Radiology

Breast Density Legislation and Opportunities for Patient-centered Outcomes Research[1]

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One important strategy for reducing breast cancer mortality is early detection through screening (1). Despite a reported decline in mortality rates because of mammography, its effectiveness remains heavily debated. Exemplified by the breast imaging community's backlash against the U.S. Preventive Services Task Force (USPSTF) for its recommendation not to routinely screen women aged 40–49 years, the interpretation of available evidence remains a highly charged and emotional issue for many stakeholders (2).

Not surprisingly, breast cancer screening continues to be one of the most heavily legislated issues in U.S. preventive medicine. Starting with the Mammography Quality Standards Act (MQSA) of 1992 and its reauthorizations in 1998 and 2004, minimum national standards in regard to the operation of mammography equipment, film processing, image interpretation, and results reporting have been instituted. These laws have assured that minimal process measures necessary for decreasing variability in screening practices are being maintained.

Breast Density Screening Legislation

Over the past decade, however, breast imaging has moved beyond the mammogram for women at increased risk. Screening breast ultrasonography (US) and breast magnetic resonance (MR) imaging are two of the available tools that can increase sensitivity for detecting early cancers, especially among women with dense breasts, who may have cancers obscured by large amounts of overlapping fibroglandular tissue. Given the rapid diffusion of these technologies and a movement toward increased shared decision making (as recommended by the USPSTF), there is now a push by patient advocacy groups for new legislation that would mandate disclosure of breast density information directly to women.

As of April 2012, Connecticut, Texas, and Virginia have adopted such a reporting requirement for women with dense breasts, and at least 10 additional states will consider similar bills in 2012. At a national level, the Breast Density and Mammography Reporting Act (H.R. 1302) was introduced in the 112th U.S. Congress and would require that every mammography report "contain information regarding the patient's breast density and language communicating that individuals with more dense breasts may benefit from supplemental screening tests" (3). If strictly enforced, these recently passed and proposed state and federal laws may drastically change screening practices for women with dense breasts.

Reporting Breast Density to Patients

Women with breast density in the upper quartile have an associated three to five times greater risk of developing breast cancer relative to women with breast density in the lower quartile, even after adjusting for associated risk factors such as age and body mass index (4–7). A previous "masking bias" hypothesis—that the observed higher relative risk was solely due to mass obscuration by dense tissues at mammography—has been debunked by recent large cohort studies (5,8–10). Indeed, breast density is now an established independent risk factor for developing breast cancer, irrespective of the influence of other known risk factors, method of density measurement, or patient population studied (11). Because dense breasts are common, with 31%–43% of the general screening population having heterogeneously dense or extremely dense breasts at mammog-

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raphy (4), a mandate to disclose the associated increased risk for cancer directly to individual patients seems ethical, reasonable, and appropriate.

Supplemental Screening

The question remains, however, as to what supplemental screening studies patients should be referred to after being informed about their dense breasts. US, given its wide availability and relatively low direct medical costs, is likely the most promising adjunct screening modality currently available. In a recent report (12) from the American College of Radiology Imaging Network (ACRIN) 6666 investigators, the addition of a screening US examination for women with dense breast tissue and at least one other known risk factor resulted in an additional 4.3 cancers detected per 1000 women screened. This finding was commensurate with findings in prior multicenter trials (13–15). In addition, ACRIN 6666 investigators found that 3.7 additional cancers were detected per 1000 women in the second and third rounds of screening (incidence rounds). Across all recent studies, the majority of cancers detected by using additional US are node negative, theoretically leading to earlier treatment for lower-stage invasive cancers and possibly leading to improved patient survival (16,17).

The addition of MR imaging to screening regimens would markedly increase detection of early breast cancer, beyond cancers found at screening mammography alone or at combined screening mammography and US (18–22). MR imaging is unaffected by breast density and, like US, incurs no ionizing radiation. In the recent ACRIN 6666 trial, screening MR imaging was performed in a subset of intermediate-risk women after three negative screening mammography and US examinations. The addition of MR imaging in this patient population yielded the detection of 14.7 additional cancers per 1000 women screened (12). Several studies have reported similar yields from supplemental MR imaging after mammography in the high-risk population (18,20,23,24).

However, additional screening is not without risks to patients. Berg et al (12) found that adjunct US resulted in biopsy in 5% of women in addition to the 2% sent for biopsy on the basis of mammographic findings alone. At these additional biopsies, only 7.4% of the women were found to have cancer. Moreover, while screening US was performed by expert, trained physicians in recent studies, such a practice cannot easily be replicated in the general community given a current manpower shortage. If performed by other personnel, the recall and biopsy rates may become much higher. The addition of screening MR imaging rather than US to mammography in the general community would likely be inappropriate given the current high false-positive rates (19,25). Indeed, 7% of women in the ACRIN 6666 study underwent biopsy on the basis of MR imaging findings alone (12). MR imaging is also less well tolerated by patients, incurs significantly higher costs, is not widely accessible, and includes the risk of adverse events from injection of intravenous contrast material (20). Currently, the American Cancer Society recommends breast MR imaging only in women at high risk for breast cancer and, at this time, considers the evidence insufficient to recommend screening breast MR imaging in women with dense breast tissue but no other risk factors (26).

Current Shortcomings

The advocacy push to legislate mandatory reporting of breast density and possible adjunct screening for all women with heterogeneously or extremely dense breasts is far outpacing the reporting of evidence that supplemental screening may provide better outcomes for these patients. Recent study results in regard to adjunct screening US and MR imaging, while encouraging, pertain only to women of intermediate or high risk, with known risk factors beyond their dense breasts. Therefore, it is uncertain what the added cancer detection yield of supplemental screening would be for women of average risk with dense breasts but no other known risk factors.

Even with increased rates of early cancer detection, the impact of supplemental screening on patient morbidity and mortality remains unknown. Recent trials did not include control groups, meaning that the impact of additional screening on patient mortality cannot be determined (12). Beyond survival benefit, the question arises as to whether detection of more abnormalities will lead to increases in overdiagnosis. Because some cancers detected at screening may not go on to cause symptoms or death, additional interventions performed on these excess cancers would only increase morbidity for these patients (27).

If the demand for supplemental screening increases at a high rate, then issues with supply will have to be addressed. Currently, there is a shortage of qualified breast imagers and breast US technologists who can perform competent screening US examinations (12). Rates of cancer detection at technologist-performed screening US appear to be similar to those at physician-performed US, but a large investment would have to be made to train more technologists (28). Automated whole-breast US promises to decrease operator variability, but this technology has just received Food and Drug Administration approval, and its accuracy for depicting smaller cancers is yet to be determined (29,30).

It is also uncertain who will pay for additional screening if recommended by law. Currently, only two states—Illinois and Connecticut—have considered mandating insurance coverage for supplemental screening US. In Illinois, "if a routine mammogram reveals heterogeneous or dense breast tissue, coverage must provide for a comprehensive ultrasound screening of an entire breast or breasts, when determined to be medically necessary by a physician" (31). Even if covered by insurance, there is cur-

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rently only one Current Procedural Terminology code available for breast US, with a low Medicare reimbursement level (approximately $90) that may not adequately cover the cost of the physician time required for performing and interpreting a comprehensive study (12). To date, from a health systems standpoint, there are no randomized control trials or cost-effectiveness analyses demonstrating that supplemental screening is a cost-effective measure for women with dense breasts.

Within the highly litigious environment of breast cancer screening, it is not unreasonable to expect an increase in reflexive ordering of unnecessary supplemental studies for women with dense breasts but no other known risk factors. If there is a legislated recommendation that the patient may benefit from additional screening, then an order for supplemental screening devoid of an individual patient-centered risk-benefit discussion may result because of the physician's concern for medical-legal protection. Such reflexive ordering would lead to increased inappropriate utilization of breast imaging technologies at increased costs and decreased net health benefits.

Building a Framework for Patient-centered Outcomes Research

Given these current shortcomings, what is needed is a unified, organized approach to building a framework for identifying and addressing the key issues in regard to determining the effects of adjunct screening on individual outcomes for women with dense breasts. The maelstrom encompassing the proposed breast density legislation, the recent USPSTF recommendations, and the Patient Protection and Affordable Care Act (PPACA) has created an unusual and fortuitous climate for change in national breast screening practices. We argue that building such a framework centered on comparative effectiveness research (CER) and patient-centered outcomes research is critical not only for addressing the needs created by new density legislation but also for collecting the evidence that will ultimately best inform individual risk-based discussions between patients and health care providers regarding breast cancer screening. In the remaining paragraphs, we introduce three core issues that will need to be addressed upfront—consensus, quality, and cost.

Consensus

CER and patient-centered outcomes research promise to inform health care decisions by providing evidence on the effectiveness, benefits, and harms of different screening options for different patients. However, before key research initiatives can be identified, all key stakeholders must come together to build consensus for a shared research agenda. Health care reform, culminating in the PPACA, has established the Patient-Centered Outcomes Research Institute (PCORI), an independent organization created to help people make informed health care decisions and improve health care delivery (32). According to the PCORI, patient-centered outcomes research is "guided by patients, caregivers and the broader health care community and will produce high integrity, evidence-based information." Thus, one of the main tenets of research in the era of health care reform will be the heavy involvement of patients at each stage of research. In fact, much of the current drive for breast density legislation likely stems from the historic lack of communication between the medical community and its patients in regard to the limitations of mammography. The breast imaging community, therefore, must welcome patient advocacy groups into the fold, along with other key stakeholders, including payer organizations.

Quality

Before performing comparative effectiveness studies involving adjunct technologies for breast cancer screening, all stakeholders collectively must establish mandatory minimum quality standards for newer modalities, similar to the MQSA for mammography. The subjectivity and variation in breast imaging remain beyond mammography, and satisfactory process measures must be created for the operation, maintenance, image processing, and reporting of screening breast US. Contrary to popular belief within the medical community, mandatory accreditation and certification of imaging facilities for breast US are not currently required by federal law. While the American College of Radiology (ACR) has breast US and US-guided biopsy accreditation and certification programs (33), these are for the most part optional. Establishing mandatory accreditation may provide a level of standardization necessary for ensuring a minimum level of competency in process measures and allow for the evaluation of the comparative effectiveness of different modalities and screening strategies. Moreover, inter- and intraobserver variability in interpretation for new screening modalities must be addressed, with the development of methods to improve standardization in physician interpretation (34). Practitioners should meet certain experience and continuing education criteria for performance and interpretation of screening US studies set by the ACR or the American Institute for Ultrasound in Medicine (16).

Cost

The cost associated with any new screening strategy is critical and should be dealt with up front, in parallel with efforts to determine improved patient outcomes. Health care reform demands that new interventions be of higher value for lower costs to patients, the health care system, and society. Randomized controlled trials in which different screening strategies are compared for women with dense breasts are unlikely to be performed because of the associated large number of patients needed to demonstrate a difference between groups, the long length of follow-up required, and the large monetary expenses incurred. In the absence of definitive randomized controlled trials to establish the comparative effectiveness of multimodality breast cancer screening, computer simulation models of breast cancer natural history and outcomes can be used to project long-term health outcomes and lifetime costs related to different screening strategies.

Therefore, while long-term prospective studies through ACRIN and other research collaboratives should be pursued, preliminary decision analyses and cost-effectiveness analyses must be performed with models based on available efficacy data and expert opinion to guide current decision making. Historically, in the United States, the key driver of widespread use of new breast imaging interventions has been reimbursement by government and third-party payers rather than the reporting of clinical efficacy (35). Thus, payers must be engaged as partners early to help establish appropriate reimbursement rates and increase access to new adjunct screening tools. Government payers, for instance, may be able to provide coverage for supplemental screening in return for requiring evidence collection, as is the case for positron emission tomography (PET) and Medicare through the national PET registry.

With engaged patient advocacy groups, research should include aspects of overall costs important to individual patients, such as out-of-pocket costs, transient levels of anxiety from false-positive findings or biopsies, and lost time for follow-up. Patients can help clarify their preferences and values, and the resulting quality-of-life utilities should be included in all analyses. Furthermore, cost-effectiveness analyses should be focused on specific subpopulations of patients, such as women with dense breasts of average risk and no other risk factors, and should compare specific strategies, such as combined mammography and US screening versus mammography alone. In an era of more personalized breast cancer care, the cost-effectiveness of a specific screening strategy may be dependent on an individual's specific risks of developing breast cancer (36–38). Our analyses should reflect this trend toward individualized breast cancer care and should truly inform the personal decision-making process.

Conclusion

The timely convergence of advocacy efforts, high political will, and health care reform provides an important opportunity for the breast cancer community to help institute positive change in screening practices. However, current legislation that mandates informing patients about possible increased breast cancer risk on the basis of breast density may not suffice in actually improving patient outcomes. Instead, the breast imaging community must partner with advocacy groups to shift efforts toward creating an infrastructure for patient-centered outcomes research that will provide the evidence needed for meaningful discussions between individuals and their physicians about screening. Through early consensus building, standardized quality measures, and a focus on cost effectiveness, we can maximize the benefits of breast cancer screening for every woman. Moreover, by partnering with all stakeholders at each stage of our research efforts, we can create an increased level of transparency to help prevent future controversies in breast cancer screening recommendations.

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