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Should This Woman With Dense Breasts Receive Supplemental Breast Cancer Screening?

Grand Rounds Discussion From Beth Israel Deaconess Medical Center

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Breast cancer will develop in 12% of women during their lifetime and is the second leading cause of cancer death among U.S. women. Mammography is the most commonly used tool to screen for breast cancer. Considerable uncertainty exists regarding the age at which to begin screening and the optimal screening interval. Breast density is a risk factor for breast cancer. In addition, for women with dense breasts, small tumors may be missed on mammography and the sensitivity of screening is diminished. At the time of publication, 35 states had passed laws mandating that breast density be reported in the letters that radiologists send to women with their mammogram results. The mandated language may be challenging for patients to understand, and such reporting may increase worry for women who are told that their risk for breast cancer is higher than average on the basis of breast density alone. The U.S. Preventive Services Task Force and the American College of Radiology (ACR) have each issued guidelines that address breast cancer screening for women with dense breasts. Both organizations found insufficient evidence to recommend for or against magnetic resonance screening, whereas the ACR advises consideration of ultrasonography for supplemental screening. In this Beyond the Guidelines, 2 experts—a radiologist and a general internist—discuss these controversies. In particular, the discussants review the role of supplemental breast cancer screening, including breast ultrasonography or magnetic resonance imaging for women with dense breasts. Finally, the experts offer specific advice for a patient who finds her mammography reports confusing.

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ABOUT BEYOND THE GUIDELINES

Beyond the Guidelines is a multimedia feature based on selected clinical conferences at Beth Israel Deaconess Medical Center (BIDMC). Each educational feature focuses on the care of a patient who "falls between the cracks" in available evidence and for whom the optimal clinical management is unclear. Such situations include those in which a guideline finds evidence insufficient to make a recommendation, a patient does not fit criteria mapped out in recommendations, or different organizations provide conflicting recommendations. Clinical experts provide opinions and comment on how they would approach the patient's care. Videos of the patient and conference, the slide presentation, and a CME/MOC activity accompany each article. For more information, visit www.annals.org/GrandRounds.

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Ms. C is a 47-year-old Asian American woman who is followed for primary care. The results of her first screening mammogram at age 40, as well as those of annual screening thereafter, were normal. Her most recent mammogram from this year revealed category "c" breast density. The letter she received from the radiologist included the following language: "Your breast tissue is heterogeneously dense. Although dense breast tissue is a common and normal finding on a mammogram, it may limit our ability to detect breast cancer and may indicate an increased risk for breast cancer. It is possible that an additional screening examination, such as breast ultrasonography or breast MRI [magnetic resonance imaging] may be appropriate. Your provider considers several risk factors." Ms. C has never had a breast biopsy. She underwent menarche at age 14 and had her first child at age 23.

Ms. C's medical history includes elevated cholesterol levels, stress urinary incontinence, diet-controlled type 2 diabetes, asthma, bronchiectasis, and recurrent urinary tract infections. Her medications are an albuterol metered-dose inhaler as needed, methenamine, and vitamin C. She is a native of Hong Kong but has lived in the United States for 29 years. She is a Chinese-language interpreter at a hospital. She has no family history of breast cancer. On examination, she has no breast masses or axillary adenopathy. The remaining examination is normal.

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Table 1. The American College of Radiology BI-RADS Scale for Classifying Mammographic Breast Density*

Breast Density Category	Prevalence of Density Category Among U.S. Women Aged 40–74 y, %†	Definition
a	13.3	The breasts are almost entirely fatty.
b	43.3	There are scattered areas of fibroglandular density.
c	35.9	The breasts are heterogeneously dense, which may obscure small masses.
d	7.4	The breasts are extremely dense, which lowers the sensitivity of mammography.

BI-RADS = Breast Imaging Reporting and Data System.
* From reference 6.
† From reference 7.

Her 5- and 10-year risks for breast cancer, according to the Breast Cancer Surveillance Consortium (BCSC) risk calculator, are 0.8% and 1.7%, respectively (1); her 5-year risk according to the National Cancer Institute breast cancer risk assessment tool (revised Gail index) is 0.5%, which places her at low risk (2). Ms. C has not thought much about mammography or how to interpret results that include a discussion of breast density. She finds the radiology results letters confusing.

Ms. C's Story

I came from Hong Kong in 1989, almost 29 years ago, and I have 2 sons. I remember that I had a mammogram a couple years ago, and they found out that I have so many scars around my chest; then they called me back to get a second screening. I was really, really worried about that, because I was concerned—like, do I have breast cancer? And then they said, "Oh no. Don't worry about that." So far, my mammogram has been normal.

If I was told I needed a biopsy, I would be really, really nervous and worried about why do I need a biopsy? Because I would have negative thinking that this could be cancer, it could be related to a cancer.

Usually, they send me the letter by mail. I remember the first time when I read the letter, I really didn't know or understand what it meant, because I thought it was only one simple sentence, say, "Your mammogram results are normal." But it is not; they have a long, long letter to try to explain the results. I don't understand what it means, but I remember that it said something like "Your mammogram is normal." No one from the radiology department explained it to me or told me what the results were right after the mammogram; I just got the letter by mail. No one called me.

Honestly, when I get the letter, I just like focus on the results, like normal or abnormal, and then all those other couple paragraphs; I didn't pay any attention. The breast density? No one explained that to me before.

See the **Patient Video** (available at Annals.org) to view the patient telling her story.

Context, Evidence, and Guidelines

Breast cancer is the most common (nonskin) cancer and the second leading cause of cancer death (after lung cancer) among U.S. women. The American Cancer Society estimates that in 2018, approximately 266 000 new cases of breast cancer will be diagnosed and 41 000 breast cancer deaths will occur among women in the United States (3). Breast cancer will develop in 12% of U.S. women during their lifetime (3). The most commonly used screening tool for early detection of breast cancer is mammography. The optimal age to begin mammography and the screening interval remain controversial. The American Cancer Society and the U.S. Preventive Services Task Force (USPSTF) differ on both these points (4, 5).

Breast density, as classified by mammography, has emerged as an important factor because of its impact on breast cancer risk as well as its effects on the sensitivity of mammography to detect breast cancer. The American College of Radiology (ACR) developed the Breast Imaging Reporting and Data System (BI-RADS) to classify breast density, with categories ranging from "a" (almost entirely fatty) to "d" (extremely dense) (Table 1) (6). The BCSC reported that among women aged 40 to 74 years, 7.4% have extremely dense breasts (BI-RADS category d) and another 36% have heterogeneously dense breasts (BI-RADS category c) (7).

Women with denser breasts are at increased risk for breast cancer. For example, in a meta-analysis, the relative risk (RR) for breast cancer in women with extremely dense versus those with almost entirely fatty breasts was 4.64 (95% CI, 3.64 to 5.91) (8). However, greater breast density does not confer a higher risk for breast cancer death (9). Breast density may obscure small masses on mammography and reduce the sensitivity of mammography for detecting breast cancer, particularly with film-screen mammography (10). Many states mandate that radiologists provide information on breast density in the results letters they send to patients. As of April 2018, a total of 35 states had legislated density-reporting mandates (11). These letters have generated worry among women who may be uncertain about what these reports mean to them and whether they need any additional screening, such as ultrasonography or MRI.

In this context, in 2016 the USPSTF published a recommendation statement regarding breast cancer screening (4). This comprehensive guideline was not limited to breast density alone. The USPSTF concluded that "The current evidence is insufficient to assess the

balance of benefits and harms of adjunctive screening for breast cancer using breast ultrasonography, magnetic resonance imaging (MRI), DBT [digital breast tomosynthesis], or other methods in women identified to have dense breasts on an otherwise negative screening mammogram (I statement)." This conclusion was based in part on the observations that although greater breast density decreases the sensitivity of mammography, women with dense breasts also are at increased risk for false-positive studies and unnecessary biopsies. The guideline authors also found insufficient evidence from the literature that supplemental screening improves breast cancer outcomes (12). In contrast, the ACR recommends that "for women with dense breasts as the only risk factor, the addition of ultrasonography to screening mammography may be useful for incremental cancer detection" (13). In a 2018 statement, the ACR recommends annual breast MRI for women with a personal history of breast cancer and dense breasts (14). It makes no recommendation regarding supplemental magnetic resonance screening for women with dense breast tissue and no other risk factors.

CLINICAL QUESTIONS

To structure a debate between our discussants, we agreed on the following key questions to consider when applying this guideline to clinical practice and to Ms. C in particular.

1. How does breast density compare in importance with other risk factors for breast cancer?

2. How should screening for breast cancer differ for women with dense breasts, in terms of screening intervals and choice of imaging studies?

3. Should radiologists or primary care providers (PCPs) engage patients in state-mandated shared decision-making discussions regarding the risk posed by dense breast tissue on mammography?

DISCUSSION

A Radiologist's Viewpoint (Dr. Christoph I. Lee)

Question 1: How does breast density compare in importance with other risk factors for breast cancer?

Mammographic density affects both a radiologist's interpretive ability and a woman's risk for breast cancer (8). Mammographic sensitivity is lower among women with dense breasts, because masses can be masked by overlying fibroglandular tissue (15). Approximately 43% of women aged 40 to 74 years, or 27.6 million women, in the United States have dense breasts (7), making it one of the most common risk factors accounting for a substantial proportion of breast cancer cases.

Although important, breast density is not the strongest risk factor; age and genetic mutations are more important (16). Within age groups, family history is a stronger risk factor than density. For women 40 to 49 years of age for whom the choice to screen is based on personal preferences, having 2 first-degree relatives with a breast cancer history imparts an RR of 3.84 (CI, 2.37 to 6.22) and having 1 first-degree relative imparts an RR of 2.14 (CI, 1.92 to 2.38) times the average risk (17). In comparison, a woman 40 to 49 years of age with extremely dense breasts has an RR of 2.04 (CI, 1.84 to 2.26) times the average risk, whereas a woman with heterogeneously dense breasts, such as Ms. C, has an RR of 1.62 (CI, 1.51 to 1.75) times the average risk (17).

Breast density is a subjective measure that decreases with age, menopause, and weight gain (18). There is both inter- and intrareader variability in radiologists' BI-RADS breast density categorization for screening mammography (19, 20). However, to minimize variability, automated software has been developed to objectively measure density, with early reports suggesting high reproducibility (21).

Question 2: How should screening for breast cancer differ for women with dense breasts, in terms of screening intervals and choice of imaging studies?

Imaging should begin with annual or biennial mammography, the only imaging method shown to decrease breast cancer mortality. For women with dense breasts, digital mammography is more accurate than screen-film mammography (22). Digital breast tomosynthesis, or 3-dimensional (3D) mammography, may further improve cancer detection, because the multiple-image slices through the breast reduce tissue overlap, decreasing the masking effect (23). Early reports suggest that DBT reduces recall and improves cancer detection rates for all women, with greatest improvements among women with dense breasts (24). With Centers for Medicare & Medicaid Services reimbursement for DBT beginning in 2015, this method is quickly being adopted in community practice as a baseline tool. Simulation modeling suggests that DBT is a cost-effective test for screening women with dense breasts (25).

Because nearly half of all screening-eligible women have dense breasts, it is not feasible for all these women to undergo supplemental screening beyond mammography or DBT. Thus, risk stratification is required to guide supplemental imaging use. According to the ACR, mammography or DBT is "usually appropriate" for women with low to average (<15% lifetime) risk. The ACR recommends no additional supplemental screening for these women. For women with a lifetime risk greater than 15% but less than 20%, the ACR states that supplemental ultrasonography "may be appropriate." For women with a lifetime risk greater than 20%, the ACR suggests that mammography screening, DBT, and breast MRI are "usually appropriate," whereas breast ultrasonography "may be appropriate" for women who lack access or have contraindications to MRI (26, 27). More recently, the ACR recommended supplemental breast MRI for women with a personal history of breast cancer and dense breasts, because these 2 factors combined usually place a woman in the high-risk category (14).

For women with dense breasts and a negative mammogram result, supplemental ultrasonography detects additional cancer at a rate of 4.4 per 1000, with

89% to 93% of these additional cases being invasive cancer (12). Proponents of supplemental ultrasonography argue that earlier detection of node-negative cancer might downstage disease and potentially decrease morbidity and mortality. Simulation modeling suggests that supplemental ultrasonography in women with dense breasts would prevent an additional 0.36 deaths per 1000 (vs. 6 per 1000 with mammography alone) (28). Although previous reports suggested high false-positive rates associated with supplemental ultrasonography (29), recent interim results from a multicenter trial comparing DBT with supplemental ultrasonographic screening among women with dense breasts suggest higher cancer detection rates with ultrasonography (7.1 vs. 4.0 per 1000, respectively), with a similar number of false-positives (1.7% vs. 2.0%, respectively) (30).

For Ms. C, supplemental ultrasonography is a consideration. If she values the potential benefits over the potential risks and desires supplemental screening, then hand held ultrasonography would be the most accessible and least costly option. Other promising supplemental screening tools are becoming available, including automated whole-breast ultrasonography (which addresses the operator dependence of hand held ultrasonography), contrast-enhanced mammography, molecular breast imaging, and abbreviated MRI (a short, 3-minute breast MRI); however, these technologies currently have less evidence to support their use (31).

Question 3: Should radiologists or PCPs engage patients in state-mandated shared decision-making discussions regarding the risk posed by dense breast tissue on mammography?

With 70% of states enforcing breast density notification laws, U.S. radiologists are already engaging in direct communication with patients regarding risks associated with dense breasts. Although radiologists and PCPs both have key roles in shared decision making around supplemental imaging, radiologists are at the front line of breast cancer screening and determining whether a woman has dense breasts.

Shared decision making regarding risk-based screening should begin with a quantitative risk assessment using an established risk calculator. These calculators, based on such risk models as the Gail, Tyrer–Cuzick, and BRCAPRO models, provide estimates of lifetime risk. The BCSC calculator, which incorporates breast density, provides 5- and 10-year cancer risk percentages (2). The National Cancer Institute's online risk assessment tool based on the Gail model has been incorporated into newer mammography reporting systems in an automated fashion, as self-reported risk factors are routinely obtained during mammography visits.

In Massachusetts, a multidisciplinary task force recommends an algorithm beginning with lifetime risk assessment at the time of screening (32). Women with a substantial family history are flagged for formal genetic evaluation. Women with a lifetime risk greater than 20% are encouraged to have screening MRI, because a large multi-institutional trial demonstrated the most benefit from supplemental MRI (vs. supplemental ultrasonography) for women at high risk (33). For women with less than a 15% risk, regardless of breast density, routine mammography or DBT alone is recommended. Finally, for women with a lifetime risk greater than 15% but less than 20% who have dense breasts, the task force recommends shared decision making.

Primary care providers are probably best positioned for conducting more personalized shared decision-making discussions, given the established relationships they have with their patients. However, radiologists may be able to apply automated workflow processes at the time of imaging to perform first-line risk calculations and include these in their reports to help triage women for these discussions. Nevertheless, for both radiologists and PCPs, incorporating risk assessment and discussions with patients about breast density remains challenging, given their already-demanding clinical workflows.

In summary, Ms. C should continue receiving routine mammography or DBT screening. Currently, the American Cancer Society recommends annual screening for women of Ms. C's age (5). Both her radiologist and PCP should be consistent in their consensus recommendations. However, because additional cancer may be detected with screening ultrasonography, the ultimate choice and individual value-based weights assigned to the risks versus benefits of supplemental imaging rest with Ms. C.

A General Internist's Viewpoint (Dr. Joann G. Elmore)

Question 1: How does breast density compare in importance with other risk factors for breast cancer?

Density is only a modest risk factor for breast cancer (Table 2) (17) and has not been clearly associated with increased mortality from breast cancer or with poor-prognosis breast cancer (34). The increased risk associated with this patient's density category of c is similar to the increased risk associated with having prior benign findings on breast biopsy or a second-degree relative with breast cancer. The greater than 4-fold elevated risk for breast cancer often described for breast density applies to the comparison of density categories d versus a (densest vs. almost completely fatty breasts). However, density legislation in the United States generally defines dense tissue more broadly, as categories c and d versus categories a and b.

So who decides what risk factors should be considered when making decisions about screening? Generally, clinicians use evidence from scientific research to help guide their discussions about risk factors with patients. However, with density, politicians have become involved; some state laws go as far as mandating that insurers pay for additional ultrasonography and MRI if a mammogram reveals dense breasts.

William Osler described medicine as "a science of uncertainty and an art of probability," and discussions with women about breast density certainly exemplify the art of medicine. Women with dense tissue who are informed that they are "high risk" may be anxious and

Table 2. Factors Significantly Associated With Increased Breast Cancer Risk for Women Aged 40 to 49 Years*

Risk Factor	Breast Cancer Risk Ratio (95% CI)
≥2-fold increased risk	
Number of first-degree relatives with breast cancer	
2	3.84 (2.37–6.22)
1	2.14 (1.92–2.38)
Age of first-degree relative with breast cancer	
<40 y	3.0 (1.8–4.9)
<50 y	2.17 (1.86–2.53)
Breast density BI-RADS category d (4)†	2.04 (1.84–2.26)
1.5- to 2.0-fold increased risk	
Previous benign breast biopsy result	1.87 (1.64–2.13)
Second-degree relative with breast cancer	1.7 (1.4–2.0)
Breast density BI-RADS category c (3)†	1.62 (1.51–1.75)
1.0- to 1.5-fold increased risk	
Current contraceptive use	1.30 (1.13–1.49)
Nulliparity	1.25 (1.08–1.46)
Age at first birth ≥30 y	1.20 (1.02–1.42)

BI-RADS = Breast Imaging Reporting and Data System.
* From reference 17.
† Density category b as the reference group.

assess their breast cancer risk to be higher than it actually is. Describing absolute risk rather than RR may provide a more meaningful reflection of a risk factor's impact. For example, among 1000 women with dense category c, like Ms. C, the estimated number of new diagnoses of breast cancer over the next decade is 20 (Figure) (35), meaning that 980 women will not be diagnosed with breast cancer. For comparison, among 1000 women with nondense category b, 13 will be diagnosed with breast cancer, and among 1000 women with a *BRCA1* gene mutation (the strongest known breast cancer risk factor), the estimate rises to 227.

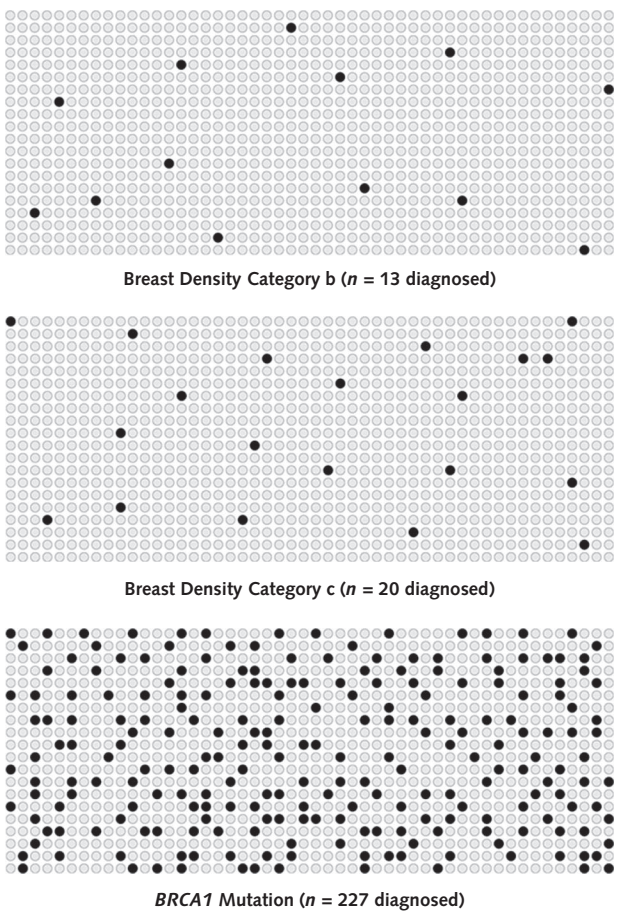
Question 2: How should screening for breast cancer differ for women with dense breasts, in terms of screening intervals and choice of imaging studies?

Decisions on screening should involve shared decision making. Women with high breast density may reasonably consider screening every year (Table 3) (36). Although the number of breast cancer deaths averted may increase with annual versus biennial screening, the absolute benefit is smaller than what many women think (that is, the lifetime benefit is estimated at approximately 2 per 1000 women) and the harms, such as false-positives, are almost 2-fold greater (36).

Regarding the choice of imaging studies, digital mammography (used for most examinations in the United States) is slightly more accurate than film mammography (22). Although 3D DBT is a promising newer technology, with early studies reporting a lower false-positive rate (24), less scientific evidence is available. Imaging technologies often disseminate quickly into clinical practice and develop strong constituencies before adequate scientific evidence is available. About 30% of screening mammograms in the United States already are obtained by using DBT. A study of DBT is ongoing if Ms. C would like to participate, although her insurance carrier may not cover the examinations, including those that may be performed as part of the research protocol (http://ecog-acrin.org/tmist).

Implementing supplemental screening with ultrasonography or breast MRI among the 28 million women in the United States with dense tissue would expose a great many to the potential harms of additional screening, with unclear benefit. Although it is true that if more imaging is done more breast cancer will be found, it is unknown what proportion of additional cases found represents overdiagnosis (that is, cancer that would cause no morbidity during a patient's lifetime) and there is no evidence that supplemental screening reduces mortality from breast cancer. Supplemental screening is also associated with higher rates of false-positive results, which cause anxiety and can lead to invasive breast biopsies. Furthermore, supplemental tests are often not covered by insurance

Figure. Ten-year risk for a breast cancer diagnosis for 3 populations of 1000 women.



Calculations were performed by using an online Tyrer–Cuzick model breast cancer evaluation tool (35). **Top.** Population of 1000 women like Ms. C but with nondense breasts (category b). **Middle.** Population of 1000 women like Ms. C, with dense breasts (category c). **Bottom.** Population of 1000 women like Ms. C but with *BRCA1* mutation.

Table 3. Lifetime Benefits and Harms of Screening Annually Versus Biennially per 1000 Women Aged 50 to 74 Years at Average Risk (e.g., RR of 1.0) Screened, by Breast Density Category*

Breast Density Category	Median Cancer Deaths Averted vs. No Screening		Median Cases of Overdiagnosis vs. No Screening		Median False-Positives vs. No Screening	
	Annual	Biennial	Annual	Biennial	Annual	Biennial
a	4.7 (3.2–5.6)	4.1 (2.4–4.3)	17 (12–24)	12 (11–20)	1101 (1094–1548)	618 (613–858)
b	6.9 (5.1–7.9)	5.2 (3.8–6.8)	23 (12–35)	17 (11–27)	1806 (1776–2440)	1009 (991–1326)
c	8.4 (6.1–11.7)	6.3 (4.4–9.8)	28 (12–38)	20 (11–26)	2123 (2080–2829)	1197 (1171–1524)
d	8.9 (6.0–14.4)	6.5 (4.2–11.7)	31 (12–32)	21 (11–22)	1668 (1647–2225)	939 (925–1200)

RR = relative risk.
* Median benefits and harms are shown (with the range across simulation models as a measure of uncertainty). Values are numbers per 1000 women (95% CIs). From reference 36.

and can present an additional expense. The U.S. expenditure for false-positive mammograms and breast cancer overdiagnoses is estimated at $4 billion annually (37) and will increase markedly if all women with dense breast tissue begin undergoing supplemental screening.

Although a 2018 statement from the ACR recommends MRI screening for women with a lifetime risk greater than 20% (38), Ms. C's lifetime risk is approximately 10% according to the IBIS (International Breast Cancer Intervention Study) tool. Breast screening MRI has been increasing among U.S. women with dense breasts but no other risk factors; because MRI is not indicated in these women, this is concerning (39). Magnetic resonance screening is especially expensive; is prohibitive for women with claustrophobia; and requires intravenous gadolinium, which has been associated with a rare risk for contrast reactions and, according to a communication from the U.S. Food and Drug Administration, gadolinium deposits in the brain (40–42).

Furthermore, although the ACR states that ultrasonography should be "considered" for women with dense breasts (14), no other major guidelines for breast cancer screening recommend using breast density as the sole factor when determining the need for supplemental screening. I concur with the American College of Physicians guidelines for high-value care and would not recommend supplemental screening for Ms. C (43, 44).

Question 3: Should radiologists or PCPs engage patients in state-mandated shared decision-making discussions regarding the risk posed by dense breast tissue on mammography?

Radiologists and PCPs both should engage patients in informed decision making. Although I do not think that politicians should be mandating this behavior, I agree with the intent regarding the importance of patient education and improving informed decisions.

Most physicians are aware of the iatrogenic potential of drugs and procedures, yet there can also be an iatrogenic potential of information (45). State-mandated breast density notifications use language that exceeds recommended readability levels, score poorly on understandability ratings, and generally do not correlate with state literacy levels (46). The importance and challenges involved in conveying test results are likely to increase as the volume and resolution of imaging tests accelerate and as more patients gain access to their full electronic medical record and imaging reports (47).

To meet these challenges, we need better tools and training about communicating risk to our patients. Studies have shown that PCPs and radiologists have trouble educating women about dense breasts (48, 49), including overestimating both the incremental risk due to dense breasts and the benefit of supplemental screening. In addition, radiologists working in breast imaging commonly overestimate an individual woman's 5-year risk for breast cancer (50).

Education is needed *before* women get to the mammography facility. Online decision aids are easy-to-access, inexpensive, and potentially effective tools to support women who are considering screening options (51).

Ms. C seems anxious about breast cancer screening and the possibility of false-positives. I would ask her about her understanding of the benefits versus harms and try to understand what her personal values and goals are for screening. We should educate her about the potential benefits of screening and caution her about the limitations of mammography and the potential for false-positives and overdiagnosis. She should be advised to seek medical care if she detects a concerning breast lump. I would talk with her annually about her wishes regarding screening and would not recommend supplemental imaging. Finally, I would remind Ms. C of other ways to reduce her breast cancer risk (52). In the end, we need a balanced message that encourages women to make an informed decision. Table 4 offers suggested dialogues for engaging women in these discussions and commentary for clinicians (2, 22, 35, 53–56).

SUMMARY

Breast cancer is common. It will develop in approximately 1 in 9 U.S. women during their lifetime. Mammography is the mainstay of breast cancer screening,

Table 4. Communicating With Women About Breast Density

Discussions With Women	Additional Comments for Clinicians
What is breast density?	
Dense breast tissue is **not** abnormal. Almost half of women have dense breast tissue.	About 43% of U.S. women have "dense" breast tissue (defined as category "c" [heterogeneously dense] or category "d" [extremely dense] tissue).
If you have category "c" breast tissue density, your risk is the same as the risk associated with having a second-degree relative (e.g., aunt) who had breast cancer.	Dense tissue on mammography can mask abnormalities, thus reducing the sensitivity of mammography. The sensitivity of mammography by density category is "a," 88.2%; "b," 82.1%; "c," 68.9%; and "d," 62.2% (53).
If you have breast density category "d" (extremely dense), your risk is the same as having a first-degree relative with breast cancer.	The increased risk for breast cancer among women with dense breasts is similar to that of having a relative with a history of breast cancer.
Dense breast tissue can make it challenging for the radiologist to identify abnormalities and interpret the examination; thus, the accuracy of mammography is lower.	
Although your risk for developing breast cancer is modestly higher if you have dense breasts, you are not at increased risk for dying of breast cancer.	
Calculate her breast cancer risk	
Many online tools allow you to calculate your risk for a breast cancer diagnosis (e.g., estimated risk for a diagnosis in the next 5 or 10 y, or over your lifetime).	The Breast Cancer Risk Assessment tool (www.cancer.gov/bcrisktool/Default.aspx) is an update of the Gail model from the BCSC (2). This tool currently does not include breast density information.
If your lifetime risk for breast cancer is <15%, then no additional screening beyond mammography is generally recommended.	The Tyrer–Cuzick tool is electronically available and may be downloaded from www.ems-trials.org/riskevaluator/ (54). This tool includes information on breast density and takes a little longer to use (35).
If your lifetime risk is 15%–20%, the ACR and ACS suggest that you discuss your concerns and preferences with your provider to determine whether you should have additional screening with other tests. However, not all societies recommend this, and it remains an uncertain area.	The approach to supplemental screening for intermediate-risk patients (lifetime risk of 15%–20%) is controversial. Among major societies, only the ACR and ACS recommend shared decision making and, potentially, additional screening.
If your calculated lifetime risk is >20%, some groups recommend supplemental MRI annually (e.g., alternate every 6 mo with mammography and then 6 mo later with MRI).	Many women assume that their risk for breast cancer is higher than it is. The "1-in-9" estimate women may have heard is 1 in 9 women will be *diagnosed* with breast cancer, not die of breast cancer. Women in the United States are more likely to die of cardiovascular disease than breast cancer.
	Explain risk estimates using absolute numbers and both positive and negative framing (e.g., Among 1000 women with category "c" density and no other risk factors, the number estimated to be diagnosed with breast cancer over 10 y is 20, meaning 980 in category "c" will **not** be diagnosed with breast cancer over the next decade).
Provide information on screening methods	
Although screening mammography is not perfect, it is the best-studied tool we have and the only imaging tool that confers reduced deaths from breast cancer.	A randomized controlled trial reported increased accuracy of digital over film mammography for women with dense breasts (22). However, almost all mammograms in the United States are now digital, so this is less clinically relevant.
Digital mammography is more accurate than the older film mammography if you have dense tissue. 3D tomosynthesis is a newer imaging test that has been less well studied; it may have a lower false-positive and higher cancer detection rate, but the examination may incur additional cost and expose you to more radiation.	Although 3D tomosynthesis has a lower false-positive rate and may detect more cancer cases, it requires additional exposure to radiation if combined with digital mammography, and women may have to cover the additional cost.
	A large DBT clinical trial is ongoing for patients who want to participate (http://ecog-acrin.org/tmist) (55).
Provide information on screening interval	
If you have dense breasts, consider annual screening.	The *lifetime* benefit of annual vs. biennial screening among women in their 50s with no other risk factors except density increases the number of breast cancer–related deaths averted by about 2 per 1000 women
If you have fatty (e.g., nondense) breasts and no other risk factors, screening every 2 y may be a reasonable risk–benefit balance.	The risk for false-positive results is almost twice as high with annual than biennial screening; the risk for overdiagnosis and overtreatment also increases with annual screening.
Provide information on ultrasonography and MRI	
Potential benefits	No long-term studies have provided data on breast cancer mortality for ultrasonographic or MRI supplemental screening.
Ultrasonography and MRI may be able to detect additional cancer that would not be seen on your mammogram	Although IV gadolinium carries a risk for nephrogenic sclerosis, this risk primarily affects patients with ESRD who are receiving dialysis. Current practice is to screen patients who may be at risk for kidney disease before administering gadolinium.
Earlier detection from screening may allow less aggressive surgery, chemotherapy, and radiation therapy.	

Continued on following page

Table 4–Continued

Discussions With Women	Additional Comments for Clinicians
Potential harms	
Your risk for false-positive results increases with ultrasonography and MRI. False-positive results are when you are asked to return for additional testing but do not have breast cancer. This can be a stressful experience for some women.	An FDA communication reported the potential adverse effects of gadolinium accumulation in the brain in autopsy findings.
Your risk for having a breast biopsy when you do not have breast cancer increases.	
You will be at increased risk for overdiagnosis (breast cancer that would cause no harm during your lifetime). Because we cannot identify which cancer cases are "overdiagnosed," you may receive overtreatment (e.g., unnecessary chemotherapy or surgery).	
Your cost will be higher (especially with MRI).	
IV gadolinium (which has uncertain long-term risks) is required for breast MRI.	
Counsel all women on risk reduction	
A healthy lifestyle has been associated with lower risk for breast cancer (e.g., limit postmenopausal weight gain, maintain an exercise regimen, limit alcohol intake).	Discuss chemoprevention for women with a 5-y breast cancer risk of ≥3% (56).
If you are at very high risk, you may consider medications (e.g., chemoprevention).	For women with BRCA mutations, discuss referral to a specialty clinic for counseling and discussion on the role of potential prophylactic mastectomy.
We would discuss prophylactic surgery only if you were at extremely high risk (e.g., you had a BRCA genetic mutation).	
Informed decision making	
What is your understanding of the benefits vs. harms?	A woman's decision may not be what the clinician would recommend.
What are your personal values and goals for screening?	
I encourage you to make an informed decision that is right for you.	

3D = 3-dimensional; ACR = American College of Radiology; ACS = American Cancer Society; BCSC = Breast Cancer Surveillance Consortium; DBT = digital breast tomosynthesis; ESRD = end-stage renal disease; FDA = U.S. Food and Drug Administration; IV = intravenous; MRI = magnetic resonance imaging.

yet the optimum age at which to begin screening and the most appropriate screening interval remain controversial. Breast density has emerged as a risk factor for breast cancer; higher degrees of density confer slightly higher breast cancer rates. In addition, dense breasts may reduce the sensitivity of mammography by obscuring small lesions.

Dr. Lee, a radiologist, notes that approximately 43% of women aged 40 to 74 years have dense breasts; hence, this discussion is applicable to many women. He acknowledges that a family history of breast cancer is a stronger risk factor than breast density. He notes that breast density is subjective—different radiologists may score density differently for the same patient, and even the same radiologist may change the density assignment from one mammogram to the next. For women with dense breasts, Dr. Lee recommends digital rather than film mammography. He observes that DBT further improves the sensitivity for cancer detection. He states that the ACR's recommendations are based on a patient's lifetime risk. For women at intermediate (15% to 20%) lifetime risk, the ACR suggests that supplemental ultrasonography may be appropriate and that breast MRI is usually appropriate for women at high (>20%) lifetime risk. Dr. Lee recommends shared decision making and suggests that automated estimates of lifetime risk may allow radiologists to provide more helpful counsel in their results letters. He advises Ms. C to consider supplemental ultrasonography screening on the basis of her values of the purported benefits and harms.

Dr. Elmore, a general internist, emphasizes that "dense tissue" is not an abnormality. She draws a distinction between the RR increase for women with dense breasts and the absolute incremental risk, which may inform discussions with patients about the effect of breast density. She notes that breast density has not been associated with increased breast cancer–specific mortality. Dr. Elmore agrees with Dr. Lee that assignment of breast density is subjective and may vary over time. She feels it is reasonable to discuss annual mammography for women with dense breasts, whereas less frequent imaging is reasonable for women with predominantly fatty breasts. Dr. Elmore notes that although DBT may lower false-positive rates, it may require more radiation exposure and the effect on clinical outcomes has not been well studied. She notes the absence of any evidence in the literature that supplemental screening (ultrasonography or MRI) for women with dense breasts reduces breast cancer mortality. In addition, supplemental screening results in higher false-positive rates and patient anxiety, overdiagnosis and overtreatment, and increased costs. Dr. Elmore does not recommend MRI for women whose only risk factor is dense breasts and advises against supplemental screening for Ms. C. Because of widespread misinformation, she encourages better tools and training for clinicians to optimize communication with patients on the effects of breast density.

A transcript of the audience question-and-answer period is available in the **Appendix** (available at Annals

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.org). To view the entire conference video, including the question-and-answer session, go to Annals.org.

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Appendix: Comments and Questions

Dr. Burns: Thank you. I wanted to start the question-and-answer session by delving further into how these conversations are conducted with patients. I think all of us have had a patient walk into the office with a letter that clearly suggests that maybe something is wrong and maybe more should be done. So, Joann, I wanted to start with you. As a primary care provider, how do you have this conversation? How do you approach the informed decision-making process?

Dr. Elmore: Since we all multitask, I probably would initially take a deep breath and think about 2 items: first, whether she has acute illnesses that I need to deal with during this visit (for example, is she also reporting chest pain?), and second, whether I have 3 other patients waiting that I need to let know that I may be running late. I probably would then cover 2 topics with her: I would explain what density is and then I would assess her knowledge, values, and goals for screening. We need to remind women that breast density, in and of itself, is not abnormal. Some women are tall, some women are short, some women have dense breast tissue, and some women don't. Thirty million women have dense tissue. Breast density is associated with a higher risk for breast cancer, but the risk is similar to having an aunt who was diagnosed with breast cancer. I would perhaps even remind her that having dense tissue does not increase your risk for dying of breast cancer, because that is really what women are worried about. We need to remind women that mammography is currently our best tool for breast cancer screening; however, we also need to warn them that mammograms aren't perfect. I think that in medicine we have oversold technology, and that has caught us. The number 1 cause of medical malpractice allegations in the United States is failure to detect cancer, with breast cancer being the most common. It is harder to interpret mammograms when women have dense tissue, so we need to warn them that if they feel a lump or an abnormality to come and see us regardless of the mammogram result. That is the first part of the density discussion. The second part involves stepping back, listening to the patient, and asking her to tell us her preferences and what worries her. That discussion needs to be individualized and also needs to be balanced. The decision may not be the one that you would make. We need to provide the facts so the patient can make an informed decision. I give women a lot of credit and, hopefully, they can follow the path that is best for them.

Dr. Burns: Dr. Lee, you suggested that radiologists have conversations with patients. How would you have this discussion?

Dr. Lee: Radiologists talk about the inherent risk of breast density and the risk for cancer, but a lot of fear and anxiety come from the thoughts of missed cancer. Jerry showed you the slides about sensitivity decreasing with increasing breast density, and so we do have to tell them that their dense breasts limits our ability to detect cancer. Cancer could be masked by dense breasts, reducing the sensitivity of mammography. With that knowledge, we can offer women who want greater sensitivity 3D mammography and screening ultrasonography. If missed cancer is their greatest source of heightened anxiety and fear, more than the RR we talked about, we can give them options.

Dr. Gregory Poland: Thank you all for your thoughtful discussion. Dr. Lee, I am delighted to know that there are health services researchers in radiology—I wasn't really aware of that. I have a question for you that's more of a technology question. I realize there are still a lot of data to gather, but molecular breast imaging appears to have exquisite sensitivity and specificity. Could you comment on that?

Dr. Lee: With molecular breast imaging, we inject a radiotracer—analogous to what we do during PET-CT [positron emission tomography and computed tomography]—and look at where that tracer is picked up in the breast, which indicates metabolic activity. This gives us information about tumor neovascularity at the molecular level. That's why we have increased sensitivity with breast MRI versus 2D or 3D mammography or ultrasonography; you're going to have increased sensitivity because you can detect what's enhancing and what's actually taking up a lot of the blood flow, and what's not. The problems with molecular breast imaging right now are the need for a radioactive tracer injection and a relatively large radiation dose. The dose is more than 1.5 times the background radiation experienced by an individual over a year. In addition, molecular breast imaging requires radiotracer availability in the form of an on-site nuclear medicine department, which is not ubiquitous. Similar to breast MRI, I think it has the potential to be a tool for those at really high risk, but its utility as a readily accessible supplemental screening tool is limited.

Dr. Sasikala Vemuri: I am a primary care physician from Flint, Michigan. My question is how to make our lives easier. I primarily see only women, so I deal with a lot of these questions on a day-to-day basis. Dr. Lee mentioned eliminating copays to help patients, but in the past few years most patients have had huge de-

ductibles, so copays are a lesser consideration. The other thing is the letters, which have added a considerable burden to our practice. Most of these letters say "Discuss with your primary." I would suggest taking out at least categories a and b and not sending any density reports to the lowest categories; then, at least half of these patients won't be getting these letters—because some of the anxious patients, even with a 25% to 50% score, are calling us asking, "What does 'density' mean?" I also think everybody should have their risk factors assessed before they have the mammogram so they know them in advance. Then, maybe we could have a letter saying, "The state mandates that we report breast density. If you are at low risk and are in category 'a' or 'b,' please call the radiologist at such and such a number to answer your questions."

Dr. Lee: I have started getting calls from patients about this, but to clarify about the letter, it's not something that we as radiologists are creating ourselves. The language used in our lay letters is actually dictated in the density-reporting law. So we're mandated by law to make a specific statement created by patient advocates with multidisciplinary input, and we can't change that language.

Dr. Karen Victor: It seems that potentially the biggest problem in additional screening is not anxiety, it's not false-positives, it's not cost: It's overtreatment. Dr. Elmore, you seem to suggest that increasing screening intervals impacts this issue more than the lives that it saves. I'd also like to hear from Dr. Lee. What are your concerns about overtreatment?

Dr. Elmore: That is really an outstanding question. Indeed, when you go from mammography every 2 years to every year, you're increasing the number of women who we think are overdiagnosed and overtreated. I don't have a magic way of describing this to patients. Articles in the lay press are trying to explain these concepts, which has helped to improve the level of understanding for some of my patients. How to explain that breast cancer could cause no harm during your lifetime is challenging. I explain how we can't currently tell which woman is overdiagnosed and which isn't, and they usually respond, "Gee, well I would want treatment," and I tell them, "I understand." It's very hard to describe. Christoph?

Dr. Lee: Well, I think it's a fantastic point and question. There is a proportion of breast cancer that is overdiagnosed, but as a radiologist there is no way to differentiate between indolent and aggressive cancer. The same appearance on imaging could signify a finding that may kill the patient, or it may not—we can't tell that from imaging alone. We know more about the prognostic features once we've had a breast biopsy. We know estrogen-receptor and progesterone-receptor positivity and negativity and HER2/neu status. We could look at molecular subtypes and manage them differently. In addition, I think people are starting to treat ductal carcinoma in situ (DCIS) differently. Tissue diagnosis is the point at which we have more information about what it might mean for that patient. Also, there are surgeons and oncologists who are willing to follow DCIS now and avoid chemotherapy for low-grade cancer. We know that cancer is heterogeneous. We know that some cases are indolent and some are aggressive, and it becomes not only a matter of overdiagnosis but overtreating, as you stated, and having an open discussion about the heterogeneity of cancer and managing it differently on the basis of molecular subtype.

Dr. Helen Strauss: This was a great discussion. I have worked in a faculty and resident practice where we have a diverse and very vulnerable patient population. I was wondering if you could comment on 2 points. The first regards risk calculators—some are validated with different ethnicities and take into account family history versus other factors. Which ones do you use? Second, you mentioned different patient resources and that it has been difficult to find the right ones for different patients. Are there any you recommend?

Dr. Lee: Most radiology practices use the Tyrer–Cuzick model. The updated model includes breast density as a risk factor and gives you a lifetime risk value. There is increasing interest in the risk prediction modeling world to get a little closer to present day and what would happen in the short term. So, the BCSC has a risk calculator tool available online through an app, and it gives you 5-year and 10-year risks for breast cancer. I think we're moving more toward 5-year and 10-year risk rather than lifetime risk values.