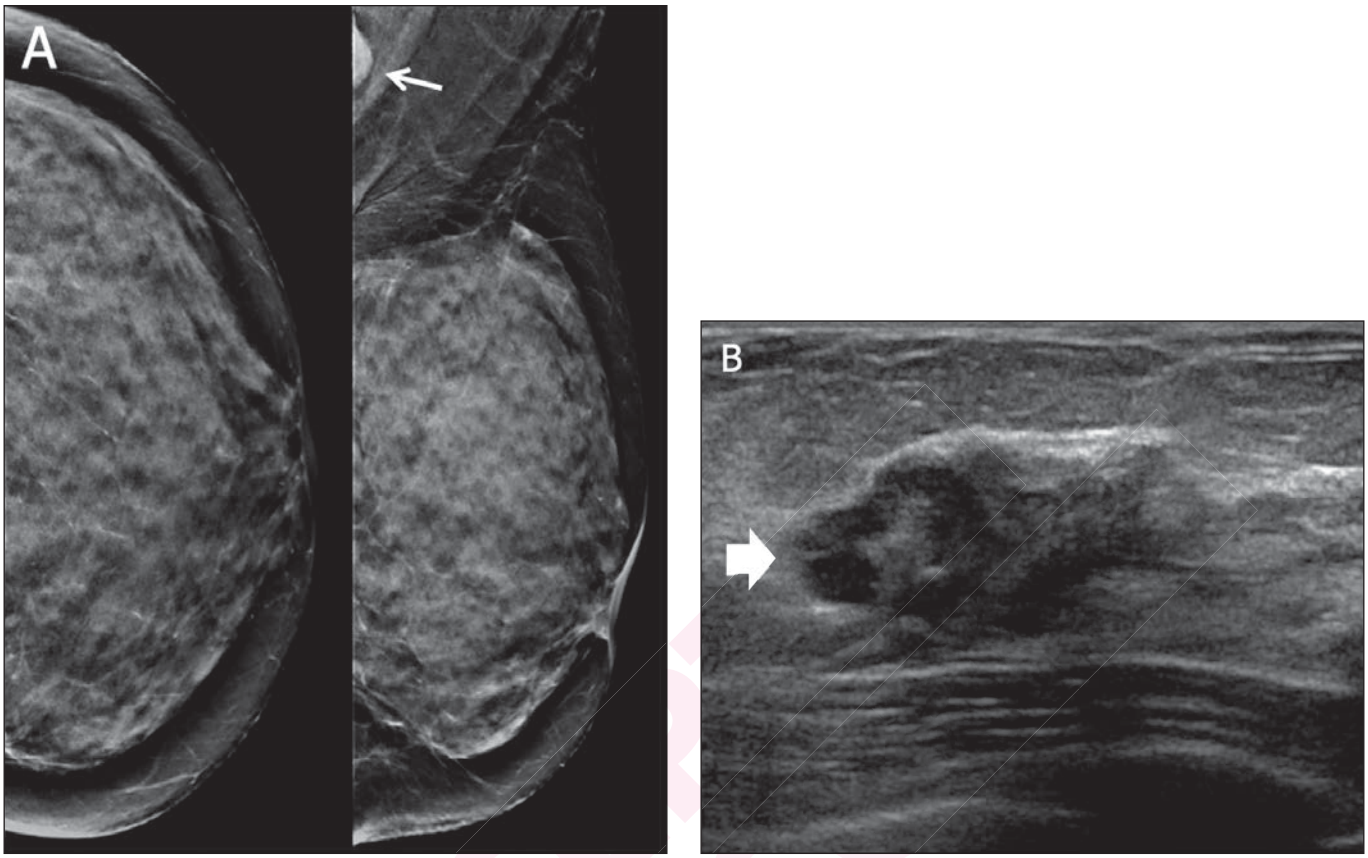
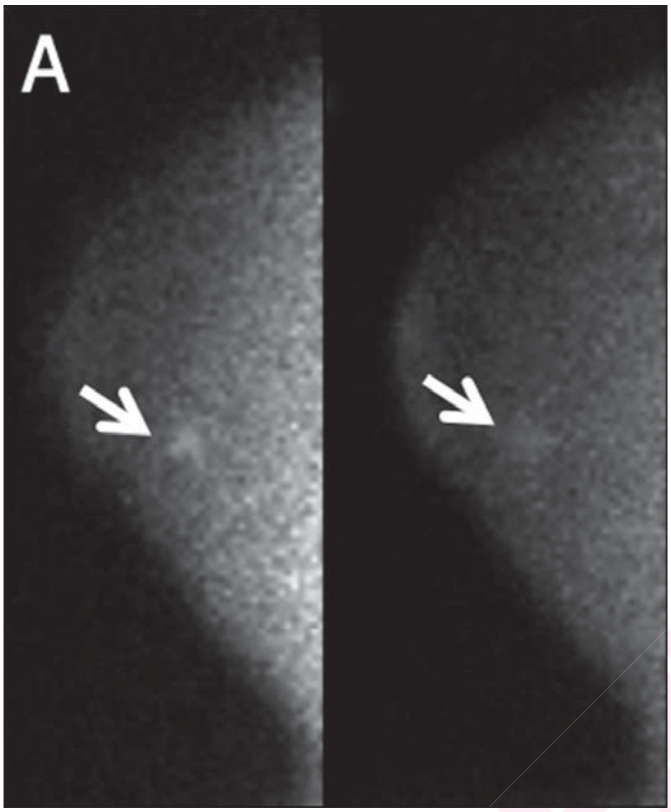
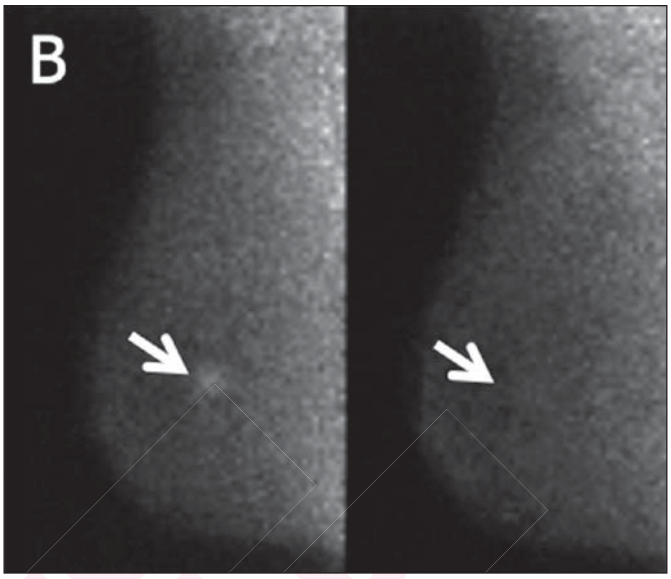


Figure 4. Cancer seen only on screening ultrasound in a 58-year-old woman with extremely dense breasts. A) CC (left) and MLO (right) synthetic 2D mammograms show normal extremely dense parenchyma, interpreted as negative also on DBT. In retrospect, a portion of a dense node is seen in the left axilla (arrow). Technologist-performed handheld screening US was performed bilaterally with standard documentation. B) Radial US image left breast 12:00 6 cm from the nipple shows an irregular, hypoechoic 1.9 cm mass (arrow). US-guided core biopsy showed grade 2 IDC, ER positive, PR negative, HER2/neu amplified by fluorescence in situ hybridization, Ki-67 proliferation index high at 40%. US-guided core biopsy of left axillary node confirmed metastatic disease. The patient had primary chemotherapy with no residual invasive carcinoma and few foci of DCIS at lumpectomy. Targeted axillary dissection (with seed-localized excision of known metastatic node) showed one metastatic node with treatment effect and three normal nodes.



A



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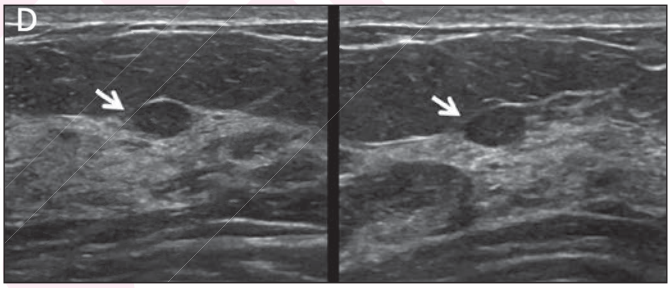

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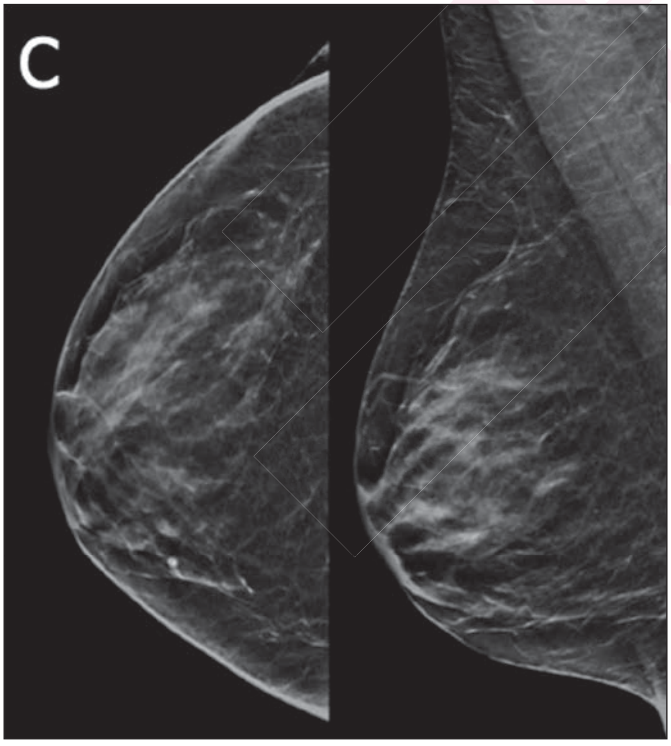

C

Figure 5. Cancer seen only on screening molecular breast imaging (MBI) in a 47-year-old woman with heterogeneously dense breasts. MBI performed after intravenous injection of 7.5 mCi Tc-99m sestamibi shows a 9-mm focal area of moderate intensity uptake (arrows) in the upper inner right breast, middle depth on A) CC views from the upper (left) and lower (right) detector heads and B) MLO views from the upper (left) and lower (right) detector heads. Diagnostic mammogram performed the same day found heterogeneously dense breasts and no abnormality to correspond with the uptake on MBI. C) Synthetic 2D CC (left) and MLO (right) mammograms from DBT acquisition show heterogeneously dense parenchyma and no abnormality. Spot compression MLO view was also normal (not shown). D) Targeted transverse (left) and longitudinal ultrasound (right) shows an oval circumscribed 0.7 cm isoechoic mass felt to correspond to the MBI finding. Ultrasound-guided core biopsy and excision revealed 0.4 cm grade 1 IDC, ER/PR positive, HER2 negative, Ki-67=8.0%, with low-grade DCIS. Sentinel node was negative. (Courtesy of Katie Hunt, Mayo Clinic)

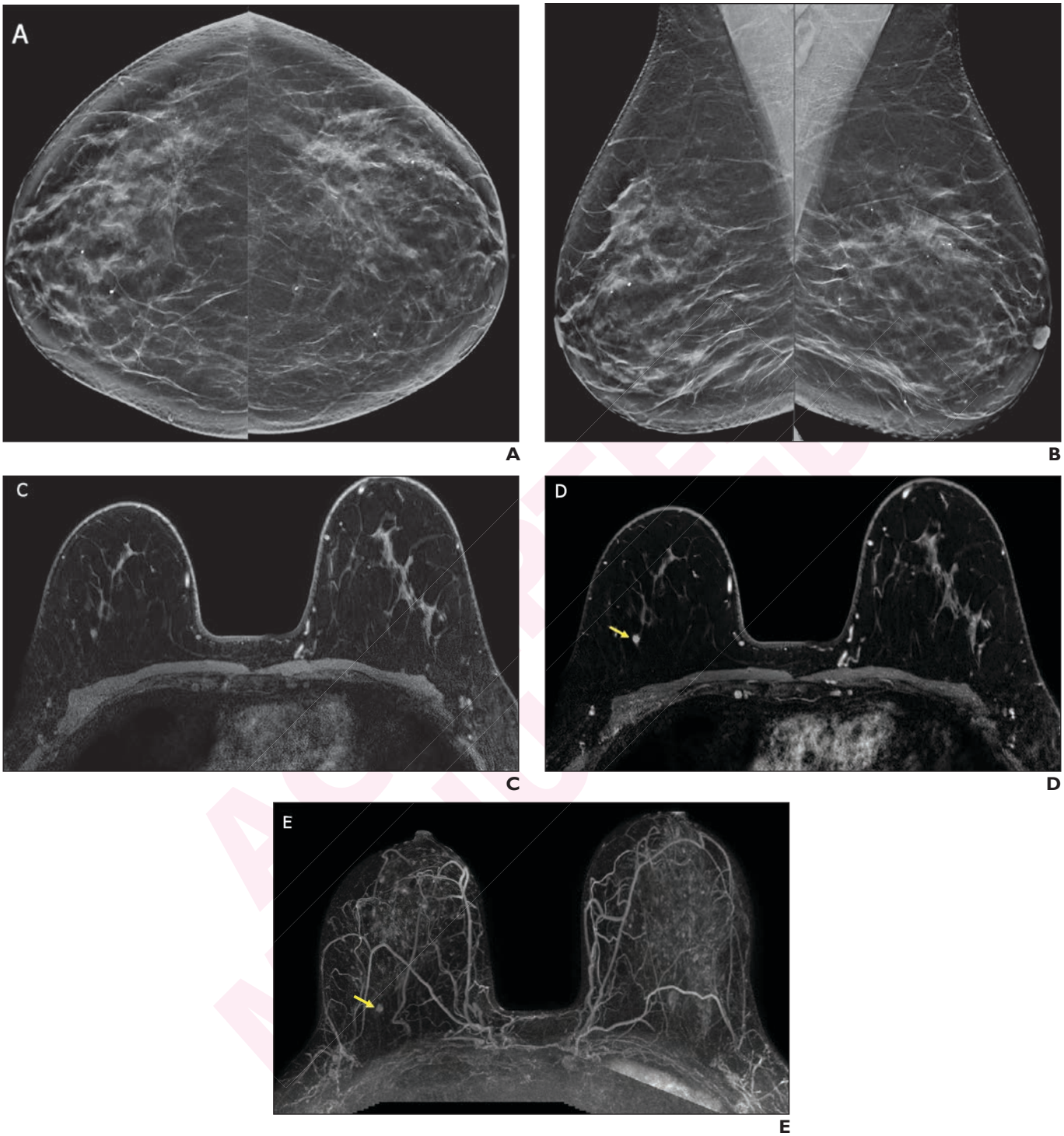

Figure 6. Cancer seen only on screening abbreviated MRI in a 69-year-old woman with dense breasts and history of lobular carcinoma in situ excised two years prior. A) CC and B) MLO synthetic 2D views from screening DBT demonstrate heterogeneously dense breasts with no abnormalities. C) Baseline screening abbreviated MRI, consisting only of a noncontrast 3D T1-weighted acquisition and D) a single post-contrast T1-weighted 3D acquisition, from which E) subtracted maximum intensity projection image is created, demonstrates an enhancing round mass with indistinct margins and heterogeneous internal enhancement in the upper outer right breast (arrows) measuring 0.6 cm. MRI-guided biopsy and excision confirmed a 0.6 cm grade 1 IDC, ER/PR positive, Her2/neu negative, with negative sentinel node biopsy.

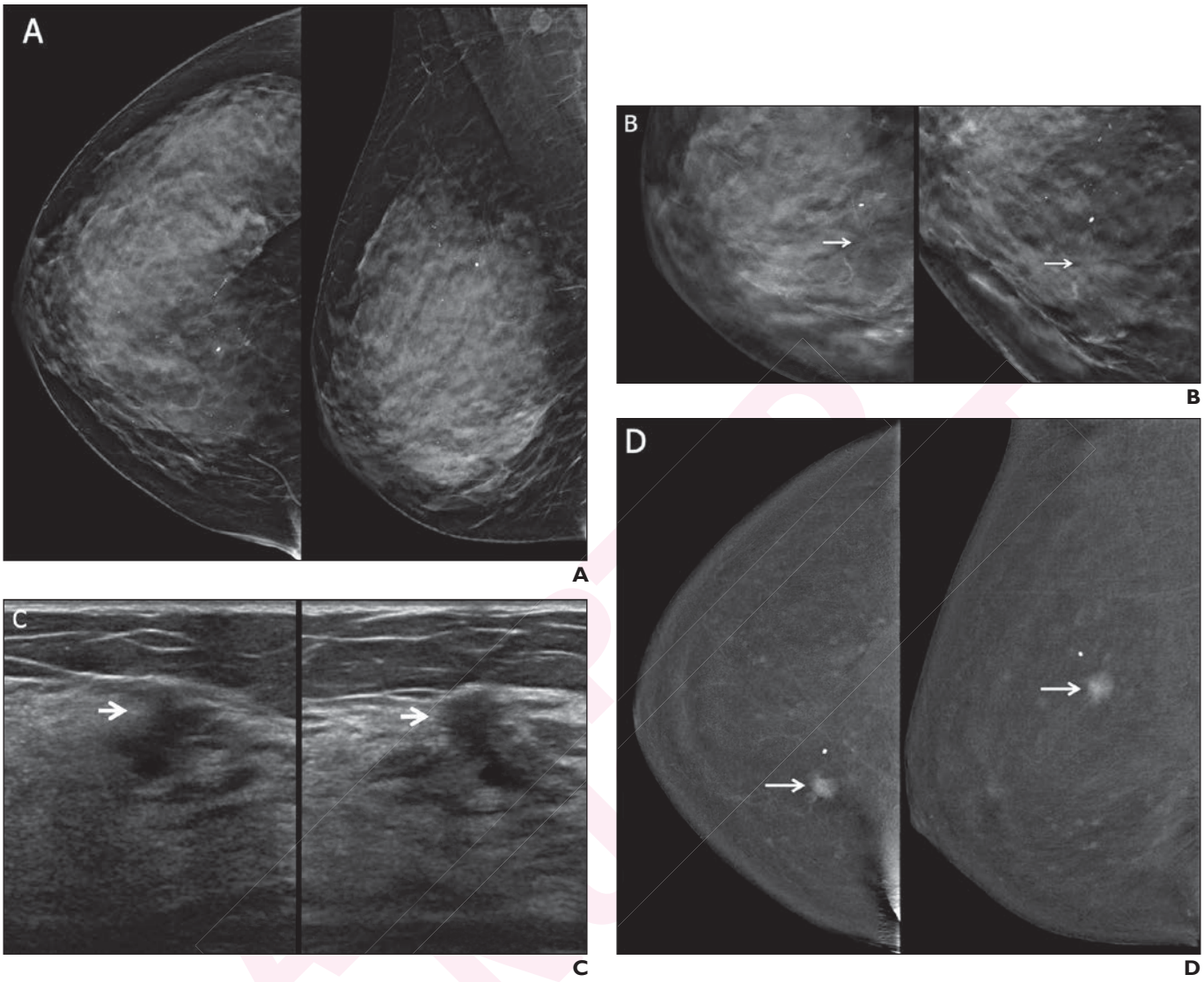

Figure 7. Invasive ductal cancer on contrast-enhanced mammogram (CEM) in a 57-year-old woman with dense breasts. A) Screening CC and MLO synthetic 2D mammograms show heterogeneously dense parenchyma and a few calcifications. B) Close-up of CC tomosynthesis inner right breast (left) and angled spot compression CC tomosynthesis (right) show subtle distortion (arrows). C) Screening handheld US was negative, but targeted radial (left) and antiradial US (right) right breast 1:00 6 cm from the nipple shows an irregular, hypoechoic 0.9 cm mass (arrows). Prior to biopsy, the patient had research CEM beginning 2.5 minutes after i.v. injection of 125 cc Isovue 370. D) CC (left) and MLO (right) subtraction CEM shows a strongly enhancing 1.2-cm irregular mass (arrows) and mild background parenchymal enhancement. US-guided core biopsy showed grade 2 IDC DCIS, ER/PR positive, HER2/neu negative, Ki-67 low at 10%, with invasive carcinoma measuring 1.3 cm at lumpectomy and four negative sentinel nodes.

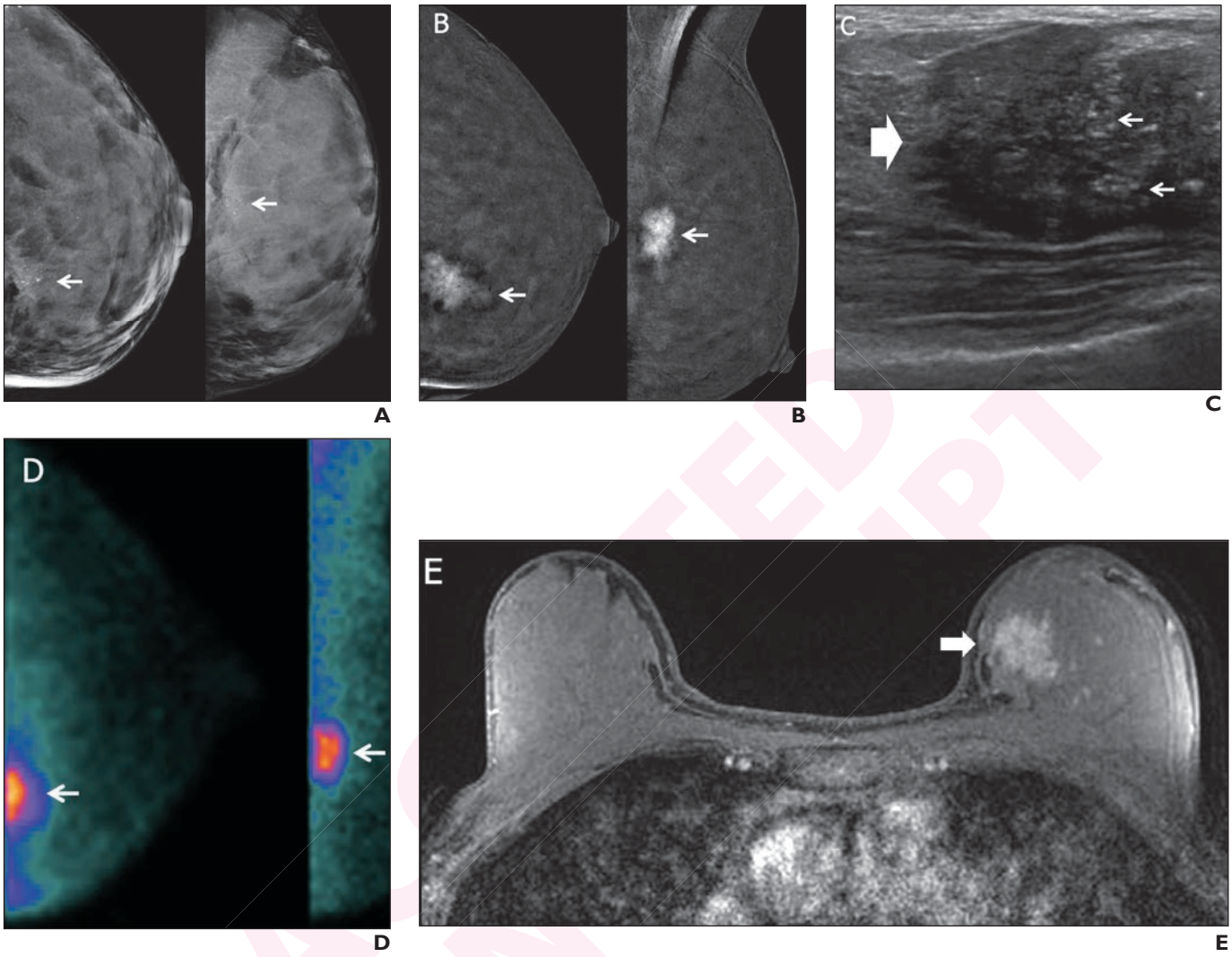

Figure 8. Invasive ductal carcinoma in 51-year-old woman across modalities. A) Screening CC (left) and MLO (right) mammograms of the left breast show regional amorphous and pleomorphic calcifications (arrows) that are well seen despite extremely dense parenchyma. B) Subtraction CC and MLO images from research CEM after i.v. injection of 125 cc Omnipaque 300 show strong enhancement of an irregular 2.7-cm mass (arrows) at the site of calcifications. C) Targeted US shows a partially circumscribed, partially indistinctly marginated slightly hypoechoic 3.1-cm mass (wide arrow) with echogenic calcifications (small arrows). Stereotactic biopsy was performed (to assure optimal sampling of calcifications), showing grade 2 IDC-DCIS, ER/PR/HER2 negative, Ki-67 low at 10%. D) Research CC and MLO molecular breast imaging (10 minute acquisitions following i.v. injection of 7.3 mCi Tc-99m sestamibi) performed after diagnosis shows intense uptake in an irregular 3.4 cm mass (arrows). Note there is slight reduction in inclusion of extreme posterior tissues relative to mammography. E) Axial fat-suppressed T1-weighted MRI shows intense enhancement of irregular 3.0 cm mass at site of known malignancy (arrow). The patient had partial response to primary chemotherapy with two sentinel nodes negative for metastases (or therapy-related changes).

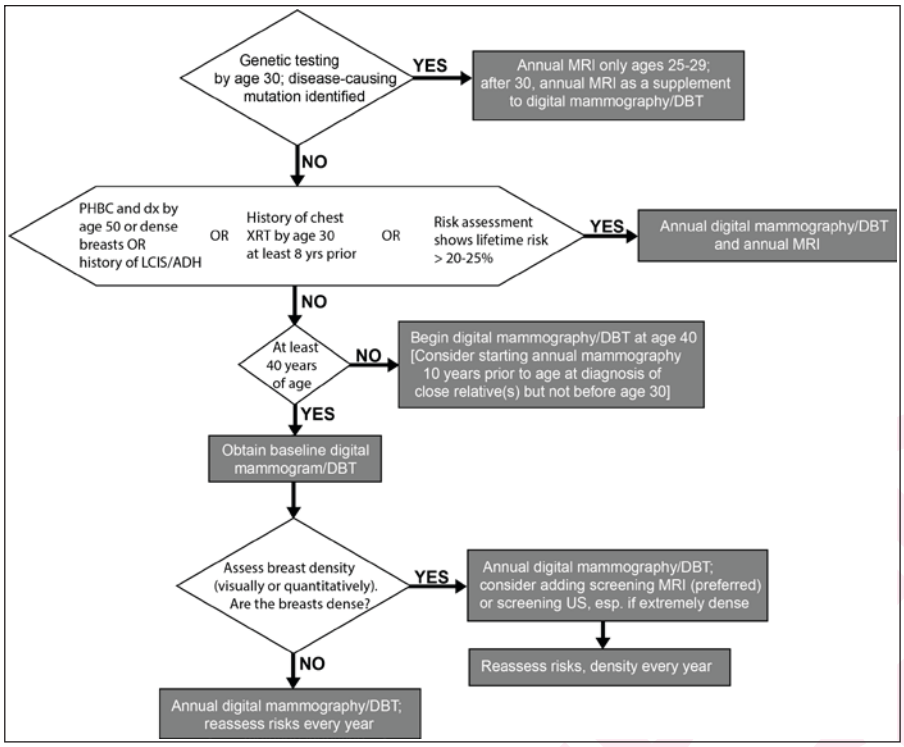

Figure 9. Flowchart illustrating current approaches to supplemental screening in the context of risk factors, including breast density. If not performed by age 30, genetic testing can be performed at the time of diagnosis with breast or ovarian cancer or when appropriate family history is identified or when a family member is found to have a pathogenic mutation. Women at high risk who are pregnant or lactating may consider screening US during that time. Similar performance has been observed for abbreviated MRI and full diagnostic protocol MRI. For women who cannot tolerate MRI, US is the most widely available alternative but produces less gain in cancer detection than MRI. MBI or CEM appear to produce cancer detection similar to MRI but are not yet widely available alternatives; further validation is needed. If a woman has screening MRI, there is no need for additional supplemental screening with US, MBI, or CEM. Supplemental screening MRI should stop by age 75 even among high-risk women. Dx = diagnosis; XRT = radiation therapy.

AJR

Screening Algorithms in Dense Breasts: Narrative Review

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Keywords: breast density, tomosynthesis, ultrasound, molecular breast imaging, MRI, contrast-enhanced mammography

Abbreviations used: DM = two-dimensional digital mammography; TMIST, tomosynthesis or mammography imaging screening trial; BCSC = Breast Cancer Surveillance Consortium; DBT = digital breast tomosynthesis; US = ultrasound; HHUS = handheld ultrasound; AUS = automated ultrasound; MRI = magnetic resonance imaging; MBI = molecular breast imaging; CEM = contrast-enhanced mammography; CPT = Current Procedural Terminology; ICDR = incremental cancer detection rate; PPV = positive predictive value; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ER = estrogen receptor; PR = progesterone receptor; HER2/neu = human epidermal growth factor 2.

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