Breast density notification drives supplemental screening tests

Cristen Bolan, MS

Women with dense breast tissue are at a disadvantage. Compelling evidence shows that density in the highest quartile represents a 4- to 6-times higher risk of breast cancer.[1] This is coupled with the fact that when mammography is the only screening test performed, sensitivity decreases by 10% to 20% for women with dense breasts.[2]

These circumstances have prompted a push for supplementary screening tests. Twelve states now have breast density inform legislation, and new bills are being drafted in many more states. All of the states with breast density laws require facilities to send a post-exam letter to women with dense breasts alerting them that the condition can interfere with the effectiveness of a mammogram.

These laws have potentially enormous implications that may result in a significant increase in supplementary screening with technologies, such as ultrasound (US), magnetic resonance imaging (MRI), tomosynthesis, molecular breast imaging (MBI), and spectral imaging.

Mammography: Benefits and limitations

The benefits of mammographic imaging are well established. Screening mammography can help reduce deaths from breast cancer among women ages 40 to 70.

However, screening mammograms miss about 20% of breast cancers present at screening.[3] The main cause of these false-negative results is high breast density,[3] which is usually collectively referred to as fibroglandular tissue.[4] A phenomenon known as masking, in which the surrounding dense breast tissue obscures a cancer, may occur during mammography.

"The medical evidence shows that masses in women with dense breast tissue are more likely to be cancerous and their masses are less likely to be detected under standard imaging. It is a real dilemma for these women—on the one hand they are at greater risk, and on the other, there is less likelihood that their cancer will be detected," said Richard Frank, MD, PhD, CMO, Siemens Healthcare.

As such, researchers have suggested that reliable and reproducible breast density measurements are a prerequisite for the use of breast density to monitor primary prevention strategies and for the use of mammographic density to define women at higher breast cancer risk who would benefit from intensified early detection and surveillance protocols.[6]

Breast density legislation gains momentum

In response to the limitations of mammography to detect cancers in women with dense breasts, several states have adopted laws requiring referring physicians to notify patients when the interpreting radiologist determines that their pattern of fibroglandular tissue is considered dense.

As approximately 50% of women undergoing screening mammography are classified as having either "heterogeneously dense" or "extremely dense" breasts,[5] breast density notification legislation could have significant impact on overall patient care.

One of the challenges with such a law, however, is the language in the notification varies across states, which can impact the quality of care delivered. Additionally, insurance coverage for supplemental screening is not part of the mandate. Only one state, Connecticut, requires insurers to cover additional screenings under its notification law. Therefore, while some patients will be able to afford additional screening, others clearly will not.

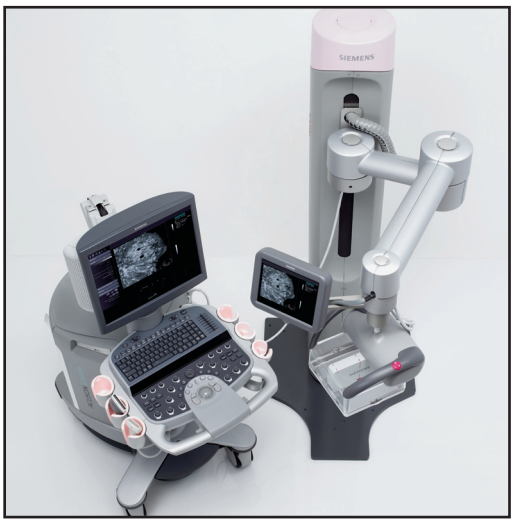


FIGURE 1. *The ACUSON S2000™ Automated Breast Volume Scanner (ABVS) from Siemens is designed to simplify and expedite volume acquisition for consistent results and improved workflow.*

Dr. Frank believes there should be a national standard for breast cancer notification. "It is this variability across state bills that is a problem and argues in favor of a federal solution or single national program perhaps channeled by way of the Mammography Quality Standards Act (MQSA)," he said.

As more states implement the law, the mandate is gaining momentum on the national stage. On January 18, 2011, federal legislation for dense breast notification was introduced in Congress, but it has yet to be enacted. Also, the U.S. Food and Drug Administration (FDA) is considering adding a breast-density reporting amendment to the MQSA. This means that women would receive standardized nationwide notification about their breast tissue density after their mammograms. The FDA said it would consider the proposed rule in December 2013.[7]

Advocates of a federal mandate point to the benefits of early detection and long-term reduced costs. "The benefits of early detection will offset the initial costs. Earlier detection leads to better efficacy, preservation of anatomy, and it is also less expensive," pointed out Dr. Frank.

Yet opinions are mixed among radiologists. While many believe information is power, there are many unanswered questions. For example, what impact could breast density notification have on patient care, and should such notification become mandatory without clinical research to back it up? Furthermore, how practical is the law if it does not require supplemental imaging to be covered by insurance?

"I think it does help a significant number of women who otherwise might not be told of their breast density, and that they could have some additional screening with ultrasound. But I think it's very important that, in conjunction with the legislation, there be a funding mandate so that people are not left in the position of wanting an exam because they have been told by the physician that it would be good for them, yet not be covered by the insurance carriers," said Laurie Margolies, MD FACR, Associate Professor of Radiology, Department of Radiology, Chief of Breast Imaging, Dubin Breast Center, Mount Sinai School of Medicine, New York, NY.

"We really have to ensure that if there is mandated information, that there will be mandated requirements for coverage of these additional modalities as there is in CT," noted Rachel Brem, MD, Professor of Radiology and Vice-Chair of Radiology, The George Washington University School of Medicine and Health Sciences.

Breast ultrasound (US): The next test

Although there are several adjunct tests to mammography, US is most often indicated due to its accessibility and low cost.

A recent study concluded that technologist-performed handheld screening breast US offered to women in the general population with dense breasts can aid detection of small mammographically occult breast cancers (cancer detection rate, 0.8-10 cancers per 1000 women screened).[8]

Where 2-dimensional mammography falls short, US can help because it acquires images differently from x-ray systems. "Ultrasound can separate masses from dense tissue, which in certain cases you cannot make any distinction, especially with extremely dense tissue. It's essentially a white out; you can't pick out mass from background dense tissue. So that's where US really shines. It also helps to distinguish between something solid from something cystic, especially when there is a new nodule," said Dr. Justin S. Torok, Diagnostic Radiologist, Women's Imaging Specialist, Heritage Valley Health System, Beaver, PA.

Recently, automated breast ultrasound systems (ABUS) have been introduced. These include the somo-v ABUS, which has been acquired by GE Healthcare (Waukesha, WI), and the ACUSON S2000™ Automated Breast Volume Scanner (ABVS) from Siemens Healthcare (Malvern, PA) (Figure 1).

Once the technician has positioned the transducer, these US systems automatically scan the whole breast, capturing multiple ultrasound images and instantly generating a 3-dimensional (3D) visualization.

The somo-v ABUS is the only US system to receive FDA 510(k) approval for breast cancer screening as an adjunct to mammography for asymptomatic women with dense breast tissue.

"If you look at the cancers detected with mammography and look at those detected by ABUS, the cancers detected by ABUS are node negative, small invasive breast cancers—exactly those cancers that you are trying to detect," said Dr. Brem.

A key shortcoming in conventional breast US is that it is usually used to evaluate a small area surrounding a palpable mass or a specific mammographic finding.[10] "ABVS surveys both breasts and is a complete scan," said Dr. Torok. "If there is an abnormality in a far lateral or a high superior position, the technician can include the tissue in the scan. We can detect more lesions and smaller lesions because you get better separation of lesions from background tissue, so when you're looking at cancers down to 3 mm size, they are easier to identify on the S2000 than on the conventional US units that we had."

Dr. Brem added, "This is really a leap forward in how we screen intermediate risk women in order to find additional cancers. We have very high-risk women who benefit from breast MRI, but how do we screen for women with intermediate risk of breast cancer where mammography can be less optimal?"

Automated workflow

One drawback of US for breast screening is that it is labor intensive and too time-consuming to accommodate a high-volume screening environment. While automated breast US is not going to replace mammography, it simplifies and expedites volume acquisition for consistent results, thereby improving workflow.

"ABUS whole-breast imaging can be easily integrated in the screening environment," indicated Dr. Brem. "US is not translatable unless it's automated because of screening workflow issues. It takes 19 minutes for a technologist to manually screen using US, but it doesn't take any time to screen with ABUS because it is automated. Now with ABUS, you only need a trained person who can acquire the image dataset, then the entire dataset can be interpreted by a physician."

Similarly, automated breast US plays an important role at Heritage Valley Health System, where Dr. Torok and staff recently adopted the ACUSON S2000. The system acquires a series of consecutive B-mode pictures and reconstructs 3D data sets of the entire breast volume. ACUSON S2000 offers applications for fatty tissue imaging, elasticity imaging, and biopsies with US guidance.

"Sometimes we will call patients direct from a screen where you have an extremely dense mammogram from the patient's baseline study. 3D US is recommended to take a closer look at each breast as sort of a baseline US. We are trying to do it on every case with a category 5 suspicious cancer so we get used to seeing what cancers look like on the 3D US. What I like most about it is on the coronal, MIP reconstructed image, architectural distortion comes out looking pretty well—it almost comes out looking like a breast MRI," said Dr. Torok.

The advantage of automation to diagnostic accuracy and workflow is significant. There is greater consistency with the automated as opposed to the manual ultrasound probe.

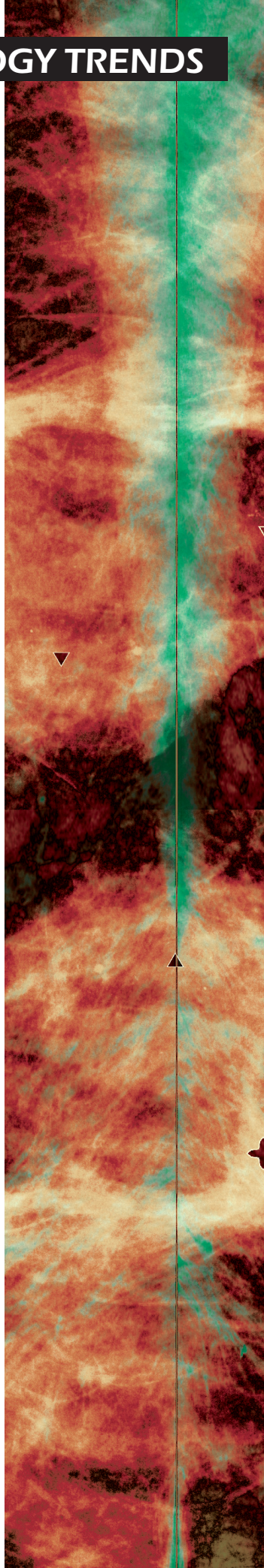
"Because ABVS is automated there is less variation with the technologists performing the exam, which gives you a more consistent exam and exam time across all technologists," indicated Beverly Feragotti, Radiology Operations Manager for Women's Health, Heritage Valley Health System. This level of reproducibility is important for the radiologist when comparing currents and prior diagnostic studies.

Additional testing

As with most diagnostic imaging technologies, US has advantages and disadvantages. The disadvantage with breast US is that it may lead to additional tests. "Supplemental US screening increases cancer detection beyond mammography alone, but may also result in an increased number of additional tests,[9]" said Richard G. Barr, MD, PhD, professor of radiology at the Northeast Ohio Medical University in Youngstown, OH, in a recent study[11] on screening breast US.

"You can find some cancers that mammography has missed, but it is operator dependent, and there is a significant number of false positives leading to many benign biopsies and a lot of anxiety," said Dr. Margolies.

As Dr. Torok noted, "On a routine basis, especially with whole-breast US, you'll find some new lesions, and you may have to do a biopsy or MRI to follow up. With 3D US, we



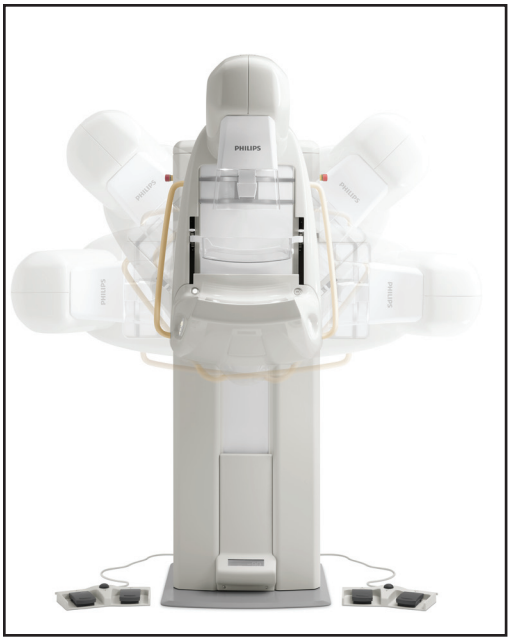


FIGURE 2. *Philips will provide single-shot spectral imaging as an add-on to its MicroDose system, a low-dose mammography system built on photon counting technology.*

will encounter a large number of lesions that we did not see on a mammogram. Although most will be malignant, we have to make a decision whether or not to follow them up or to do a biopsy. It's information that's good to have and increases sensitivity for picking up a tumor, but there are a lot of other benign things you have to sort through to get to that end point," indicated Dr. Torok.

Nevertheless, a breast density notification law could actually enhance workflow at Heritage Valley Health System. "If in Pennsylvania we did get breast density notification legislation, it would permit doing these as a screening study or at least as an adjunctive screening study. We could then do exams in batches, which would be much more efficient," said Dr. Torok.

Breast MRI

Similar to US, contrast-enhanced breast MR imaging frequently reveals mammographically occult cancers. Screening breast MRI has been shown to substantially increase the rate of cancer detection; however, it is much less common than breast US. Based on the American Cancer Society (ACS) guidelines,[12] breast MRI is recommended as an adjunctive screening tool to mammography[12] only in patients at very high risk for breast cancer—such as those with an estimated lifetime risk of 20% to 25%, patients with a BRCA mutation, those with a nontested first-degree relative who is a BRCA carrier, and those who received radiation therapy to the chest between the ages of 10 and 30 years.

Compared to mammography and US, the sensitivity of contrast-enhanced breast MRI in cancer detection is considerable at > 94%,, and specificity ranging from 37% to 97%.[13]

The dedicated MRI systems offer proven advantages. The first FDA approved MRI device designed specifically for breast imaging is the Aurora 1.5T Dedicated Breast MRI System by Aurora Imaging Technology Inc. A recent study showed that the system led to better sensitivity, specificity, negative predictive value, positive predictive value, and receiver-operating characteristic area than has been historically reported in trials for breast MRI on whole-body MRI scanners.[14]

Hologic's Sentinelle Breast MRI coil system, provides a Variable Coil Geometry that transforms MRI systems into dedicated systems for breast MR imaging and intervention.

The MAGNETOM Espree - Pink uses the Sentinelle Vanguard for Siemens coil solution, which makes imaging and biopsies possible using only a single coil. Enhanced image quality is obtained through an improved signal-to-noise ratio and with the help of eight RF channels. In addition, some GE Healthcare and Toshiba breast MRI units leverage the Sentinelle Breast MRI coil system on their breast MRI units.

As with US, MRI should be used as a complement to, not instead of, screening mammography. Although an MRI is a more sensitive test, it may still miss some cancers that a mammogram would detect.[15]

Will breast density notification laws ramp up the numbers of patients with dense breast seeking adjunct breast MRI procedures? It is questionable, since reimbursement as an adjunct test to mammography is limited to high-risk patients. "Only people who have ≥ 20% lifetime risk of breast cancer will get the extra screening with MRI; otherwise, they will get an ultrasound for supplemental screening," said Dr. Margolies, adding that MRI has other drawbacks. "There are a significant number of false positives, it's a costly procedure, and a time-intensive procedure and uncomfortable for patients. Yet it is exquisitely sensitive," indicated Dr. Margolies.

Dr. Brem points out that breast-specific gamma imaging (BSGI), can be used as a supplemental

test to mammography, offers comparable sensitivity to MRI, and is far less expensive.

"BSGI works equally well in women with dense breasts and nondense breasts. It is less common, but it is at least equally effective as the other modalities. If we are comparing MRI and BSGI, we have shown that the sensitivity is equal on MRI and BSGI, but the specificity is better with BSGI," said Dr. Brem. "It's also important to remember if you go with the physiological imaging approach, 15% to 20% of patients can't have an MRI because they have an implantable device, are too large, have renal deficiency, or are claustrophobic."

Up-and-coming solutions: Tomosynthesis and spectral imaging

Other evolving technologies that support lesion detection in patients with dense breasts are breast tomosynthesis and spectral imaging.

Tomosynthesis

Breast tomosynthesis, which creates a 3D rendering of the entire breast, combined with conventional 2D mammography, is highly indicated for patients with dense breast tissue. The ability to review images slice by slice allows breast tissue to be displayed with less tissue superimposition compared to 2D mammography. This demonstrates true lesions much more clearly. A recent study compared screening recall rates and cancer detection rates of tomosynthesis plus conventional digital mammography to those of conventional digital mammography alone. Researchers found that the addition of tomosynthesis reduced recall rates for all breast density and patient age groups, with significant differences found for scattered fibroglandular, heterogeneously dense, and extremely dense breasts.[16]

Another study concluded that combining mammography with tomosynthesis in a screening environment resulted in a significantly higher cancer detection rate and enabled the detection of more invasive cancers.[17]

While breast tomosynthesis is widely used in Europe, Selenia Dimensions from Hologic Inc. (Danbury, CT) is the first, and currently only, FDA-cleared system indicated for breast tomosynthesis. According to the literature,[18] Hologic's system has a higher cancer detection rate than conventional digital mammography and improves the radiologists' confidence to significantly reduce recall rates.[19]

GE Healthcare recently submitted its premarket approval application (PMA1) to the FDA for its breast tomosynthesis solution, an add-on option to the Senographe Essential unit, to generate 3D digital breast tomosynthesis images for screening and diagnosis of breast cancer. According to Pilar Anton Serrano, Global Communications Manager, GE Healthcare, the company's goal is to gain FDA approval for a single 3D MLO view as a replacement for the current 2-view mammography done in 2D. "With GE's Breast Tomosynthesis, a single MLO view will provide clinical noninferiority (as measured by ROC analysis) compared to a 2-view digital mammography exam—at half the dose and with just one compression. This solution has the potential to replace digital mammography exams in screening to help radiologists detect breast cancer," said Ms. Anton Serrano.

For now, tomosynthesis used with routine mammography is not a substitute for additional screening with ultrasound or MRI, said Dr. Margolies.

"With tomosynthesis there has been a decrease in the callback rates, and clearly there are some cancers that we have seen on the tomosynthesis that we haven't seen on the 2D mammogram. There is a benefit to using tomosynthesis with 2D over just using 2D mammography alone," said Dr. Margolies.

Spectral imaging on digital mammography

Another technology designed to enhance the detection of lesions in dense breasts is single-shot spectral imaging. Earlier this year, Philips (Andover, CT) received 510(k) clearance from the FDA for its MicroDose SI system, the first full-field digital mammography (FFDM) system on the market with the capability to enable future single-shot spectral imaging applications. Single-shot spectral imaging is built upon the premise that breast density comprises different tissue types and materials that absorb x-rays at various energies. The technology powering the MicroDose SI uses this fundamental behavior of x-rays, allowing clinicians to see more than just a shadow in mammogram images by separating high- and low-energy x-ray within one exposure. What is unique about spectral imaging is that it will generate quantitative breast density data.

"This new innovation with MicroDose technology will give quantitative breast density information with low-dose data, which will be incredibly

valuable for radiologists to apply to their reports, particularly when reimbursement is tied to performance," said Raymond Tu, MD, FACR, Chairman, Department of Radiology, NFPHC/United Medical Center, Washington, DC.

Dr. Tu is looking forward to updating single-shot spectral imaging on its existing MicroDose digital mammographic system (Figure 2), a low-dose mammography system built on photon counting technology.

The impact of legislation on care

How important is breast density notification legislation? While there is ample evidence that supplemental tests often detect cancers that screening mammography misses, the verdict is still out on how breast density notification legislation will impact patient care.

Dr. Tu believes "whole breast US and breast MRI is going to be important, and all of these adjunct risk factors are something that patients should know, and that [dense breast awareness] will emphasize very diligent clinical screening and careful clinical follow up." However, he also offers caution with respect to the dangers of a federal mandate. "To make it a rule is questionable because breast density is very subjective in a lot of ways, and how it's going to play out long term depends on how it is truly measured, and if it's accurate. At the same time, we don't want to alarm people unnecessarily and give them unnecessary tests when their real true risk is much lower," said Dr. Tu.

Although there is no proven correlation between breast-density notification and improved patient outcomes, breast density notification legislation continues to gain momentum and, for some, shows promise.

"Information is an important and powerful tool, and the more we know about our health care, the better advocates we can be for ourselves," said Dr. Brem. "Perhaps, a federal regulation is a way to ensure that all women in our country are informed of what their breast density is, and hopefully, along with that strategy, it will improve breast cancer detection."

References

1. Schreer I. Dense Breast Tissue as an Important Risk Factor for Breast Cancer and Implications for Early Detection. Breast Care (Basel). 2009 May; 4(2):89-92.
2. Bevers TB, Anderson BO, Bonaccio E, et al. NCCN clinical practice guidelines in oncology: breast cancer screening and diagnosis. Journal of the National Comprehensive Cancer Network. *JNCCN*. 2009;7(10):1060-1096.
3. National Cancer Institute FactSheet. National Cancer Institute. http://www.cancer.gov/cancertopics/factsheet/detection/mammograms. Updated July 24, 2012. Accessed September 4, 2013.
4. Ding H, Molloi S. Quantification of breast density with spectral mammography based on a scanned multi-slit photon-counting detector: A feasibility study. Phys. Med. Biol. 57 (2012) 4719-4738.
5. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA*. 2008;299:2151-2163.
6. Schreer I. Dense Breast Tissue as an Important Risk Factor for Breast Cancer and Implications for Early Detection. Breast Care (Basel). 2009 May; 4(2):89-92.
7. Federal Register. https://www.federalregister.gov/articles/2013/07/23/2013-17060/regulatory-agenda. Updated July 22, 2013. Accessed September 3, 2013.
8. Hooley RJ, Greenberg KL, Stackhouse RM. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. Radiology. 2012 Oct;265(1):59-69. Epub 2012 Jun 21.
9. Boyd, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007 Jan 18;356(3):227-36.
10. Porter BA. Automated breast volume scanning. Visualization of mammographically occult breast cancer - two cases. White Paper. Siemens Medical Solutions USA, Inc. July 2009.
11. Barr G, Zhang Z, Cormack JB . Probably Benign Lesions at Screening Breast US in a Population with Elevated Risk: Prevalence and Rate of Malignancy in the ACRIN 6666 Trial. Radiology. 2013 Aug 20. [Epub ahead of print].
12. Saslow D, Boetes C, Burke W, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA: a cancer journal for clinicians. 2007;57(2):75-89.
13. DeMartini W, Lehman C, Partridge S. Breast MRI for cancer detection and characterization: a review of evidence-based clinical applications. Acad Radiol. 2008 Apr;15(4):408-16. doi: 10.1016/j.acra.2007.11.006.
14. Hillman BJ, Harms SE, Stevens G, et al. Diagnostic performance of a dedicated 1.5-T breast MR imaging system. Radiology. 2012 Oct;265(1):51-8. Epub 2012 Aug 24.
15. American Cancer Society recommendations for early breast cancer detection in women without breast symptoms. Breast Cancer: Early Detection. Cancer. http://www.cancer.org/cancer/breastcancer/moreinformation/breastcancerearlydetection/breast-cancer-early-detection-acs-recs. Updated February 6, 2013. Accessed September 9, 2013.
16. Haas BM, Kalra V, Geisel J. Comparison of Tomosynthesis Plus Digital Mammography and Digital Mammography Alone for Breast Cancer Screening. Radiology. 2013 Jul 30. [Epub ahead of print].
17. [Skaane P, Bandos AI, Gullien RT, et al. Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology 2013; Epub ahead of print.]
18. Skaane P, Gullien R, Eben EB, et. al. Reading time of FFDM and tomosynthesis in a population-based screening program. Radiological Society of North America annual meeting. Chicago, Il, 2011.
19. FDA executive summary. Hologic. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/RadiologicalDevicesPanel/ucm226757.pdf. Updated September 24, 2010. Accessed September 9, 2013.