American College of Radiology
ACR Appropriateness Criteria®

Supplemental Breast Cancer Screening Based on Breast Density

Variant: 1 Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
US breast	Usually Not Appropriate	O
Mammography with IV contrast	Usually Not Appropriate	☢☢
MRI breast without and with IV contrast	Usually Not Appropriate	O
MRI breast without and with IV contrast abbreviated	Usually Not Appropriate	O
MRI breast without IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast abbreviated	Usually Not Appropriate	O
FDG-PET breast dedicated	Usually Not Appropriate	☢☢☢
Sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant: 2 Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
US breast	May Be Appropriate	O
MRI breast without and with IV contrast	May Be Appropriate	O
MRI breast without and with IV contrast abbreviated	May Be Appropriate	O
Mammography with IV contrast	Usually Not Appropriate	☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast abbreviated	Usually Not Appropriate	O
FDG-PET breast dedicated	Usually Not Appropriate	☢☢☢
Sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant: 3 Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
MRI breast without and with IV contrast	Usually Appropriate	O
MRI breast without and with IV contrast abbreviated	Usually Appropriate	O
US breast	May Be Appropriate	O
Mammography with IV contrast	Usually Not Appropriate	☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast abbreviated	Usually Not Appropriate	O
FDG-PET breast dedicated	Usually Not Appropriate	☢☢☢
Sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant: 4 Adult female. Supplemental breast cancer screening. Intermediate risk.

Nondense breasts.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
MRI breast without and with IV contrast	May Be Appropriate (Disagreement)	O
MRI breast without and with IV contrast abbreviated	May Be Appropriate	O
US breast	Usually Not Appropriate	O
Mammography with IV contrast	Usually Not Appropriate	☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast abbreviated	Usually Not Appropriate	O
FDG-PET breast dedicated	Usually Not Appropriate	☢☢☢
Sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant: 5 Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
MRI breast without and with IV contrast	Usually Appropriate	O
MRI breast without and with IV contrast abbreviated	Usually Appropriate	O
US breast	May Be Appropriate	O
Mammography with IV contrast	May Be Appropriate	☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast abbreviated	Usually Not Appropriate	O
FDG-PET breast dedicated	Usually Not Appropriate	☢☢☢
Sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant: 6 Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
MRI breast without and with IV contrast	Usually Appropriate	O
MRI breast without and with IV contrast abbreviated	Usually Appropriate	O
US breast	May Be Appropriate	O
Mammography with IV contrast	May Be Appropriate	☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast abbreviated	Usually Not Appropriate	O
FDG-PET breast dedicated	Usually Not Appropriate	☢☢☢
Sestamibi MBI	Usually Not Appropriate	☢☢☢

Variant: 7 Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

Procedure	Appropriateness Category	Relative Radiation Level
Digital breast tomosynthesis screening	Usually Appropriate	☢☢
MRI breast without and with IV contrast	Usually Appropriate	O
MRI breast without and with IV contrast abbreviated	Usually Appropriate	O

US breast	May Be Appropriate	O
Mammography with IV contrast	May Be Appropriate	☢☢
MRI breast without IV contrast	Usually Not Appropriate	O
MRI breast without IV contrast abbreviated	Usually Not Appropriate	O
FDG-PET breast dedicated	Usually Not Appropriate	☢☢☢
Sestamibi MBI	Usually Not Appropriate	☢☢☢

Panel Members

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Summary of Literature Review

Introduction/Background

In March 2023, the FDA issued a national requirement for dense breast reporting to patients and their referring providers. All mammography facilities will have to comply by September 10, 2024. Once in effect, patients must be notified of their breast density and informed that supplemental imaging studies may be beneficial to aid in cancer detection [1].

The ACR BI-RADS atlas divides breast density into 4 categories: almost entirely fatty, scattered fibroglandular elements, heterogeneously dense, and extremely dense based on the proportion of fibroglandular tissue (compared with fat) and its potential for masking of noncalcified lesions [2]. Breast density assignments can be made by visual assessment or by using automated computer software. It is estimated that approximately half of women undergoing screening mammography have dense tissue, defined here as either heterogeneously or extremely dense breasts. Mammography is the main imaging modality for breast cancer detection and has repeatedly been proven to demonstrate a 30% to 40% reduction in mortality [3,4], however, the sensitivity of mammography in women with dense tissue is decreased [5]. In addition, breast density has been proven as an independent risk factor for the development of breast cancer. Women with extremely dense breast tissue have a 4- to 6-fold greater risk as compared with those with fatty tissue [6]. Thus, women with dense breasts are at higher risk of developing breast cancer and at greater risk of the cancer not being detected on mammography [5]. Additionally, there is an increased rate of interval cancers in women with dense tissue, and these cancers often have a worse prognosis than cancers found on routine screening [5].

Supplemental screening modalities have been suggested to overcome the limitation of mammography in women with dense breasts and to increase cancer detection in this population. Such modalities include digital breast tomosynthesis (DBT), whole breast ultrasound (US), breast MRI, abbreviated breast MRI (AB-MRI), contrast-enhanced mammography (CEM), molecular breast imaging (MBI), and flourine-18-2-flouro-2-deoxy-D-glucose (FDG)-PET of the breast.

Although improved cancer detection with DBT and whole breast US focus on morphologic

assessment, functional imaging studies such as contrast-enhanced breast MRI, CEM, AB-MRI, MBI, and FDG-PET exploit vascular differentiation of neoangiogenesis to identify malignancy. Several of these supplemental imaging modalities have shown an increased cancer detection rate (CDR) compared with mammography alone in women with dense and nondense tissue.

Stratification of risk can aid health care providers in recommending a particular type of supplemental imaging. Risk assessment should be performed for all women by 25 years of age, especially Black women and those of Ashkenazi Jewish descent [7]. Average lifetime risk (<15%), intermediate-risk (15%-20%), and high-risk (20%) women may benefit from different supplemental screening studies based on their breast density.

These recommendations address breast cancer risk in cisgender females (assigned female at birth with a female gender identity). For breast cancer screening in transgender and gender nonconforming patients, please reference the ACR Appropriateness Criteria topic on "Transgender Breast Cancer Screening" [8].

The guidelines detailed in this document are established by a multidisciplinary panel and based on current evidence. This document expands on the report issued in 2023 by the Breast Commission of the ACR [7].

Discussion of Procedures by Variant

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

The goal of screening is early detection of breast cancer prior to it being detected clinically, improving morbidity and mortality. The expected outcome is longevity to the patient and decreased burden of disease.

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

A. Digital breast tomosynthesis screening

Screening mammography has been shown to reduce mortality by approximately 30% to 40% [3,4]. It is most sensitive in women with nondense tissue.

In DBT the x-ray tube moves in an arc obtaining multiple low-dose mammographic images that are reconstructed into 2-D images. The additional information from varying angles aims to reduce summation shadows and overlapping structures to maximize visibility [2].

The retrospective Population-based Research Optimizing Screening Through Personalized Regimens (PROSPR) consortium review evaluated more than 180,000 women; approximately 130,000 were screened with digital mammography (DM) and 50,000 with DBT. Women with nondense tissue accounted for 64% of the cohort as compared with 36% with dense tissue. A statistically significant increase in CDR was found in women with both nondense tissue (1.7/1,000) and dense tissue (2.27/1,000) screened with DBT. Cancers tended to be smaller, lymph node negative, and less biologically aggressive [9]. Li et al [10] reviewed several studies comparing DBT with 2-D mammography in Europe and the United States and found the pooled CDR to be statistically significant in both nondense and dense tissue.

Another advantage of DBT is a reduction in recall rate with improved specificity. A few studies have demonstrated this benefit with the reduction ranging between 15% to 63% in observational, retrospective studies in the United States [11,12]. In a retrospective cohort study evaluating multiple screening rounds, Sprague et al [13] found no difference in the interval cancer rate between DBT and DM. The randomized prospective Tomosynthesis Mammographic Imaging Screening Trial (TMIST) trial comparing DBT with 2-D mammography is currently active.

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

B. FDG-PET breast dedicated

There is no relevant literature regarding the use of FDG-PET breast dedicated for supplemental screening in average-risk women with nondense breasts.

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

C. Mammography with IV contrast

There is no relevant literature to support CEM screening in average-risk women with nondense breast tissue.

CEM uses a dual-energy technique to acquire 8 standard mammographic images after the administration of intravenous (IV) iodinated contrast material. Four low-energy images mimic a conventional 2-D mammogram. The additional 4 diagnostic recombined images show contrast enhancement, which offers morphologic and functional assessment to identify malignancies. CEM has been valuable in evaluating abnormalities in the diagnostic setting [14], however, recent literature has indicated that it may play a beneficial role in screening women with dense tissue at an intermediate risk of developing breast cancer or those seeking an alternative supplemental screening modality to MRI [15].

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

D. MRI breast without and with IV contrast

There are limited data to support the use of breast MRI in average-risk women with nondense breast tissue. Kuhl et al [16] demonstrated a CDR of 15.5 per 1,000 with a high specificity (97.1%) and positive predictive value (PPV) (35.7%) in average-risk women of all breast densities.

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

E. MRI breast without and with IV contrast abbreviated

There is no relevant literature regarding the use of AB-MRI without and with IV contrast for supplemental screening in average-risk women with nondense breasts.

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

F. MRI breast without IV contrast

There is no relevant literature regarding the use of MRI breast without IV contrast for supplemental screening in average-risk women with nondense breasts.

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.

G. MRI breast without IV contrast abbreviated

There is no relevant literature regarding the use of AB-MRI breast without IV contrast for supplemental screening in average-risk women with nondense breasts.

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.
H. Sestamibi MBI

There is no relevant literature regarding the use of Tc-99m sestamibi MBI for supplemental screening in average-risk women with nondense breasts. This modality is not yet widely used in clinical practice.

Variant 1: Adult female. Supplemental breast cancer screening. Average risk. Nondense breasts.
I. US breast

Screening breast US can be performed using hand-held (HHUS) or automated (ABUS) techniques. Although the sensitivity of mammography in nondense tissue approaches 90%, it can be as low as 30% in women with extremely dense tissue [17]. Screening US offers improved the sensitivity and interval cancer detection particularly in women with dense tissue. In women with nondense tissue, the Japan Strategic Anti-cancer Randomized Trial (J-START) trial demonstrated increased cancer detection, but this was not supported in 2 other large cohort studies [18]. Although studies have demonstrated increased CDR with the addition of screening US to mammography, this comes at the at the expense of low biopsy PPVs and high false-positive rates including a high rate of short-term follow-up recommendations [7,19]. No added benefit of screening US has been found in women who undergo MRI breast or AB-MRI screening [20].

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.

The goal of screening is early detection of breast cancer prior to it being detected clinically, improving morbidity and mortality. Supplemental imaging studies can improve sensitivity in women with dense breast tissue. The expected outcome is longevity to the patient and decreased burden of disease.

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.
A. Digital breast tomosynthesis screening

Screening mammography has been shown to reduce mortality by approximately 30% to 40% [3,4]. It is most sensitive in women with nondense tissue. Women with heterogeneously and extremely dense tissue, who can comprise up to half of screening-aged women in the United States, may not receive the same benefit from mammography alone because sensitivity can be reduced by 30% to 48% in extremely dense tissue [17].

In DBT, the x-ray tube moves in an arc obtaining multiple low-dose mammographic images that are reconstructed into 2-D images. The additional information from varying angles aims to reduce summation shadows and overlapping structures to maximize visibility [2].

The retrospective PROSPR consortium review evaluated more than 180,000 women; approximately 130,000 were screened with DM and 50,000 with DBT. Women with nondense tissue accounted for 64% of the cohort as compared with 36% with dense tissue. A statistically significant increase in CDR was found in women with both nondense tissue (1.7/1,000) and dense tissue (2.27/1,000)

screened with DBT. Cancers tended to be smaller, lymph node negative, and less biologically aggressive [9]. Li et al [10] reviewed several studies comparing DBT with 2-D mammography in Europe and the United States and found the pooled CDR to be statistically significant in both nondense and dense tissue. However, Berg et al [20] found the greatest increase in CDR to be in women with heterogeneously dense breasts. No significant increase in detection was identified in women with extremely dense tissue [20], highlighting the need for other methods of supplemental screening in this population.

Another advantage of DBT is a reduction in recall rate with improved specificity. A few studies have demonstrated this benefit, with the reduction ranging between 15% to 63% in observational, retrospective studies in the United States [11,12]. In a retrospective cohort study evaluating multiple screening rounds, Sprague et al [13] found no difference in the interval cancer rate between DBT and DM. The randomized prospective TMIST trial comparing DBT with 2-D mammography is currently active.

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.
B. FDG-PET breast dedicated

There is no relevant literature regarding the use of FDG-PET breast dedicated for supplemental screening in average-risk women with heterogeneously dense breasts.

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.
C. Mammography with IV contrast

There is no relevant literature to support CEM screening in average-risk women with heterogeneously dense breast tissue.

CEM uses a dual-energy technique to acquire 8 standard mammographic images after the administration of IV iodinated contrast material. Four low-energy images mimic a conventional 2-D mammogram. The additional 4 diagnostic recombined images demonstrate contrast enhancement, which offers morphologic as well as functional assessment to identify malignancies. CEM has been valuable in evaluating abnormalities in the diagnostic setting [14], however, recent literature has indicated that it may play a beneficial role in screening women with dense tissue at an intermediate risk of developing breast cancer or those seeking an alternative supplemental screening modality to MRI [15]. The CDR in screening studies has ranged from 8.6 to 13.1 cancers per 1,000 screening examinations [21,22], although most of these were conducted retrospectively at a single institution. CEM offers a higher sensitivity compared with mammography, with the benefit statistically significant in women with dense breast tissue [21]. The Contrast Mammography Enhanced Imaging Screening Trial (CMIST) is currently enrolling intermediate-risk women with dense breasts to participate in a prospective study comparing DBT and CEM.

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.
D. MRI breast without and with IV contrast

There are data to support the use of breast MRI in average-risk women with heterogeneously dense breasts. Kuhl et al [16] demonstrated a CDR of 15.5 per 1,000 with a high specificity (97.1%) and PPV (35.7%) in average-risk women of all breast densities.

In a review of 22 randomized clinical trials and observational prospective studies, supplemental MRI had a CDR of 19.9 per 1,000 as compared with 4.5 per 1000 (HHUS) and 3.2 per 1,000 (DBT) in average- and intermediate-risk women with dense tissue [17].

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.
E. MRI breast without and with IV contrast abbreviated

The standard MRI protocol uses multiple sequences to identify malignancy and characterize benign breast findings requiring longer magnet and interpretation times. The protocol for AB-MRI is variable and even customizable, however, all protocols use a limited number of images to highlight findings in the early postcontrast phase. This technique maximizes cancer detection while reducing the time burden on the patient and the radiologist. Negative studies can be quickly interpreted, reducing physician workload. Lawson et al [23] found no statistical difference when comparing the sensitivity of standard MRI with AB-MRI (100% to 88.9%). This is consistent with findings from Kuhl et al [24], Baxter et al [19], and others [25,26]. The EA1141 trial demonstrated a CDR (invasive and ductal carcinoma in situ [DCIS]) of 15.2 per 1,000 examinations with AB-MRI compared with 6.2 per 1,000 examinations with DBT in average-risk women with dense tissue [27]. The specificity of AB-MRI was reduced when compared with DBT (87% versus 97%). Clinicians should be aware that baseline imaging may result in benign biopsies or short-term interval follow-ups [28]. Weinstein et al [29] reported a CDR of 27.4 per 1,000 in a retrospective review of average-risk women previously screened with DBT.

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.
F. MRI breast without IV contrast

There is no relevant literature regarding the use of MRI breast without IV contrast for supplemental screening in average-risk women with heterogeneously dense breasts.

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.
G. MRI breast without IV contrast abbreviated

There is no relevant literature regarding the use of AB-MRI breast without IV contrast for supplemental screening in average-risk women with heterogeneously dense breasts.

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.
H. Sestamibi MBI

Currently, there is insufficient evidence to support the use of Tc-99m sestamibi MBI as a supplemental screening exam in average-risk women with heterogeneously dense tissue, however, there are emerging data. At present, barriers include lack of incidence around screening, longer examination times, and limited studies addressing the spectrum of breast densities and risk [7].

MBI is a nuclear medicine study that uses the IV injection of Tc-99m sestamibi to identify mitotically active areas within breast tissue, ideally differentiating malignant tumors from background parenchyma. Although breast-specific gamma imaging (BSGI) uses single detector sodium iodide cameras, MBI employs dual-head cadmium zinc telluride detectors to obtain a functional imaging study, which takes approximately 40 minutes [30]. The prospective study (1,585 women) by Rhodes et al [31] and a retrospective study (1,696 women) by Shermis et al [32]

reported a CDR of 7.7 to 8.8 per 1,000 in women with dense breasts. Preliminary data from the Density Molecular Breast Imaging and Tomosynthesis to Eliminate the Reservoir of Undetected Cancers (MATTERS) trial, comparing DBT and MBI, found 7 cancers in 537 women, 6 of which were found by MBI only. All were invasive. The incremental CDR of MBI was 9.3 per 1,000 [31].

Variant 2: Adult female. Supplemental breast cancer screening. Average risk. Heterogeneously dense breasts.

I. US breast

Screening breast US can be performed using HHUS or ABUS techniques. Although the sensitivity of mammography in nondense tissue approaches 90%, it can be as low as 30% in women with extremely dense tissue [17]. Screening US offers improved sensitivity and interval cancer detection, particularly in women with dense tissue. A statistically significant CDR of an additional 3.0 per 1,000 breast cancers was identified in average-risk women with dense tissue in a secondary review of the J-START [33,34]. Additionally, a significant decrease was observed in the interval cancer rate (0.5 per 1,000 compared with 2.0 per 1,000 in the control group). In women with nondense tissue, the J-START trial demonstrated increased cancer detection as well, but this was not supported in 2 other large cohort studies [18]. The prospective, multicenter ASTOUND-2 (adjunct screening with tomosynthesis or US in women with mammography-negative dense breasts) trial conducted in screening women with dense tissue found 4.9 per 1,000 additional cancers with HHUS as compared with 2.8 per 1,000 with DBT, although the former had more false-positives [35]. Although studies have demonstrated increased CDR with the addition of screening US to mammography, this comes at the expense of low biopsy PPVs and high false-positive rates including a high rate of short-term follow-up recommendations [7,19]. No added benefit of screening US has been found in women who undergo MRI breast or AB-MRI screening [20].

In women with elevated risk only due to breast density, supplemental screening US could be considered [7].

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.

The goal of screening is early detection of breast cancer prior to it being detected clinically, improving morbidity and mortality. Supplemental imaging studies can improve sensitivity in women with dense breast tissue. The expected outcome is longevity to the patient and decreased burden of disease.

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.

A. Digital breast tomosynthesis screening

Screening mammography has been shown to reduce mortality by approximately 30% to 40% [3,4]. It is most sensitive in women with nondense tissue. Women with heterogeneously and extremely dense tissue, who can comprise up to half of screening-aged women in the United States, may not receive the same benefit from mammography alone because sensitivity can be reduced by 30% to 48% in extremely dense tissue [17].

In DBT, the x-ray tube moves in an arc obtaining multiple low-dose mammographic images that are reconstructed into 2-D images. The additional information from varying angles aims to reduce summation shadows and overlapping structures to maximize visibility [2].

The retrospective PROSPR consortium review evaluated more than 180,000 women; approximately 130,000 were screened with DM and 50,000 with DBT. Women with nondense tissue accounted for 64% of the cohort as compared with 36% with dense tissue. A statistically significant increase in CDR was found in women with both nondense tissue (1.7/1,000) and dense tissue (2.27/1,000) screened with DBT. Cancers tended to be smaller, lymph node negative, and less biologically aggressive [9]. Li et al [10] reviewed several studies comparing DBT with 2-D mammography in Europe and the United States and found the pooled CDR to be statistically significant in both nondense and dense tissue. However, Berg et al [20] found the greatest increase in CDR to be in women with heterogeneously dense breasts. No significant increase in detection was identified in women with extremely dense tissue [20], highlighting the need for other methods of supplemental screening in this population.

Another advantage of DBT is a reduction in recall rate with improved specificity. A few studies have demonstrated this benefit, with the reduction ranging between 15% to 63% in observational, retrospective studies in the United States [11,12]. In a retrospective cohort study evaluating multiple screening rounds, Sprague et al [13] found no difference in the interval cancer rate between DBT and DM. The randomized prospective TMIST trial comparing DBT with 2-D mammography is currently active.

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.
B. FDG-PET breast dedicated

There is no relevant literature regarding the use of FDG-PET breast dedicated for supplemental screening in average-risk women with extremely dense breasts.

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.
C. Mammography with IV contrast

There is no relevant literature to support CEM screening in average-risk women with extremely dense breast tissue.

CEM uses a dual-energy technique to acquire 8 standard mammographic images after the administration of IV iodinated contrast material. Four low-energy images mimic a conventional 2-D mammogram. The additional 4 diagnostic recombined images demonstrate contrast enhancement, which offers morphologic as well as functional assessment to identify malignancies. CEM has been valuable in evaluating abnormalities in the diagnostic setting [14], however, recent literature has indicated that it may play a beneficial role in screening women with dense tissue at an intermediate risk of developing breast cancer or those seeking an alternative supplemental screening modality to MRI [15]. The CDR in screening studies has ranged from 8.6 to 13.1 cancers per 1,000 screening examinations [21,22], although most of these were conducted retrospectively at a single institution. CEM offers a higher sensitivity compared with mammography, with the benefit statistically significant in women with dense breast tissue [21]. The CMIST is currently enrolling intermediate-risk women with dense breasts to participate in a prospective study comparing DBT and CEM.

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.
D. MRI breast without and with IV contrast

The Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial is a Dutch multicenter, randomized trial in which supplemental MRI identified an additional 16.5 cancers per 1,000 screened in women of all risk stratification [36]. Additionally, the interval cancer rate of the MRI group was 0.8 per 1,000 compared with the control group, 5.0 per 1,000, suggesting a mortality benefit. In the second round of screening, the false-positive rate dropped to 26.3 per 1,000 from 79.8 per 1,000, and the incremental CDR was 5.8 per 1,000 [37]. Given the superior detection rate of MRI compared with DBT or US in women with dense breasts, the European Society of Breast Imaging now recommends supplemental screening with MRI in women with extremely dense breast tissue, regardless of risk [38].

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.
E. MRI breast without and with IV contrast abbreviated

The standard MRI protocol uses multiple sequences to identify malignancy and characterize benign breast findings requiring longer magnet and interpretation times. The protocol for AB-MRI is variable and even customizable, however, all protocols use a limited number of images to highlight findings in the early postcontrast phase. This technique maximizes cancer detection while reducing the time burden on the patient and the radiologist. Negative studies can be quickly interpreted, reducing physician workload. Lawson et al [23] found no statistical difference when comparing the sensitivity of standard MRI with AB-MRI (100% to 88.9%). This is consistent with findings from Kuhl et al [24], Baxter et al [19], and others [25,26]. The EA1141 trial demonstrated a CDR (invasive and DCIS) of 15.2 per 1,000 examinations with AB-MRI compared with 6.2 per 1,000 examinations with DBT in average-risk women with dense tissue [27]. The specificity of AB-MRI was reduced when compared with DBT (87% versus 97%). Clinicians should be aware that baseline imaging may result in benign biopsies or short-term interval follow-ups [28]. Weinstein et al [29] reported a CDR of 27.4 per 1,000 in a retrospective review of average-risk women previously screened with DBT.

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.
F. MRI breast without IV contrast

There is no relevant literature regarding the use of MRI breast without IV contrast for supplemental screening in average-risk women with extremely dense breasts.

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.
G. MRI breast without IV contrast abbreviated

There is no relevant literature regarding the use of AB-MRI breast without IV contrast for supplemental screening in average-risk women with extremely dense breasts.

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.
H. Sestamibi MBI

Currently, there is insufficient evidence to support the use of Tc-99m sestamibi MBI as a supplemental screening examination in average-risk women with extremely dense tissue, however, there are emerging data. At present, barriers include lack of incidence around screening, longer examination times, and limited studies addressing the spectrum of breast densities and risk [7].

MBI is a nuclear medicine study that uses the IV injection of Tc-99m sestamibi to identify mitotically active areas within breast tissue, ideally differentiating malignant tumors from background parenchyma. Although BSGI uses single detector sodium iodide cameras, MBI employs dual-head cadmium zinc telluride detectors to obtain a functional imaging study, which takes approximately 40 minutes [30]. The prospective study (1,585 women) by Rhodes et al [31] and a retrospective study (1,696 women) by Shermis et al [32] reported a CDR of 7.7 to 8.8 per 1,000 in women with dense breasts. Preliminary data from the MATTERS trial, comparing DBT and MBI, found 7 cancers in 537 women, 6 of which were found by MBI only. All were invasive. The incremental CDR of MBI was 9.3 per 1,000 [31].

Variant 3: Adult female. Supplemental breast cancer screening. Average risk. Extremely dense breasts.

I. US breast

Screening breast US can be performed using HHUS or ABUS techniques. Although the sensitivity of mammography in nondense tissue approaches 90%, it can be as low as 30% in women with extremely dense tissue [17]. Screening US offers improved sensitivity and interval cancer detection particularly in women with dense tissue. A statistically significant CDR of an additional 3.0 per 1,000 breast cancers was identified in average-risk women with dense tissue in a secondary review of the J-START [33,34]. Additionally, a significant decrease was observed in the interval cancer rate (0.5 per 1,000 compared with 2.0 per 1,000 in the control group). In women with nondense tissue, the J-START trial demonstrated increased cancer detection as well, but this was not supported in 2 other large cohort studies [18]. The prospective, multicenter ASTOUND-2 trial conducted in screening women with dense tissue found 4.9 per 1,000 additional cancers with HHUS as compared with 2.8 per 1,000 with DBT, although the former had more false-positives [35]. Although studies have demonstrated increased CDR with the addition of screening US to mammography, this comes at the expense of low biopsy PPVs and high false-positive rates including a high rate of short-term follow-up recommendations [7,19]. No added benefit of screening US has been found in women who undergo MRI breast or AB-MRI screening [20].

In women with elevated risk only due to breast density, supplemental screening US could be considered [7].

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

The goal of screening is early detection of breast cancer prior to it being detected clinically, improving morbidity and mortality. The expected outcome is longevity to the patient and decreased burden of disease.

Women with a history of lobular neoplasia, composed of lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH) or atypical ductal hyperplasia (ADH), frequently receive an intermediate risk determination (15%-20%). Lobular hyperplasia confers a 6- to 10-fold greater risk of developing breast cancer as compared with ADH with a 4- to 5-fold greater risk [39,40].

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

A. Digital breast tomosynthesis screening

Screening mammography has been shown to reduce mortality by approximately 30% to 40% [3,4]. It is most sensitive in women with nondense tissue.

In DBT, the x-ray tube moves in an arc obtaining multiple low-dose mammographic images that are reconstructed into 2-D images. The additional information from varying angles aims to reduce summation shadows and overlapping structures to maximize visibility [2].

The retrospective PROSPR consortium review evaluated more than 180,000 women; approximately 130,000 were screened with DM and 50,000 with DBT. Women with nondense tissue accounted for 64% of the cohort as compared with 36% with dense tissue. A statistically significant increase in CDR was found in women with both nondense tissue (1.7/1,000) and dense tissue (2.27/1,000) screened with DBT. Cancers tended to be smaller, lymph node negative, and less biologically aggressive [9]. Li et al [10] reviewed several studies comparing DBT with 2-D mammography in Europe and the United States and found the pooled CDR to be statistically significant in both nondense and dense tissue.

Another advantage of DBT is a reduction in recall rate with improved specificity. A few studies have demonstrated this benefit with the reduction ranging between 15% to 63% in observational, retrospective studies in the United States [11,12]. In a retrospective cohort study evaluating multiple screening rounds, Sprague et al [13] found no difference in the interval cancer rate between DBT and DM. The randomized prospective TMIST trial comparing DBT with 2-D mammography is currently active.

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

B. FDG-PET breast dedicated

There is no relevant literature regarding the use of FDG-PET breast dedicated for supplemental screening in intermediate-risk women with nondense breasts.

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

C. Mammography with IV contrast

CEM uses a dual-energy technique to acquire 8 standard mammographic images after the administration of IV iodinated contrast material. Four low-energy images mimic a conventional 2-D mammogram. The additional 4 diagnostic recombined images demonstrate contrast enhancement, which offers morphologic as well as functional assessment to identify malignancies. CEM has been valuable in evaluating abnormalities in the diagnostic setting [14], however, recent literature has indicated that it may play a beneficial role in screening women with dense tissue at an intermediate risk of developing breast cancer or those seeking an alternative supplemental screening modality to MRI [15]. The CDR in screening studies has ranged from 8.6 to 13.1 cancers per 1,000 screening examinations [21,22], although most of these were conducted retrospectively at a single institution. In an observational, retrospective study evaluating diagnostic accuracy of lobular neoplasia, CEM had a sensitivity of 100% and a specificity of 88% [41].

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

D. MRI breast without and with IV contrast

A retrospective review by Sippo et al [3] demonstrated similar CDRs in the high-risk group (BRCA mutation carrier/history of chest radiation therapy [RT]), compared with the intermediate-risk group (personal history/high-risk lesion). The CDR for BRCA/RT was 26 per 1,000 as compared with

12 per 1,000 (personal history) and 15 per 1,000 (high-risk lesion). The group with elevated risk from family history alone did not show a similar benefit. The groups were not stratified by breast density. A review of several single-institution retrospective studies conducted by Bahl [39] in women with intermediate risk with varying breast densities demonstrated CDRs ranging between 11-16/1000. Women with a history of ALH or ADH did not benefit as greatly as women with LCIS.

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

E. MRI breast without and with IV contrast abbreviated

There is limited relevant specific literature regarding the use of AB-MRI without and with IV contrast for supplemental screening in intermediate-risk women with nondense breasts. However, given the multiplicity of studies that demonstrate similar diagnostic accuracy between full protocol MRI and AB-MRI [23-28], the benefit may be comparable in certain patient populations.

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

F. MRI breast without IV contrast

There is no relevant literature regarding the use of MRI breast without IV contrast for supplemental screening in intermediate-risk women with nondense breasts.

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

G. MRI breast without IV contrast abbreviated

There is no relevant literature regarding the use of AB-MRI breast without IV contrast for supplemental screening in intermediate-risk women with nondense breasts.

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

H. Sestamibi MBI

There is no relevant literature regarding the use of Tc-99m sestamibi MBI for supplemental screening in intermediate-risk women with nondense breasts. This modality is not yet widely used in clinical practice.

Variant 4: Adult female. Supplemental breast cancer screening. Intermediate risk. Nondense breasts.

I. US breast

Screening breast US can be performed using HHUS or ABUS techniques. Although the sensitivity of mammography in nondense tissue approaches 90%, it can be as low as 30% in women with extremely dense tissue [17]. In women with nondense tissue, the J-START trial demonstrated increased cancer detection, but this was not supported in 2 other large cohort studies [18]. Although studies have demonstrated increased CDR with the addition of screening US to mammography, this comes at the expense of low biopsy PPVs and high false-positive rates including a high rate of short-term follow-up recommendations [7,19]. No added benefit of screening US has been found in women who undergo MRI breast or AB-MRI screening [20].

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.

The goal of screening is early detection of breast cancer prior to it being detected clinically, improving morbidity and mortality. Supplemental imaging studies can improve sensitivity in

women with dense breast tissue. The expected outcome is longevity to the patient and decreased burden of disease.

Women with a history of lobular neoplasia, composed of LCIS and ALH or ADH, frequently receive an intermediate risk determination (15%-20%). Lobular hyperplasia confers a 6- to 10-fold greater risk of developing breast cancer as compared with ADH with a 4- to 5-fold greater risk [39,40].

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
A. Digital breast tomosynthesis screening

Screening mammography has been shown to reduce mortality by approximately 30% to 40% [3,4]. It is most sensitive in women with nondense tissue. Women with heterogeneously and extremely dense tissue, who can comprise up to half of screening-aged women in the United States, may not receive the same benefit from mammography alone because the sensitivity can be reduced by 30% to 48% in extremely dense tissue [17].

In DBT, the x-ray tube moves in an arc obtaining multiple low-dose mammographic images that are reconstructed into 2-D images. The additional information from varying angles aims to reduce summation shadows and overlapping structures to maximize visibility [2].

The retrospective PROSPR consortium review evaluated more than 180,000 women; approximately 130,000 were screened with DM and 50,000 with DBT. Women with nondense tissue accounted for 64% of the cohort as compared with 36% with dense tissue. A statistically significant increase in CDR was found in women with both nondense tissue (1.7/1,000) and dense tissue (2.27/1,000) screened with DBT. Cancers tended to be smaller, lymph node negative, and less biologically aggressive [9]. Li et al [10] reviewed several studies comparing DBT with 2-D mammography in Europe and the United States and found the pooled CDR to be statistically significant in both nondense and dense tissue. However, Berg et al [20] found the greatest increase in CDR to be in women with heterogeneously dense breasts. No significant increase in detection was identified in women with extremely dense tissue [20], highlighting the need for other methods of supplemental screening in this population.

Another advantage of DBT is a reduction in recall rate with improved specificity. A few studies have demonstrated this benefit with the reduction ranging between 15% to 63% in observational, retrospective studies in the United States [11,12]. In a retrospective cohort study evaluating multiple screening rounds, Sprague et al [13] found no difference in the interval cancer rate between DBT and DM. The randomized prospective TMIST trial comparing DBT with 2-D mammography is currently active.

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
B. FDG-PET breast dedicated

There is no relevant literature regarding the use of FDG-PET breast dedicated for supplemental screening in intermediate-risk women with heterogeneously dense breasts.

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
C. Mammography with IV contrast

CEM uses a dual-energy technique to acquire 8 standard mammographic images after the administration of IV iodinated contrast material. Four low-energy images mimic a conventional 2-D

mammogram. The additional 4 diagnostic recombined images demonstrate contrast enhancement, which offers morphologic as well as functional assessment to identify malignancies. CEM has been valuable in evaluating abnormalities in the diagnostic setting [14], however, recent literature has indicated that it may play a beneficial role in screening women with dense tissue at an intermediate risk of developing breast cancer or those seeking an alternative supplemental screening modality to MRI [15]. The CDR in screening studies has ranged from 8.6 to 13.1 cancers per 1,000 screening examinations [21,22], although most of these were conducted retrospectively at a single institution. CEM offers a higher sensitivity compared with mammography, with the benefit statistically significant in women with dense breast tissue [21]. The CMIST is currently enrolling intermediate-risk women with dense breasts to participate in a prospective study comparing DBT and CEM.

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
D. MRI breast without and with IV contrast

A retrospective review by Sippo et al [3] demonstrated similar CDRs in the high-risk group (BRCA mutation carrier/history of chest RT), compared with the intermediate-risk group (personal history/high-risk lesion). The CDR for BRCA/RT was 26 per 1,000 as compared with 12 per 1,000 (personal history) and 15 per 1,000 (high-risk lesion). The group with elevated risk from family history alone did not show a similar benefit. The groups were not stratified by breast density.

In a review of 22 randomized clinical trials and observational prospective studies, supplemental MRI had a CDR of 19.9 per 1,000 versus 4.5 per 100 HHUS versus 3.2 per 1,000 DBT in average- and intermediate-risk women with dense tissue [17]. In women with a higher than average risk of developing breast cancer and dense tissue, supplemental screening with breast MRI is advised [7].

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
E. MRI breast without and with IV contrast abbreviated

The standard MRI protocol uses multiple sequences to identify malignancy and characterize benign breast findings requiring longer magnet and interpretation times. The protocol for AB-MRI is variable and even customizable, however, all protocols use a limited number of images to highlight findings in the early postcontrast phase. This technique maximizes cancer detection while reducing the time burden on the patient and the radiologist. Negative studies can be quickly interpreted, reducing physician workload. Lawson et al [23] found no statistical difference when comparing the sensitivity of standard MRI with AB-MRI (100% to 88.9%). This is consistent with findings from Kuhl et al [24], Baxter et al [19], and others [25,26]. The EA1141 trial demonstrated a CDR (invasive and DCIS) of 15.2 per 1,000 examinations with AB-MRI compared with 6.2 per 1,000 examinations with DBT in average-risk women with dense tissue [27]. The specificity of AB-MRI was reduced when compared with DBT (87% versus 97%). Clinicians should be aware that baseline imaging may result in benign biopsies or short-term interval follow-ups [28]. Weinstein et al [29] reported a CDR of 27.4 per 1,000 in a retrospective review of average-risk women previously screened with DBT.

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
F. MRI breast without IV contrast

There is no relevant literature regarding the use of MRI breast without IV contrast for supplemental

screening in intermediate-risk women with heterogeneously dense breasts.

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
G. MRI breast without IV contrast abbreviated

There is no relevant literature regarding the use of AB-MRI breast without IV contrast for supplemental screening in intermediate-risk women with heterogeneously dense breasts.

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
H. Sestamibi MBI

Currently, there is insufficient evidence to support the use of Tc-99m sestamibi MBI as a supplemental screening exam in intermediate-risk women with heterogeneously dense tissue, however, there are emerging data. At present, barriers include lack of incidence around screening, longer examination times, and limited studies addressing the spectrum of breast densities and risk [7].

MBI is a nuclear medicine study that uses the IV injection of Tc-99m sestamibi to identify mitotically active areas within breast tissue, ideally differentiating malignant tumors from background parenchyma. Although BSGI uses single detector sodium iodide cameras, MBI employs dual-head cadmium zinc telluride detectors to obtain a functional imaging study, which takes approximately 40 minutes [30]. The prospective study (1,585 women) by Rhodes et al [31] and a retrospective study (1,696 women) by Shermis et al [32] reported a CDR of 7.7 to 8.8 per 1,000 in women with dense breasts. Preliminary data from the MATTERS trial, comparing DBT and MBI, found 7 cancers in 537 women, 6 of which were found by MBI only. All were invasive. The incremental CDR of MBI was 9.3 per 1,000 [31].

Variant 5: Adult female. Supplemental breast cancer screening. Intermediate risk. Heterogeneously dense breasts.
I. US breast

Screening breast US can be performed using HHUS or ABUS techniques. Although the sensitivity of mammography in nondense tissue approaches 90%, it can be as low as 30% in women with extremely dense tissue [17]. Screening US offers improved sensitivity and interval cancer detection particularly in women with dense tissue. A statistically significant CDR of an additional 3.0 per 1,000 breast cancers was identified in average-risk women with dense tissue in a secondary review of the J-START [33,34]. Additionally, a significant decrease was observed in the interval cancer rate (0.5 per 1,000 as compared with 2.0 per 1,000 in the control group). In women with nondense tissue, the J-START trial demonstrated increased cancer detection as well, but this was not supported in 2 other large cohort studies [18]. The prospective, multicenter ASTOUND-2 trial conducted in screening women with dense tissue found 4.9 per 1,000 additional cancers with HHUS as compared with 2.8 per 1,000 with DBT, although the former had more false-positives [35]. Although studies have demonstrated increased CDR with the addition of screening US to mammography, this comes at the expense of low biopsy PPVs and high false-positive rates including a high rate of short-term follow-up recommendations [7,19]. No added benefit of screening US has been found in women who undergo MRI breast or AB-MRI screening [20].

In women with an elevated risk of breast cancer and dense tissue who cannot undergo supplemental screening with MRI, breast US could be considered [7].

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely

dense breasts.

The goal of screening is early detection of breast cancer prior to it being detected clinically, improving morbidity and mortality. Supplemental imaging studies can improve sensitivity in women with dense breast tissue. The expected outcome is longevity to the patient and decreased burden of disease.

Women with a history of lobular neoplasia, composed of LCIS and ALH or ADH, frequently receive an intermediate risk determination (15%-20%). Lobular hyperplasia confers a 6- to 10-fold greater risk of developing breast cancer compared with ADH with a 4- to 5-fold greater risk [39,40].

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.

A. Digital breast tomosynthesis screening

Screening mammography has been shown to reduce mortality by approximately 30% to 40% [3,4]. It is most sensitive in women with nondense tissue. Women with heterogeneously and extremely dense tissue, who can comprise up to half of screening-aged women in the United States, may not receive the same benefit from mammography alone because sensitivity can be reduced by 30% to 48% in extremely dense tissue [17].

In DBT, the x-ray tube moves in an arc obtaining multiple low-dose mammographic images that are reconstructed into 2-D images. The additional information from varying angles aims to reduce summation shadows and overlapping structures to maximize visibility [2].

The retrospective PROSPR consortium review evaluated more than 180,000 women; approximately 130,000 were screened with DM and 50,000 with DBT. Women with nondense tissue accounted for 64% of the cohort as compared with 36% with dense tissue. A statistically significant increase in CDR was found in women with both nondense tissue (1.7/1,000) and dense tissue (2.27/1,000) screened with DBT. Cancers tended to be smaller, lymph node negative, and less biologically aggressive [9]. Li et al [10] reviewed several studies comparing DBT with 2-D mammography in Europe and the United States and found the pooled CDR to be statistically significant in both nondense and dense tissue. However, Berg et al [20] found the greatest increase in CDR to be in women with heterogeneously dense breasts. No significant increase in detection was identified in women with extremely dense tissue [20], highlighting the need for other methods of supplemental screening in this population.

Another advantage of DBT is a reduction in recall rate with improved specificity. A few studies have demonstrated this benefit, with the reduction ranging between 15% to 63% in observational, retrospective studies in the United States [11,12]. In a retrospective cohort study evaluating multiple screening rounds, Sprague et al [13] found no difference in the interval cancer rate between DBT and DM. The randomized prospective TMIST trial comparing DBT with 2-D mammography is currently active.

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.

B. FDG-PET breast dedicated

There is no relevant literature regarding the use of FDG-PET breast dedicated for supplemental screening in intermediate-risk women with extremely dense breasts.

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.

C. Mammography with IV contrast

CEM uses a dual-energy technique to acquire 8 standard mammographic images after the administration of IV iodinated contrast material. Four low-energy images mimic a conventional 2-D mammogram. The additional 4 diagnostic recombined images demonstrate contrast enhancement, which offers morphologic as well as functional assessment to identify malignancies. CEM has been valuable in evaluating abnormalities in the diagnostic setting [14], however, recent literature has indicated that it may play a beneficial role in screening women with dense tissue at an intermediate risk of developing breast cancer or those seeking an alternative supplemental screening modality to MRI [15]. The CDR in screening studies has ranged from 8.6 to 13.1 cancers per 1,000 screening examinations [21,22], although most of these were conducted retrospectively at a single institution. CEM offers a higher sensitivity compared with mammography, with the benefit statistically significant in women with dense breast tissue [21]. The CMIST is currently enrolling intermediate-risk women with dense breasts to participate in a prospective study comparing DBT and CEM.

In an observational, retrospective study evaluating diagnostic accuracy of lobular neoplasia, CEM had a sensitivity of 100% and a specificity of 88% [41].

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.

D. MRI breast without and with IV contrast

The DENSE trial is a Dutch multicenter, randomized trial in which supplemental MRI identified an additional 16.5 cancers per 1,000 screened in women of all risk stratification [36]. Additionally, the interval cancer rate of the MRI group was 0.8 per 1,000 as compared with the control group 5.0 per 1,000, suggesting a mortality benefit. In the second round of screening, the false-positive rate dropped to 26.3 per 1,000 from 79.8 per 1,000, and the incremental CDR was 5.8 per 1,000 [37]. Given the superior detection rate of MRI compared with DBT or US in women with dense breasts, the European Society of Breast Imaging now recommends supplemental screening with MRI in women with extremely dense breast tissue, regardless of risk [38].

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.

E. MRI breast without and with IV contrast abbreviated

The standard MRI protocol uses multiple sequences to identify malignancy and characterize benign breast findings requiring longer magnet and interpretation times. The protocol for AB-MRI is variable and even customizable, however, all protocols use a limited number of images to highlight findings in the early postcontrast phase. This technique maximizes cancer detection while reducing the time burden on the patient and the radiologist. Negative studies can be quickly interpreted, reducing physician workload. Lawson et al [23] found no statistical difference when comparing the sensitivity of standard MRI with AB-MRI (100% to 88.9%). This is consistent with findings from Kuhl et al [24], Baxter et al [19], and others [25,26]. In a prospective observational reader study of 443 women with mild to moderate increased risk, AB-MRI had a CDR of 18.2 per 1,000 after a negative mammogram [24]. Clinicians should be aware that baseline imaging may result in benign biopsies or short-term interval follow-ups [28].

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.

F. MRI breast without IV contrast

There is no relevant literature regarding the use of MRI breast without IV contrast for supplemental screening in intermediate-risk women with extremely dense breasts.

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.
G. MRI breast without IV contrast abbreviated

There is no relevant literature regarding the use of AB-MRI breast without IV contrast for supplemental screening in intermediate-risk women with extremely dense breasts.

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.
H. Sestamibi MBI

Currently, there is insufficient evidence to support the use of Tc-99m sestamibi MBI as a supplemental screening exam in intermediate-risk women with extremely dense tissue, however, there are emerging data. At present, barriers include lack of incidence around screening, longer examination times, and limited studies addressing the spectrum of breast densities and risk [7].

MBI is a nuclear medicine study that uses the IV injection of Tc-99m sestamibi to identify mitotically active areas within breast tissue, ideally differentiating malignant tumors from background parenchyma. Although BSGI uses single detector sodium iodide cameras, MBI employs dual-head cadmium zinc telluride detectors to obtain a functional imaging study, which takes approximately 40 minutes [30]. The prospective study (1,585 women) by Rhodes et al [31] and a retrospective study (1,696 women) by Shermis et al [32] reported a CDR of 7.7 to 8.8 per 1,000 in women with dense breasts. Preliminary data from the MATTERS trial, comparing DBT and MBI, found 7 cancers in 537 women, 6 of which were found by MBI only. All were invasive. The incremental CDR of MBI was 9.3 per 1,000 [31].

Variant 6: Adult female. Supplemental breast cancer screening. Intermediate risk. Extremely dense breasts.
I. US breast

Screening breast US can be performed using HHUS or ABUS techniques. Although the sensitivity of mammography in nondense tissue approaches 90%, it can be as low as 30% in women with extremely dense tissue [17]. Screening US offers improved sensitivity and interval cancer detection, particularly in women with dense tissue. A statistically significant CDR of an additional 3.0 per 1,000 breast cancers was identified in average-risk women with dense tissue in a secondary review of the J-START [33,34]. Additionally, a significant decrease was observed in the interval cancer rate (0.5 per 1,000 compared with 2.0 per 1,000 in the control group). In women with nondense tissue, the J-START trial demonstrated increased cancer detection as well, but this was not supported in 2 other large cohort studies [18]. The prospective, multicenter ASTOUND-2 trial conducted in screening women with dense tissue found 4.9 per 1,000 additional cancers with HHUS as compared with 2.8 per 1,000 with DBT, although the former had more false-positives [35]. Although studies have demonstrated increased CDR with the addition of screening US to mammography, this comes at the expense of low biopsy PPVs and high false-positive rates including a high rate of short-term follow-up recommendations [7,19]. No added benefit of screening US has been found in women who undergo MRI breast or AB-MRI screening [20].

In women with an elevated risk of breast cancer and dense tissue who cannot undergo supplemental screening with MRI, breast US could be considered [7].

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

The goal of screening is early detection of breast cancer prior to it being detected clinically, improving morbidity and mortality. Supplemental imaging studies can improve sensitivity in women with dense breast tissue. The expected outcome is longevity to the patient and decreased burden of disease.

High-risk women have a ≥20% lifetime risk of developing breast cancer. This group includes BRCA mutation carriers and their first degree, untested relatives; women with Li-Fraumeni and other high-risk predisposition syndromes; women who received radiation to the chest between 10 to 30 years of age; and women diagnosed before the age of 50 treated with breast-conserving therapy.

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

A. Digital breast tomosynthesis screening

Screening mammography has been shown to reduce mortality by approximately 30% to 40% [3,4]. It is most sensitive in women with nondense tissue. Women with heterogeneously and extremely dense tissue, who can comprise up to half of screening-aged women in the United States, may not receive the same benefit from mammography alone because sensitivity can be reduced by 30% to 48% in extremely dense tissue [17].

In DBT, the x-ray tube moves in an arc obtaining multiple low-dose mammographic images that are reconstructed into 2-D images. The additional information from varying angles aims to reduce summation shadows and overlapping structures to maximize visibility [2].

The retrospective PROSPR consortium review evaluated more than 180,000 women; approximately 130,000 were screened with DM and 50,000 with DBT. Women with nondense tissue accounted for 64% of the cohort as compared with 36% with dense tissue. A statistically significant increase in CDR was found in women with both nondense tissue (1.7/1,000) and dense tissue (2.27/1,000) screened with DBT. Cancers tended to be smaller, lymph node negative, and less biologically aggressive [9]. Li et al [10] reviewed several studies comparing DBT with 2-D mammography in Europe and the United States and found the pooled CDR to be statistically significant in both nondense and dense tissue. However, Berg et al [20] found the greatest increase in CDR to be in women with heterogeneously dense breasts. No significant increase in detection was identified in women with extremely dense tissue, highlighting the need for other methods of supplemental screening in this population.

Another advantage of DBT is a reduction in recall rate with improved specificity. A few studies have demonstrated this benefit with the reduction ranging between 15% to 63% in observational, retrospective studies in the United States [11,12]. In a retrospective cohort study evaluating multiple screening rounds, Sprague et al [13] found no difference in the interval cancer rate between DBT and DM. The randomized prospective TMIST trial comparing DBT with 2-D mammography is currently active.

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

B. FDG-PET breast dedicated

There is no relevant literature regarding the use of FDG-PET breast dedicated for supplemental screening in high-risk women with nondense and dense breasts.

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

C. Mammography with IV contrast

CEM uses a dual-energy technique to acquire 8 standard mammographic images after the administration of IV iodinated contrast material. Four low-energy images mimic a conventional 2-D mammogram. The additional 4 diagnostic recombined images demonstrate contrast enhancement, which offers morphologic as well as functional assessment to identify malignancies. CEM has been valuable in evaluating abnormalities in the diagnostic setting [14], however, recent literature has indicated that it may play a beneficial role in screening women with dense tissue at an intermediate risk of developing breast cancer or those seeking an alternative supplemental screening modality to MRI [15]. The CDR in screening studies has ranged from 8.6 to 13.1 cancers per 1,000 screening examinations [21,22], although most of these were conducted retrospectively at a single institution. CEM offers a higher sensitivity compared with mammography, with the benefit statistically significant in women with dense breast tissue [21]. The CMIST is currently enrolling intermediate-risk women with dense breasts to participate in a prospective study comparing DBT and CEM. Although in a single-institution, prospective study, Lawson et al [23] found the sensitivity of standard and AB-MRI to be higher, and CEM reduced recall rates and had a higher PPV when compared with MRI or AB-MRI.

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

D. MRI breast without and with IV contrast

American Cancer Society and NCCN guidelines support the use of annual breast MRI in high-risk individuals regardless of breast density. MRI has the highest CDR of all modalities (8.2-15.9 per 1,000 for MRI alone), and in the high-risk population, sensitivity is not affected by breast density [5]. Sippo et al [3] demonstrated a CDR of 26 per 1,000 in the BRCA/RT group with a high PPV of 41%. In a multicenter, prospective trial the sensitivity of MRI (91%) was greater than US (52%) or mammography plus US (63%) in the high-risk population [42].

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

E. MRI breast without and with IV contrast abbreviated

The standard MRI protocol uses multiple sequences to identify malignancy and characterize benign breast findings requiring longer magnet and interpretation times. The protocol for AB-MRI is variable and even customizable, however, all protocols use a limited number of images to highlight findings in the early postcontrast phase. This technique maximizes cancer detection while reducing the time burden on the patient and the radiologist. Negative studies can be quickly interpreted, reducing physician workload. Lawson et al [23] found no statistical difference when comparing the sensitivity of standard MRI with AB-MRI (100% to 88.9%). This is consistent with findings from Kuhl et al [24], Baxter et al [19], and others [25,26]. In a retrospective review of 568 high-risk women by Harvey et al [43], no difference was identified in CDR (12.3/1,000) when comparing abbreviated and full protocol MRI.

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

F. MRI breast without IV contrast

There is no relevant literature regarding the use of MRI breast without IV contrast for supplemental screening in high-risk women with nondense or dense breasts.

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

G. MRI breast without IV contrast abbreviated

There is no relevant literature regarding the use of AB-MRI breast without IV contrast for supplemental screening in high-risk women with nondense or dense breasts.

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

H. Sestamibi MBI

Currently, there is insufficient evidence to support the use of Tc-99m sestamibi MBI as a supplemental screening exam in high-risk women with nondense and dense breast tissue, however, there are emerging data. At present, barriers include lack of incidence around screening, longer examination times, and limited studies addressing the spectrum of breast densities and risk [7].

MBI is a nuclear medicine study that uses the IV injection of Tc-99m sestamibi to identify mitotically active areas within breast tissue, ideally differentiating malignant tumors from background parenchyma. Although BSGI uses single detector sodium iodide cameras, MBI employs dual-head cadmium zinc telluride detectors to obtain a functional imaging study, which takes approximately 40 minutes [30]. The prospective study (1585 women) by Rhodes et al [31] and a retrospective study (1696 women) by Shermis et al [32] reported a CDR of 7.7 to 8.8 per 1,000 in women with dense breasts. Preliminary data from the MATTERS trial, comparing DBT and MBI, found 7 cancers in 537 women, 6 of which were found by MBI only. All were invasive. The incremental CDR of MBI was 9.3 per 1,000 [31].

Variant 7: Adult female. Supplemental breast cancer screening. High risk. Nondense or dense breasts.

I. US breast

Screening breast US can be performed using HHUS or ABUS techniques. Although the sensitivity of mammography in nondense tissue approaches 90%, it can be as low as 30% in women with extremely dense tissue [17]. Screening US offers improved sensitivity and interval cancer detection particularly in women with dense tissue. A statistically significant CDR of an additional 3.0 per 1,000 breast cancers was identified in average-risk women with dense tissue in a secondary review of the J-START [33,34]. Additionally, a significant decrease was observed in the interval cancer rate (0.5 per 1,000 compared with 2.0 per 1,000 in the control group). In women with nondense tissue, the J-START trial demonstrated increased cancer detection as well, but this was not supported in 2 other large cohort studies [18]. The prospective, multicenter ASTOUND-2 trial conducted in screening women with dense tissue found 4.9 per 1,000 additional cancers with HHUS as compared with 2.8 per 1,000 with DBT, although the former had more false-positives [35]. Although studies have demonstrated increased CDR with the addition of screening US to mammography, this comes at the expense of low biopsy PPVs and high false-positive rates including a high rate of short-term follow-up recommendations [7,19]. No added benefit of screening US has been found in women who undergo MRI breast or AB-MRI screening [20].

In women with an elevated risk of breast cancer and dense tissue who cannot undergo supplemental screening with MRI, breast US could be considered [7].

Summary of Highlights

This is a summary of the key recommendations from the variant tables. Refer to the complete narrative document for more information.

- **All Variants:** Supplemental screening with DBT is recommended for all women regardless of risk status or breast density. DBT has a higher CDR than DM and tends to find cancers that are smaller, lymph node negative, and less biologically aggressive.
- **Variants 2 and 5:** Women with heterogeneously dense tissue may benefit from supplemental screening with breast MRI, AB-MRI, or US based on risk. In women with average risk, breast MRI and AB-MRI may be appropriate, and these studies are usually appropriate for women of intermediate risk. In higher-than-average-risk women, breast US may be appropriate although studies have demonstrated increased CDR comes at the expense of low biopsy PPVs and high false-positive rates. Preliminary data suggest CEM may be appropriate in higher than average risk women.
- **Variant 4**: There are limited data regarding intermediate-risk women with stratification by breast density. However, a retrospective study demonstrates similar CDRs between the high-risk and intermediate-risk groups on breast MRI. Multiple studies indicate similar diagnostic accuracy between breast MRI and AB-MRI; therefore, both may be appropriate as supplemental screening examinations in this population.
- **Variants 3 and 6:** In women with extremely dense tissue, breast MRI and AB-MRI is usually appropriate regardless of risk based on the DENSE trial, which demonstrated a high CDR and low interval cancer rate and suggested a mortality benefit. In both average- and intermediate-risk women, breast US may be appropriate, although studies have demonstrated increased CDR comes at the expense of low biopsy PPVs and high false-positive rates. Preliminary data suggest CEM may be appropriate in higher than average-risk women.
- **Variant 7:** In high-risk women, breast MRI and AB-MRI are usually appropriate regardless of breast density. CEM and breast US may also be appropriate in this population.

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents, please go to the ACR website at https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria.

Gender Equality and Inclusivity Clause

The ACR acknowledges the limitations in applying inclusive language when citing research studies that predates the use of the current understanding of language inclusive of diversity in sex, intersex, gender, and gender-diverse people. The data variables regarding sex and gender used in the cited literature will not be changed. However, this guideline will use the terminology and definitions as proposed by the National Institutes of Health.

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document.

Relative Radiation Level Designations

Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv

*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (e.g., region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."

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Disclaimer

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

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