

Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue



The New England Comparative Effectiveness Public Advisory Council

An Action Guide for Supplemental Cancer Screening for Women with Dense Breasts: Next Steps for Patients, Clinicians, and Insurers

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Introduction

About this guide

Evidence from clinical effectiveness reviews is critical to judgments that patients, clinicians, and health insurers must make about treatment choices and coverage policies. Yet evidence is often not translated in a way that is helpful to inform healthcare decisions. This document is a companion policy guide designed to help patients, clinicians, and insurers make use of the results of a recent technology assessment titled “[The Comparative Clinical Effectiveness and Value of Supplemental Screening Tests Following Negative Mammography in Women with Dense Breast Tissue](#)”. Faculty at the University of California, San Francisco, University of Washington, and the Institute for Clinical and Economic Review developed this report, which formed the basis for the deliberations and votes of a recent meeting of the New England Comparative Effectiveness Public Advisory Council (CEPAC). CEPAC is an independent body comprised of New England-based physicians, methodologists, and patient/public representatives that provides objective guidance to decision-makers on how to apply information from evidence reviews to improve the quality and value of healthcare services.¹

CEPAC held its meeting on supplemental cancer screening for women with dense breast tissue on December 13, 2013 in Boston, Massachusetts. A full report summarizing the discussion and votes taken is available on the [CEPAC website](#). We have developed this Action Guide in order to provide a user-friendly overview of the CEPAC findings and an associated list of specific evidence-based action steps that patients, clinicians, and insurers can take to improve patient outcomes and the overall value of supplemental screening. The content provided here is for informational purposes only, and does not replace professional medical advice.

A note on CEPAC evidence voting and best practice recommendations

Each public meeting of CEPAC involves deliberation and voting on key questions on the comparative clinical effectiveness and value of the various diagnosis and treatment options discussed. When voting on economic impact, CEPAC Council members do not receive prescribed thresholds or boundaries for how to interpret value. Rather, CEPAC assumes the perspective of a state Medicaid program or provider organization making resources decisions within a fixed budget of care.

After voting, CEPAC members engage in a Policy Roundtable with New England-based experts representing patient, clinical, payer, and provider group perspectives. The goal of the Roundtable is to discuss ways the evidence can inform policy and practice on a regional basis. CEPAC’s deliberation with the Policy Roundtable leads to recommendations and suggestions for best practices that form the basis for this document.

¹ For more information on CEPAC, visit: <http://cepac.icer-review.org/>

Executive Summary

Background

In 2009, the state of Connecticut passed a law requiring that health care facilities performing mammograms inform women with dense breasts, who comprise approximately 50% of all screening-age women, about the potential for dense breast tissue to hide, or “mask” breast cancer in routine screening mammograms. Because of the law, in Connecticut patients with dense breast tissue receive the following language with every normal mammogram result:

*If your mammogram demonstrated that you have dense breast tissue, which could hide small abnormalities, you might benefit from supplemental screening tests, which can include a breast ultrasound screening or a breast MRI examination, or both, depending on your individual risk factors. A report of your mammography results, which contains information about your breast density, has been sent to your physician’s office and you should contact your physician if you have any questions or concerns about this report.*¹

Massachusetts legislators are currently considering similar breast density notification legislation, and notification laws have already been passed in nine other states.^{2,3} A number of tests have been promoted as potential methods for supplemental screening in women with dense breasts, including hand-held and automated breast ultrasound, digital breast tomosynthesis (DBT), and magnetic resonance imaging (MRI). This review evaluates the evidence on the comparative effectiveness and value of various supplemental screening options, and seeks to place consideration of the evidence within the broader context of the relationship of dense breast tissue to women’s overall risk for developing breast cancer.

Breast density and overall breast cancer risk assessment

In the United States, the Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology classifies breast density into one of the following four categories: 1) Almost entirely fatty; 2) Scattered fibroglandular densities; 3) Heterogeneously dense; and 4) Extremely dense tissue. Breast density is a strong independent risk factor for breast cancer, with a relative risk of 1.5 for heterogeneously dense and 2.0 for extremely dense tissue compared to scattered fibroglandular density.⁴

The link between overall risk for breast cancer and breast cancer screening recommendations is well established, but ways to calculate and apply risk thresholds differ. The American Cancer Society recommends annual MRI screening for women with a lifetime risk for breast cancer above 20-25%. Experts selected this risk threshold, which is based largely on considerations of genetic susceptibility. Another commonly cited risk threshold is a five-year risk of breast cancer greater than 1.66%, the risk above which tamoxifen has been demonstrated to reduce the risk of breast cancer by about 50%. For considerations of the risks and benefits of supplemental screening, a 5-year risk threshold is more relevant than lifetime breast cancer risk. Because breast density is both common and an independent risk factor for breast cancer,

researchers have added it to newer risk models, including the BCSC model, which uses BI-RADS density in combination with a woman’s age, race/ethnicity, family history, and history of breast biopsies to estimate her 5-year risk for breast cancer.⁵

Evidence Summary

First-line screening options for women with dense breasts

It is well established that the sensitivity of regular film mammography is lower in women with dense breasts than in women with fatty breasts.² In contrast, evidence suggests that digital mammography improves sensitivity while preserving specificity in women with dense breast tissue.⁴⁻⁶ The Digital Mammography Imaging Screening Trial (DMIST) study, the largest trial directly comparing digital mammography to plain film mammography, found digital mammography was more sensitive than film mammography (70% versus 55%, p=0.02) among women of all ages with dense breasts.⁷ Moreover, the best recent data from a large representative registry have demonstrated that there is no significant decrease in the sensitivity of digital mammography among women with dense breast tissue.⁸ Despite the superior performance of digital mammography, however, radiologists and patients are still concerned about the potential for breast density to mask small, potentially curable cancers, particularly among women with an overall increased risk of breast cancer.

Supplemental screening options for women with dense breasts

Magnetic Resonance Imaging (MRI)

There are no data evaluating MRI in a general screening population with dense breasts, nor in populations at intermediate lifetime risk (15% to 20% lifetime risk). The data from high-risk populations suggests that the addition of MRI would more than double the cancer detection rate (best estimate 2.4-fold increase) with a four-fold increase in the recall rate (best estimate 4.3-fold increase). Table ES1 below shows estimates based on these data. There is a high level of uncertainty around these values because of the lack of direct evidence from studies of MRI in women with dense breast tissue and because of the heterogeneity of the findings in studies of high-risk women.

Table ES1: Estimated incremental yield of MRI after negative digital mammography in women with dense breast tissue

Statistic	Digital mammography	Incremental yield with MRI	Uncertainty
Recall rate per 1000	128	100	High
Biopsy rate per 1000	17.8	17-36	High
Cancer Detection Rate per 1000	4.2	8	High
Positive Predictive Value (PPV ₃)	24%	22%-48%	High

Hand-held Ultrasound (HHUS)

There are no studies evaluating the impact of adding HHUS to mammographic screening among women with dense breast tissue that address the key patient-centered outcomes of breast cancer mortality and disease-free survival. The available body of evidence, focusing largely on shorter-term recall rates, biopsy rates, cancer detection rates and false positive rates, is limited by the heterogeneity of the study designs, populations, and results. The best estimates for sensitivity and specificity come from the ACRIN 6666 trial⁹ (87.5% and 81.9% respectively) because it is the highest quality study and sensitivity and specificity are usually not influenced by the risk of the population being studied. The best estimate for the incremental cancer detection rate is centered around 3-4 cancers per 1000 examinations, but the results from the three studies on the Connecticut experience were closer to 2 cancers per 1000. The results from Connecticut are more likely to be representative of routine clinical practice in the United States. The recall rates and positive predictive values in these studies were greater than those of mammography, indicating that the addition of HHUS approximately more than doubles the recall rate. The recall rate doubled in the ACRIN 6666 study as well. Finally, the biopsy rates were 3-5 times higher than those of mammography, suggesting that the biopsy rate of ultrasound after negative mammography is likely to be at least four times that of mammography alone. This is the major limitation of screening ultrasound.

Table ES2 shows the estimates based on these data below. There is a low level of uncertainty around the PPV₃ because it was consistent in the literature. There is high uncertainty about the recall rate because of the lack of direct evidence from studies of HHUS in women with dense breast tissue and because of the heterogeneity of the findings in the studies.

Table ES2: Estimated incremental yield of HHUS after negative digital mammography in women with dense breast tissue

Statistic	Digital mammography	Incremental yield with HHUS	Uncertainty
Recall rate per 1000	128	98	High
Biopsy rate per 1000	17.8	49	Low-moderate
Cancer Detection Rate per 1000	4.2	2-3	Low
Positive Predictive Value (PPV ₃)	24%	7%	Low

Automated Breast Ultrasound (ABUS)

No available studies directly address the use of ABUS following negative digital mammography in a screening population of women with dense breasts. Only three studies evaluate ABUS diagnostic performance and all are of poor quality.¹⁰⁻¹² The study of Kelly and colleagues offers the only reasonable estimates (sensitivity 67.6%, specificity 92.9%, recall rate 74.8 per 1000, biopsy rate 12.1 per 1000, cancer detection rate 3.7 per 1000), but the validity and relevance of these data are limited by concerns about spectrum bias and the use of film rather than digital mammography. These factors would decrease the cancer detection rate of mammography in the population of women with dense breasts. Across the three studies, the recall rate varied from 5 to 207 per 1000 examinations, the biopsy rate was not reported or up to

15 per 1000 examinations, the PPV₃ varied from not reported to 31% and the cancer detection rate ranged from zero to 7.6 per 1000 examinations. Overall, the paucity of studies, the lack of high quality studies, and the wide range of estimates across the three studies mean that there is considerable uncertainty surrounding all of the estimates for the diagnostic test statistics for ABUS.

Because of the uncertainty described above, the most reliable estimates for the test characteristics for ABUS in women with dense breast tissue come from the HHUS literature as shown above in Table ES2, but all these estimates are extrapolations with high uncertainty.

Digital Breast Tomosynthesis (DBT)

The available research primarily studies DBT in combination with digital mammography in all women coming in for breast cancer screening, not as supplemental screening for women with dense breasts. Four studies performed in over 50,000 women (34,000 with DBT) presenting for routine screening for breast cancer found that DBT increased the cancer detection rate relative to mammography while decreasing the recall rate and the biopsy rate. One Italian study¹³ is the only publication that allowed for the calculation of statistics of interest to this assessment: women with dense breasts who have a negative digital mammogram. In that subgroup, DBT identified an additional 2.7 cancers per 1000 examinations with a recall rate of 21.3 per 1000 examinations. The estimates for sensitivity and specificity were 100% and 98.1% respectively, but these are likely overestimates because of the lack of follow-up for interval cancers. The PPV₁ was 12.5%, which is more than double the PPV₁ for digital mammography in dense breasts in the study and more than twice the PPV₁ usually reported for digital mammography in the United States.

Table ES3 shows estimates based on these data below. There is a low-to-moderate level of uncertainty around the PPV₃; while only one of the four available studies reported this measure¹⁴ rates were comparable between DBT and digital mammography and there is no reason to expect that DBT would be inferior given that digital mammography is a component of DBT. There is greater uncertainty about rates of cancer detection and biopsy rate, as only one of the studies included results from the target population (i.e., women with dense breast tissue and negative mammography), and there were issues of study heterogeneity as well as comparability of screening populations. The greatest level of uncertainty is with recall rates, since the most rigorous studies come from outside the US where patterns of recall differ markedly.

Table ES3: Estimated incremental yield of DBT after negative digital mammography in women with dense breast tissue

Statistic	Digital mammography	Incremental yield with DBT	Uncertainty
Recall rate per 1000	128	20	Moderate-high
Biopsy rate per 1000	17.8	5	Moderate
Cancer Detection Rate per 1000	4.2	1-3	Moderate
Positive Predictive Value (PPV ₃)	24%	25%	Low-moderate

Overall Summary of Evidence on Comparative Clinical Effectiveness

The available literature consistently has shown that all four of the advanced imaging technologies evaluated in this assessment can detect additional breast cancers in women with negative mammograms. Table ES5 below summarizes the estimates for each of the four technologies among women with dense breast tissue based on the clinical data published through mid-2013. Many of the estimates have a high degree of uncertainty and will likely change as more high quality data become available. However, they provide reasonable estimates of the clinical benefits and harms relative to each other.

Table ES5: Summary of the key statistics for four supplemental screening technologies in women with dense breast tissue

Statistic	Digital mammography	MRI	HHUS/ABUS	DBT
Recall rate per 1000	128	100	98	20
Biopsy rate per 1000	17.8	17-36	49	5
Cancer Detection Rate per 1000	4.2	8	2-3	1-3
Positive Predictive Value (PPV ₃)	24%	22%-48%	7%	25%

Table ES5 highlights the low PPV₃ of ultrasound compared to the other technologies, which translates into a large number of unnecessary biopsies for every cancer detected by ultrasound. The table also clearly illustrates that DBT has a much lower recall rate than the other technologies and that MRI detects the greatest number of additional breast cancers.

Thus, we know with a high degree of certainty that all forms of supplemental screening find additional breast cancers. Most of the cancers are small, lymph node negative, and thus are potentially curable. MRI finds the most cancers and DBT has the fewest false positives. HHUS results in the largest number of false positive biopsies.

The major unanswered question is whether the identification of additional cancers through supplemental screening improves outcomes for women. Some advocates of supplemental screening will argue that the majority of the cancers identified through supplemental screening are early stage cancers with an excellent prognosis following treatment. These represent the spectrum of cancers identified with mammography that led to the reduction in mortality seen with the randomized trials of screening mammography. In their view, there is no question that patient outcomes will improve with supplemental screening. Others will argue that many of these supplemental screen-detected cancers would have been cured when detected on physical exam or subsequent screening mammograms and that some of these cancers represent overdiagnosis, which leads to net harm for the patient. They will highlight the growing evidence for significant overdiagnosis with mammography alone. These individuals will suggest that much of the incremental cancer detection rate with HHUS (2 to 6 or more per 1000 examinations), which is much higher than the expected interval cancer rate (1 per 1000 examinations), can only represent overdiagnosis. Only large randomized trials can definitively answer this question.

Comparative Value

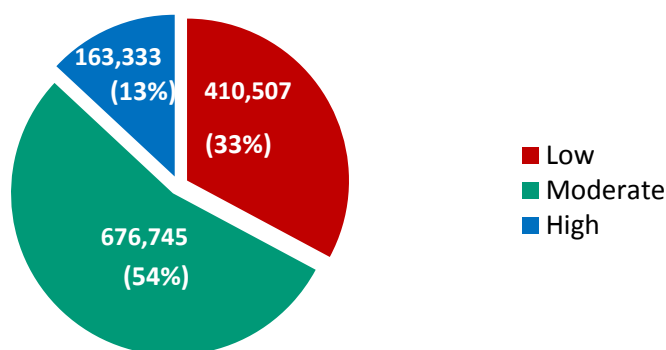
The published literature on the clinical and economic impact of supplemental breast cancer screening modalities in women with dense breast tissue is noticeably limited. We therefore developed a cohort model to perform a population-based, one-year analysis of clinical and economic outcomes specific to New England.

The population we modeled included all women age 40-74 except for those with known genetic susceptibility, a personal history of breast cancer, and/or a history of mantle radiation to the chest. We limited risk factors for breast cancer in our assignment of risk category to age, breast density, and close family history (at least one 1st degree relative). The percentage of women with dense breast tissue and a close family history was estimated to be 22.7% based on data from a New Hampshire mammography registry study.¹⁵ Using these three risk factors alone in the BCSC Risk Calculator⁸, we defined categories of low, moderate, and high risk as below:

- Low: BI-RADS density 3 or 4, age 40-49, no close family history (corresponds to 5-year risks generally <1.7%). Risk assumed in the model: 1% (0.2% per year)
- Moderate: BI-RADS density 3 or 4, age 40-49, with a close family history; OR BI-RADS density 3 or 4, age 50-74, no close family history (corresponds to 5-year risks generally between 1.7% and 3.0%). Risk assumed in the model: 2.5% (0.5% per year)
- High: BI-RADS density 3 or 4, age 50-74, with a close family history (corresponds to 5-year risks generally >3.0%). Risk assumed in the model: 5.0% (1.0% per year)

Based on the risk categories described above, we estimate that, of all New England women with dense breast tissue and a negative digital mammogram, 33% would be low-risk, 54% moderate-risk and 13% high-risk. Figure ES1 displays these proportions below along with the relevant estimated population sizes for each risk group.

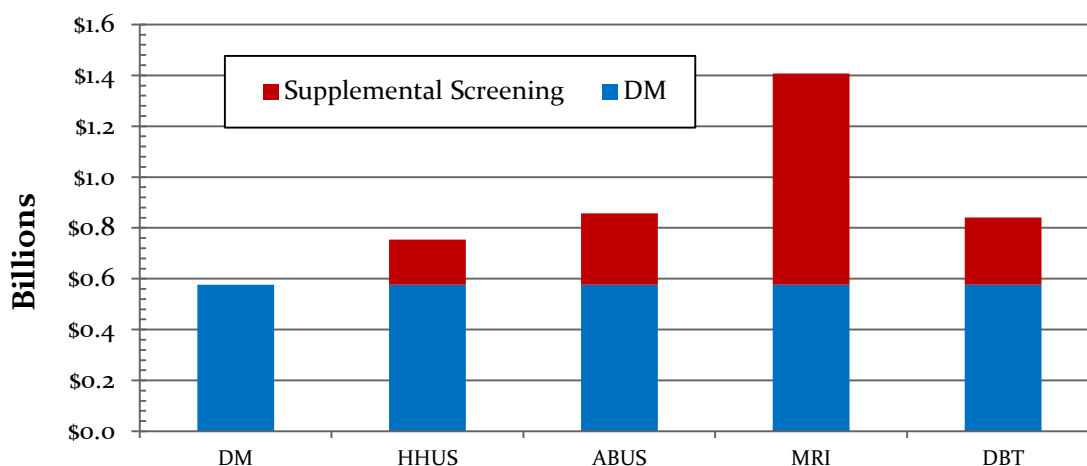
Figure ES1: Estimated numbers of New England women with dense breast tissue and negative mammography results, by level of overall breast cancer risk.



Incremental Effects of Supplemental Screening in Women with Dense Breast Tissue and a Negative Digital Mammogram

Figure ES2 below illustrates the estimated budgetary impact to New England of supplemental screening in all women with dense breasts and negative mammography. The annual cost of digital mammography screening, including costs of mammography, diagnostic workup, and biopsy, is estimated to total approximately \$576 million. Supplemental screening of all women with an initial negative digital mammogram with HHUS would increase annual costs by approximately 30%, to \$750 million. Use of higher-cost ABUS as the modality of choice would result in a 49% increase in costs (to \$860 million) for the same assumed clinical benefit. DBT would realize a similar cost increase; while assumed test costs would be higher with DBT vs. ABUS, costs of biopsy would be much lower. Finally, use of MRI results in a more than twofold increase in overall costs (to \$1.4 billion) annually.

Figure ES2: Costs of digital mammography and supplemental screening among New England women, by screening modality.



DM: Digital mammography; HHUS: Handheld ultrasound; ABUS: automated breast ultrasound; MRI: magnetic resonance imaging; DBT: digital breast tomosynthesis

The low-risk population generates a substantial proportion of the additional costs of supplemental screening, the subgroup in which the fewest additional cancers are detected. Figure 5 on the following page shows the additional costs of supplemental screening when limited to women in the “high risk” category. If supplemental screening were limited to women age 50-74 with dense breast tissue, a family history in a first-degree relative, and a negative digital mammogram (i.e., the high-risk cohort), total costs of screening would rise by a much smaller increment. However, the potential yield of additional cancers detected in this subgroup would be comparable to or better than with digital mammography alone. For example, supplemental MRI screening in high-risk women would increase costs by approximately \$110 million (19%) to \$690 million, and would find 3,028 cases of cancer (1,290 cancers from digital mammography alone + 1,738 additional cancers from MRI). Increases in cost would be lower with the other supplemental modalities (5-7%), but the additional cancer yield would also be lower (1,000 – 1,100 additional cancers detected over digital mammography alone). Findings such as these are important to consider in any evaluation of the

tradeoffs of supplemental screening, including numbers of biopsies required, additional cancers detected and missed, and screening costs.

CEPAC Votes and Recommendations

CEPAC Votes and Deliberation on Screening for Breast Cancer in Women with Dense Breasts

Digital mammography vs. Film mammography

- The majority of CEPAC voted that for women with dense breast tissue, digital mammography offers superior diagnostic accuracy (i.e. fewer false positives and false negatives) than film mammography [15 yes; 0 no]
- CEPAC also voted that for women with dense breast tissue, digital mammography substantially reduces the risk of “masking” of breast cancers compared to film mammography [15 yes; 0 no]
- During the Policy Roundtable, Council members agreed with experts that technological advances may eventually supersede digital mammography and that DBT may supplant digital mammography as the first-line screening test of choice. CEPAC members noted that future research evaluating DBT as a first-line screening test should specifically analyze women with dense breast tissue to better understand the false positive rate and incremental number of cancers detected in this population.

CEPAC Votes and Deliberation on Supplemental Screening Tests for Women with Dense Breasts

Benefit of Supplemental Screening by Overall Cancer Risk

- For women with dense breast tissue with 5-year risks of breast cancer considered “low” (<1.7%), a majority of CEPAC voted that the harms of supplemental screening outweigh the benefits when compared with no supplemental screening
- CEPAC narrowly voted that for women with an overall “moderate” 5-year risk of breast cancer (1.7%-3%) supplemental screening provides more benefit than harm compared with no supplemental screening [9 yes; 6 no]. For women with an overall “high” 5-year risk of breast cancer (>3%), CEPAC nearly unanimously voted that the benefits of supplemental screening outweigh the harms [14 yes; 1 abstain]. A majority of CEPAC [13/15] voted MRI as the supplemental screening modality they would most recommend,

Comparative Value of Supplemental Screening Tests for Women with Dense Breasts

- HHUS is the lowest cost supplemental screening test. When asked to judge the value of performing supplemental screening in women with dense breast tissue using MRI compared to HHUS (the lowest cost test), a majority of CEPAC voted that MRI represented high (5/15) or reasonable (9/15) value. Council members abstained from voting on the relative value of other screening modalities due to insufficient evidence to demonstrate comparative clinical benefit between the various options.

Action Steps for Patients

The following section provides information for women with dense breast tissue to help them:

- Better understand their screening options for breast cancer
- Effectively engage with their physicians about these choices

The following key steps reflect the most up-to-date evidence concerning which screening tests are most effective for women with dense breasts, including information about risks and benefits that may be associated with each test type. These Action Steps are also available in a stand-alone *Patient Aid*, which is available on the CEPAC website: http://cepac.icer-review.org/?page_id=1077.

1. Understand what it means to have dense breast tissue and how breast density may affect breast cancer screening.

The appearance of the breasts on mammograms varies among women due to differences in breast tissue composition. Different types of tissue make up the breast – including fibrous connective tissue, glandular tissue, and fatty tissue. These different types of tissue appear differently on mammograms. Fatty tissue appears dark, while glandular and fibrous tissue appears white.

Women who have mostly fibrous or glandular tissue but little fatty tissue have dense breasts. It is important to note that breast density does not refer to breast firmness or size. Having dense breast tissue is very common – approximately 50% of women have dense breasts. Dense breast tissue may make it more difficult for radiologists to spot cancer on mammograms, since breast tumors may appear white, like dense breast tissue, potentially “hiding” tumors. In contrast, because fatty tissue appears dark, physicians can more easily see a breast tumor that appears white. As a result, mammograms may be less accurate for women who have dense breast tissue.

Multiple factors may affect breast density. These may include hormonal levels, age, age at first pregnancy, body weight, and other factors. Evidence also suggests that having dense breasts may increase your risk for developing breast cancer when compared to women of similar age who have no or little dense breast tissue. However, breast density only has a small impact on your overall risk for developing the disease. You should not be alarmed if you have dense breasts, but you should seek information about your overall risk for breast cancer and speak with your doctor concerning which screening options make the most sense for you.

The following list of resources on the following page contains information helpful for women with dense breast tissue.

- a. **American Cancer Society – Breast Density and Your Breast Mammogram Report:**
<http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-039989.pdf>
- b. **Are You Dense? – Patient Brochure and Pamphlet:**
http://www.areyoudense.org/worxcms_published/resources_page60.shtml
- c. **Black Women’s Health Imperative – Black Women and Breast Cancer:**
<http://www.blackwomenshealth.org/issues-and-resources/black-women-and-breast-cancer/>
- d. **California Breast Density Information Group – American College of Radiology Brochure for Patients:** <http://www.breastdensity.info/>
- e. **Harvard Women’s Health Watch – The breast density – breast cancer connection:**
http://www.health.harvard.edu/newsletters/Harvard_Womens_Health_Watch/2011/October/the-breast-density-breast-cancer-connection
- f. **Michigan Cancer Consortium – Breast Density Fact Sheet:**
http://www.michigancancer.org/CancerPlan/BreastCancer_Resources.cfm

2. Know your overall risk for breast cancer.

Understanding your **overall** risk for breast cancer can help you make informed, evidence-based choices concerning whether you should consider further screening after receiving the results of your mammogram. Importantly, even though dense breast tissue is a risk factor for breast cancer, having dense breast tissue does not mean that you are at “high” risk for developing the disease in your lifetime. Other known risk factors to consider include:

- Age
- History of breast cancer in a first-degree family member, such as mother, daughter, or sister
- Certain inherited gene mutations, including BRCA1 and BRCA2
- Personal history of breast cancer
- Early menstruation
- Late menopause
- First pregnancy after age 30 or never having been pregnant
- Lifestyle issues, such as alcohol use, physical inactivity, and overweight/obesity

It is important that you speak with your doctor about how to judge your overall risk for breast cancer. Having this knowledge will help you and your doctor determine the potential benefits and risks associated with additional screening tests following detection of dense breasts on your mammogram.

The following websites provide patient guides and additional information to help women with dense breast tissue understand their overall risk factors for developing breast cancer:

- a. **American Cancer Society:** <http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-risk-factors>
- b. **Cancer Research, UK:** <http://www.cancerresearchuk.org/cancer-help/type/breast-cancer/about/risks/definite-breast-cancer-risks>
- c. **Centers for Disease Control and Prevention:**
http://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm
- d. **Facing Our Risk of Cancer Empowered, Inc.:** http://www.facingourrisk.org/info_research/risk-factors/breast-cancer-risks/index.php

3. Receive regular mammograms based on your doctor's recommendations.

Based on current evidence-based guidelines, many women who should receive regular mammograms do not. For these women, breast cancer may be detected in more advanced stages when it is not as easily treated. As noted above, dense breast tissue can make mammograms more difficult to interpret, but it is important that women with dense breasts continue to receive mammograms at regular intervals based on their doctor's recommendations.

4. Seek digital mammography for your regular mammograms.

The best available evidence suggests that digital mammography is more accurate than film mammography for women with dense breast tissue. Studies found that digital mammograms can more effectively "see" through dense breast tissue, substantially reducing the risk of missing a small cancer hidden within dense breast tissue. Most facilities now offer digital mammography; therefore, if your clinic does not offer digital mammography, consider asking your doctor for a referral to a center that offers this technology. However, always check with your health insurance company first to understand any out-of-pocket costs for screening.

5. Speak with your doctor concerning the potential risks and benefits of having additional testing following mammography.

There are a number of tests available for additional screening after mammography. These include magnetic resonance imaging (MRI) and breast ultrasound. Further screening with these tests may help find breast cancers not seen on a mammogram and may detect cancers that are smaller and, depending on breast cancer type, may be easier to treat. However, it is also important to note that further testing detects many more findings that are not cancer. Additional screening may lead to added testing and biopsies to investigate suspicious findings that ultimately may be a false alarm (called a “false positive”). Costs are another important issue. Your health insurance policy may not cover additional testing, and unnecessary tests increase overall costs in the health care system. Your overall risk for breast cancer is crucial in determining the best decision for you (see Action Step #2). If your overall risk for breast cancer is low, there is a higher chance that additional screening may lead to false alarms rather than finding cancer. In contrast, for the smaller number of women who are at high risk for breast cancer, the balance of benefits of additional testing may tend to outweigh the risks. Nevertheless, there is no single “correct” answer, since every woman’s case is different. Ask your doctor about your overall risk for breast cancer and discuss options to help you decide whether additional screening is the right choice for you.

To help facilitate conversations concerning the Action Steps above, we have provided sample questions on the following page to ask your doctor about breast cancer screening options and considerations.

Five Questions for Women with Dense Breast Tissue to Ask Their Doctors about Screening:

1. **Q.** How often should I receive screening mammography, and is my test being performed with digital mammography?
2. **Q.** What is my overall risk for breast cancer given my breast density, family history, and other factors?
3. **Q.** Given my overall risk, what are the potential benefits and potential harms for me with additional screening?
4. **Q.** If additional screening is recommended, which screening test has the best evidence to suggest it would be right for me?
5. **Q.** Are there important differences in my out-of-pocket expenses for the different options?

Action Steps for Clinicians

The following section provides information to clinicians assessing patients with dense breast tissue to support the development of care management plans that incorporate the best available evidence.

- 1. Recommend digital mammography over film mammography as a first-line screening test for women with dense breast tissue.**

The published evidence suggests that digital mammography greatly reduces the risk of “masking” of smaller breast cancers. Certain distributions of dense breast tissue, however, can still mask small cancers. Clinicians should inform patients that no screening test is perfect and screening may miss some rapidly growing cancers.

- 2. Adopt consistent messaging with patients around breast density and breast cancer risk to help inform decisions about future screening.**

Patients with dense breast tissue are likely to have a range of questions for their providers. Clinicians should inform patients if they have dense breasts, but that messaging should promote a dialogue with patients and be consistent and clear in its explanation of the implications of dense breast tissue and options for additional screening. It is important that communication with patients a) helps women to understand the cancer risk associated with breast density, b) emphasizes that breast density alone has a minimal impact on overall breast cancer risk, and c) stresses the importance of continued mammography screening. Women should also be made aware of the trade-offs involved in supplemental screening, and that while additional screening finds more cancer, it also increases the risk of false positives and unnecessary testing that can cause some women great anxiety and worry.

Sample FAQs and educational information that clinical societies and practice groups have provided to their patients to help them understand their breast density status and future screening options are provided in the [Appendix](#) (Note: some of these resources are framed for patients living in a state with a breast density notification policy in place).

- 3. Integrate considerations of supplemental screening for women with dense breast tissue in systems that assess their overall breast cancer risk.**

Though dense breast tissue does carry some increased risk for breast cancer, breast density by itself should not be a reason to consider a woman at “high risk” of developing the disease. Therefore, practices need systems that integrate the management of questions regarding a patient’s breast density with a reliable, efficient method for assessing a patient’s overall risk for breast cancer.

Achieving this goal will require automated processes for capturing breast cancer risk information and a detailed workflow model for how clinicians record that information and communicate it across providers and settings. Once breast cancer risk information is gathered it should be made readily available to clinicians and patients during any future encounter in the health system. The individual provider tasked with capturing risk-information will vary by practice and setting, and may include genetic counselors, radiologists, mammogram technologists, primary care physicians, or other appropriately trained staff. Ideally, automated systems for gathering family history and other risk information from women would be available at multiple points in the health care process, including at the time of mammography, annual physical exams, and urgent visits to ensure that clinicians capture information from patients who may not be concordant with mammography screening. When appropriate, clinicians may refer women with certain risk factors to specialized breast cancer centers and/or genetic counseling for further consultation.

Systems should also support dialogue between patients and physicians regarding the various screening modalities available, and the patient's preference for additional screening. The ultimate goal of these systems should be to embody the principle of shared decision-making within mechanisms that would prove feasible across different practice settings.

4. When assessing a patient's overall breast cancer risk, use consistent risk thresholds and assessment tools in order to avoid confusion among clinicians and patients.

A range of mathematical models are available to calculate breast cancer risk, including [the Gail Model](#) and the [Breast Cancer Surveillance Consortium \(BCSC\) model](#). The CEPAC report also modeled the patient outcomes of different screening strategies based on categorizing risk according to a simplified, 3-variable version of the BCSC that could be used by primary care clinicians without direct access to computerized risk calculators (see page 83 in the [final CEPAC report](#)). Whereas 5-year risk thresholds make conceptual sense in considering supplemental screening, insurance coverage criteria for MRI focus on determining lifetime risks high enough to warrant annual MRI. Practice and provider group should develop robust systems for gathering breast cancer risk and applying that risk consistently to guide practice and policy decisions. Whatever approach clinicians use to calculate risk, breast cancer risk information should be readily available to clinicians and patients.

5. The decision regarding whether to perform supplemental screening should be strongly guided by considerations of an individual woman's overall risk for breast cancer.

The emphasis on overall cancer risk is critical because the potential benefits from supplemental screening are directly related to how high the underlying risk of breast cancer is, and when that risk is very low, the potential harms of further screening -- false positive results and unnecessary biopsies -- weigh more heavily in the balance.

6. **Engage patients in shared decision making about their options for supplemental screening.** Primary care physicians and other health personnel should have access to training and support on how to discuss with patients their choices for secondary screening and overall breast cancer risk.

Shared-decision making creates an opportunity for physicians to counsel women on their best options for supplemental screening given their overall risk for breast cancer. Information about the potential harms and benefits of supplemental screening, and steps patients can take for prevention should be part of these conversations. Honest discussions that help patients better understand what to expect from supplemental screening and prepare for the risk of false positives are vitally important.

The Roundtable and CEPAC noted the importance of developing educational materials for clinicians to help them understand the evidence on the various options for supplemental screening and provide a basis for discussions about these choices with women. Since PCPs are already burdened with numerous clinical goals and a range of practice issues, clinicians should utilize shared decision-making aids or physician communication tools to support these conversations. In states confronting a shortage of PCPs, practices and provider groups need advanced training and education for other health personnel (e.g., physician assistants, nurse practitioners, and screening technologists) on how to discuss with patients the issues around secondary screening and breast cancer risk.

Ensuring that radiologists, other specialists, and primary care clinicians share a common platform of information is critical to make certain that women receive consistent information and can participate with confidence in shared decision-making with their clinicians.

For practices without their own training or education available, the following resources are free and publicly available to help facilitate conversations with your patients around the various options for supplemental screening:

- a. **Healthwise Patient Decision Aid:**

Breast Cancer Screening and Dense Breasts: What Are My Options?

This decision aid provides patients with information on breast density, compares various choices for supplemental screening, and provides tools to help you patients weigh their different priorities and preferences when making a decision about screening:

<http://decisionaid.ohri.ca/AZsumm.php?ID=1648>

- b. **California Breast Density Group:**

Breast Density, Breast Cancer Risk, and California Breast Density Notification Law SB 1538: Scenarios for Clinicians

Developed by a group of radiologists and breast cancer risk specialists representing academic and community-based practices in California, this resource provides succinct information around

the evidence for different supplemental screening options, and guidance for how to discuss these options with patients. Written specifically for clinicians responding to patient questions following breast density notification legislation in the state, the topics it addresses have broader application and may support physicians in New England in their conversations with women about their options for secondary screening: <http://www.breastdensity.info/>

- 7. For women with dense breast tissue at “high risk” of breast cancer (>3%) over the next 5 years, consider supplemental screening with MRI, which the evidence supports as offering the best diagnostic performance at a reasonable value.**

The CEPAC report used a 3% threshold for the 5-year risk of breast cancer to define women as “high risk.” This risk threshold mirrors that used by the United States Preventive Services Task Force (USPSTF) in its most recent recommendations regarding preventive therapy for breast cancer. This threshold also serves as a useful dividing line between risk categories when the most important common risk factors for breast cancer -- age, family history, and breast density -- are entered into the BCSC risk calculator.

While acknowledging that breast MRI has not been studied for use of supplemental screening and that many unknowns remain regarding the effect of screening with MRI on patient mortality, CEPAC voted that this modality had the strongest evidence to support its use. CEPAC noted, however, that all women should understand the potential benefits and harms of supplemental screening before opting to undergo additional testing.

For women at low risk (<1.7% 5-year risk) of breast cancer, CEPAC judged that the evidence is inadequate to demonstrate that the benefit of supplemental screening outweighs the harms. Current insurer coverage policies do not cover supplemental screening tests for these women (MRI is covered by most insurers if the lifetime risk is >20%), but Council members noted the importance of improving patient and clinician education regarding the evidence on potential benefits and harms of supplemental screening in this group.

- 8. Support the development of guidelines to help physicians appropriately manage intervals for supplemental screening and subsequent follow-up for women with dense breast tissue.**
- 9. Promote the development of further research on the long-term outcomes of supplemental screening among representative populations of women with dense breast tissue.**

CEPAC and Roundtable members agreed that randomized trials or prospective cohort studies that follow all patients out for one year in order to capture interval cancers would be very informative.

Action Steps for Payers and Policymakers

The following section provides information to help payers and policymakers develop policies that incentivize the use of evidence-based screening for women with dense breast tissue:

- 1. Collaborate with providers and other decision-makers to adopt consistent risk thresholds for assessing patients and determining appropriateness for supplemental screening.**

Many existing screening guidelines and coverage policies currently use a >20% lifetime risk of breast cancer as a threshold for high-risk status. This threshold is based largely on expert consensus, whereas empirically-derived risk calculators produce estimates of breast cancer risk within either 5 or 10-year horizons. There is general agreement that the 5-year horizon used in the CEPAC report is appropriate for judgments of the potential added clinical value of supplemental screening. Experts accept this time horizon since the risk for cancer in the shorter time horizon is most closely related to the chance that additional cancer would be detected by supplemental screening during the near term after a negative mammogram. Developing a consistent approach may warrant further discussion among stakeholders.

- 2. Develop incentives to encourage the use of automated processes for risk assessment.**

Payers and policymakers should embed determinations of supplemental screening for women with dense breasts in models for assessing overall breast cancer risk. Practice and provider groups require processes to systematically capture information on risk from patients and communicate it back to patients and their clinicians at the point of examination to help inform decisions for further screening. Payers have a role to play in incentivizing risk assessment processes, either through pay for performance initiatives or other quality improvement programs.

- 3. States considering breast density notification policies should also consider complementary information campaigns to educate women on breast density, risk, and their options for supplemental screening.**

Women with dense breast tissue are likely to have a range of questions for their providers regarding the implication of dense breast tissue and options for additional screening. It is important that information is available that a) helps women to understand the cancer risk associated with breast density, b) emphasizes that breast density alone has a minimal impact on overall breast cancer risk, and c) stresses the importance of continued mammography screening. Women should also be made aware of the trade-offs involved in supplemental screening, and that while additional screening finds more cancer, it also increases the risk of false positives and unnecessary testing that can cause some women great anxiety and worry. Many of these

conversations will take place between a woman and her physician, but policymakers can support these efforts by collaborating with specialty society and patient advocate groups to disseminate educational materials and resources.

References

1. Connecticut State Legislature. SB 458: An act requiring communication of mammographic breast density information to patients. Accessed at: <http://www.cga.ct.gov/2009/ACT/PA/2009PA-00041-RooSB-00458-PA.htm>, Oct. 1, 2013.
2. Brower V. Breast density legislation fueling controversy. *J Natl Cancer Inst* 2013;105(8):510-1.
3. Lee CI, Bassett LW, Lehman CD. Breast density legislation and opportunities for patient-centered outcomes research. *Radiology* 2012;264(3):632-6.
4. Cummings SR, Tice JA, Bauer S, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. *Journal of the National Cancer Institute*. Mar 18 2009;101(6):384-398.
5. Berrington de Gonzalez A, Reeves G. Mammographic screening before age 50 years in the UK: comparison of the radiation risks with the mortality benefits. *British journal of cancer*. Sep 5 2005;93(5):590-596.
6. Alexander FE. The Edinburgh Randomized Trial of Breast Cancer Screening. *J Natl Cancer Inst Monogr*. 1997(22):31-35.
7. Andersson I, Aspegren K, Janzon L, et al. Mammographic screening and mortality from breast cancer: the Malmö mammographic screening trial. *Bmj*. Oct 15 1988;297(6654):943-948.
8. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Annals of internal medicine*. Mar 4 2008;148(5):337-347.
9. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA: the journal of the American Medical Association*. Apr 4 2012;307(13):1394-1404.
10. Kelly KM, Dean J, Lee SJ, Comulada WS. Breast cancer detection: radiologists' performance using mammography with and without automated whole-breast ultrasound. *Eur Radiol*. Nov 2010;20(11):2557-2564.
11. Stoblen F, Landt S, Stelkens-Gebhardt R, Sehouli J, Rezai M, Kummel S. First evaluation of the diagnostic accuracy of an automated 3D ultrasound system in a breast screening setting. *Anticancer Res*. Aug 2011;31(8):2569-2574.
12. Giuliano V, Giuliano C. Using automated breast sonography as part of a multimodality approach to dense breast screening. *Journal of Diagnostic Medical Sonography*. 2012;28(4):159-165.

13. Ciatto S, Houssami N, Bernardi D, et al. Integration of 3D digital mammography with tomosynthesis for population breast-cancer screening (STORM): a prospective comparison study. *Lancet Oncol*. Jun 2013;14(7):583-589.
14. Rose SL, Tidwell AL, Bujnoch LJ, Kushwaha AC, Nordmann AS, Sexton R, Jr. Implementation of breast tomosynthesis in a routine screening practice: an observational study. *AJR Am J Roentgenol*. Jun 2013;200(6):1401-1408.
15. Titus-Ernstoff L, Tosteson AN, Kasales C, et al. Breast cancer risk factors in relation to breast density (United States). *Cancer causes & control : CCC*. Dec 2006;17(10):1281-1290.

APPENDIX



Understanding Breast Density: Frequently Asked Questions

What is breast density? How do I know if I have dense breast tissue?

Breast density refers to the amount of fibroglandular tissue seen on a mammogram. This is the white opaque area one would see on the mammogram image. The dark black area on a mammogram is fatty tissue. Every breast has a combination of these two types of tissues and this is unique to each individual. The dense white tissue is the tissue that is hormonal in nature and contains ducts and lobules used for milk production. Breast density is determined by a mammogram. It cannot be accurately assessed by a physical exam. A breast may feel lumpy, but not have much dense or fibroglandular tissue.

Radiologists grade breast tissue as one of four breast density categories depending on the volume of fibroglandular tissue compared to fatty tissue: fatty (less than 25% of the volume is fibroglandular tissue), scattered tissue (25-50%), heterogeneously dense (50-75% of breast) and extremely dense (greater than 75%).

Breast density can vary with time and hormonal status. Pregnancy and lactation will greatly increase the density of breast tissue. For some women, breast density will decrease after menopause. Weight fluctuations can also affect the density of breast tissue.

With the passage of the new breast density law, your mammogram report will inform you if you have dense breast tissue.

Why is breast density important?

Some studies have shown an increased risk of breast cancer with increasing breast density. Also, detecting breast cancer in dense tissue is more difficult due to the masking of masses from the overlying dense tissue. On mammography, a cancerous mass is “white” which can be obscured by the white dense breast tissue surrounding it.

What should I do if my mammogram report says I have dense tissue? What are my options?

If your mammogram report states that you have dense breast tissue, it means that your breast density is greater than 50%. You can discuss this further with your health care provider. An important point to consider is other risk factors for breast cancer that you may have in addition to dense breast tissue.

One of the most important factors in determining breast cancer risk is family history. In addition, factors such as previous biopsies, hormone usage, radiation exposure and certain genetic syndromes may add to risk. There are several risk models available to determine a woman’s lifetime risk of breast cancer. Your health care provider can discuss these models further with you, or refer you to a genetic counselor who can help you choose an appropriate model and interpret the results. Some common risk models include the Gail model, Tyrer-Cuzick model, and BODICEA model, among others.

Supplemental testing can involve either breast MRI or screening breast ultrasound. Much less commonly, nuclear medicine scans, such as BSGI (breast specific gamma imaging) can be considered. If an MRI is indicated, a screening ultrasound is not necessary.

In general, the American Cancer Society advises women with a greater than 20% lifetime risk of breast cancer to have both yearly mammograms as well as yearly MRI

examinations. Women who reach the 20% lifetime risk typically will have more than one family member affected with breast cancer, or have a history of premenopausal breast cancer in their family history. This also applies to women who carry the BRCA gene or have a history of chest radiation in childhood.

In women with a less than 20% lifetime risk of breast cancer, breast ultrasound can be considered for supplemental testing.

Alternatively, women may choose no further testing beyond mammography.

What does screening breast ultrasound involve? What are the benefits and drawbacks?

Screening breast ultrasound is performed on both breasts. It can be performed with a handheld instrument by a technologist or doctor. There are also automated breast ultrasound machines available which perform the ultrasound in an automated fashion. Ultrasound works by utilizing sound waves, so no radiation is involved.

Current studies have demonstrated that breast ultrasound will detect approximately three additional cancers per thousand patients with an otherwise normal mammogram.

The drawback is that breast ultrasound finds many solid masses which require biopsy for definitive

diagnosis. According to recent medical literature, approximately one cancer is found for every 20 ultrasound biopsies. This is in contrast to mammography, where approximately one cancer is found for every 3-4 biopsies. A problem with screening ultrasound (that is performing ultrasound with a normal mammogram and no problems), is finding many benign masses and subsequent high rate of biopsy compared to the number of cancers found.

A recent study from Yale University in Connecticut, where a similar breast density law was passed, revealed that in 935 women with dense breast tissue and normal mammograms, 63 procedures were performed in 53 patients, with three cancers found. All three cancers were smaller than 1 cm (Stage 1) and found in postmenopausal women. A single cancer was found in each of three risk groups – low, intermediate and high risk.

Will my insurance cover supplemental breast ultrasound?

The law enacted in New York State does not require that insurance cover screening breast ultrasound examinations. At this time, most of the major insurers have indicated that they will cover breast ultrasound. If your plan has a deductible, it will not be automatically covered unless the deductible is met prior to the ultrasound.

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DENSE BREASTS

Why was I notified that I have dense breasts?

New York Governor Andrew Cuomo signed a law that requires mammogram providers to let a woman know when she has dense breast tissue.

Do dense breasts mean I could have breast cancer?

All women are at risk of developing breast cancer, regardless of their tissue patterns.

How common are dense breasts?

Dense breast tissue is very common, particularly before the age of menopause. Dense breast tissue may make it more difficult to see abnormal tissue on a mammogram.

Are there guidelines for additional dense breast testing?

There are no medical guidelines indicating what type of additional testing - if any - should be performed for women when mammograms detect dense breasts.

What screening and diagnostic options are available?

Discuss options with your doctor to decide which - if any - are right for you:

- **Ultrasound** – sound waves are used to examine the breast for abnormal densities or show characteristics of a breast lump
- **MRI** – magnetic resonance imaging uses radio waves and strong magnets to produce detailed images that can illustrate blood flow patterns and abnormal masses in the breast

According to the American College of Radiology –

“...Studies have shown that ultrasound and magnetic resonance imaging (MRI) can help find breast cancers that can’t be seen on a mammogram. However, both MRI and ultrasound, show more findings that are not cancer, which can result in added testing and unnecessary biopsies. Also, the cost of ultrasound and MRI may not be covered by insurance.”

What else should I know to keep my breasts healthy?

ACOG Recommends annual mammograms starting at age 40 and annual clinical breast exams for women 40 and older and every one to three years for women ages 20 to 39. The traditional monthly breast self-exam has been replaced with a newer concept called “breast awareness”—knowing how your breasts normally look and feel.