Mammography and Beyond:
Developing Technologies for the Early Detection of Breast Cancer

Breast cancer takes a tremendous toll in the United States. Each year, over 180,000 new cases of invasive breast cancer are diagnosed, and more than 40,000 women die from the disease. Until research uncovers a way to prevent breast cancer or to cure all women regardless of when their tumors are found, early detection will be looked upon as the best hope for reducing the burden of this disease. The hope is that early detection of breast cancer by screening could be as effective in saving lives as the Papanicolau smear used for cervical cancer screening.

X-ray mammography has been shown in clinical trials to reduce breast cancer deaths. However, mammography is not perfect. Routine screening in clinical trials resulted in a 25–30% decrease in breast cancer mortality among women between the ages of 50 and 70. A lesser benefit was seen among women aged 40–49. The benefit of screening mammography for women over 70 was more difficult to assess due to a lack of data.

Screening mammography cannot eliminate all breast cancer deaths because it does not detect all cancers. Some tumors may also develop too quickly to be identified at the most treatable stage using the standard screening intervals. Furthermore, it is technically difficult to consistently produce mammograms of high quality and interpretation is subjective.

Mammography can also have deleterious effects for some women, in the form of false positive results and overdiagnosis and overtreatment. As many as three-quarters of all breast lesions biopsied because of suspicious findings on a mammogram turn out to be benign, i.e., the mammographic findings were falsely positive. “Overdiagnosis” is the labeling of small lesions as cancer or precancer when in fact the lesions may never have progressed to a life-threatening disease if left undetected and untreated. In such cases, some of the “cures” following early detection may not be real, and thus such women are unnecessarily “overtreated.” Technical improvements in breast imaging techniques have led to an increase in the identification of these small abnormalities, such as carcinoma in situ, whose biology is not well understood. Currently, methods for classifying such lesions detected by mammography are based on tissue structure, and the ability to determine the lethal potential of breast abnormalities is crude at best.

The immense burden of breast cancer and the inherent limitations of mammography have been the driving forces behind efforts to develop technologies for the early detection of breast cancer. The Institute of Medicine (IOM), an arm of the National Academies, released a report called Mammography and Beyond in...
The immense burden of breast cancer and the inherent limitations of mammography have been the driving forces behind efforts to develop technologies for the early detection of breast cancer. March 2001 that reviews breast cancer detection technologies in development and examines the many steps in technology development and adoption.

Technologies in Development

Most progress thus far has resulted in incremental improvements in traditional imaging technologies. One recent example is full-field digital mammography (FFDM). FFDM systems are identical to traditional film-screen mammography systems except that electronic detectors capture and display x-ray signals on a computer rather than directly on film. This digital process provides the opportunity to adjust contrast, brightness, and magnification of images without additional exposures. FFDM is considered by many to be a major technical advance over film mammography, but studies to date have not demonstrated a meaningful improvement in screening accuracy. The technology could potentially improve the practice of screening mammography in other ways, for example, by facilitating electronic storage, retrieval, and transmission of mammograms.

Computer-aided detection, through use of sophisticated computer programs designed for recognizing patterns in images, has shown potential for improving the accuracy of screening mammography. However, questions remain as to how this technology will ultimately be used, and whether it will have a beneficial impact on screening practices.

Other breast imaging technologies approved by the Food and Drug Administration (FDA) include ultrasound (US), magnetic resonance imaging (MRI), scintimammography, thermography, and electrical impedance imaging. Many additional technologies are at earlier stages of development, but to date it appears that no quantum steps forward have been taken and a great deal of work remains to optimize the benefits of breast cancer screening.

Several new technologies may help define the biological nature of breast lesions, including culture of breast cancer cells in the laboratory, measurement of protein expression in cancer cells, or identification of cancer markers in blood or breast fluid. Further progress will depend on patient specimen banks, new high-throughput technologies, and bioinformatics.

Technologies based on biology could potentially contribute to improved patient outcomes in several ways. For example, they could distinguish between early lesions that require treatment because they are highly likely to become lethal and those that are not. These technologies could also potentially identify fundamental changes in the breast that appear before a lesion can be detected by imaging. Thus, they might identify women at high risk of developing breast cancer, or, more importantly, women at high risk of dying from breast cancer.
The Technology Development Process

The pathway from technical innovation to accepted clinical practice is long and costly. Although research on new technologies for early cancer detection has increased substantially over the last decade, biomedical research has also become more complex and capital intensive. Moreover, many organizations evaluate medical technologies at various steps, making decisions about FDA approval, insurance coverage, and reimbursement that ultimately determine whether new technologies are adopted. In assessing new technologies, many factors are considered, including clinical need, technical and clinical performance, economic issues, and patient and societal perspectives.

Government funding of research has traditionally focused on basic scientific discovery, but recently a new emphasis on the translation of science into practice through the development of technology has received considerable attention, including the creation of joint public/private-sector initiatives. Investment by the private sector is also considerable, although private investment in breast imaging technologies appears to be less attractive than investment in other areas of health care. This may be due to a perception of high economic risk based on the time and resources needed to develop technologies, and the size of the potential market. Research is always unpredictable, but for medical devices, the requirements for FDA approval and insurance coverage have been variable and unpredictable, adding additional levels of risk. Development of devices also tends to be iterative and thus assessment at early stages of development may not recognize the full potential of a new medical device. That is, most technologies that ultimately achieve widespread use go through successive stages of development, variation, and appraisal of experience in the market.

Assessment of New Technologies

The dominant framework for medical technology regulation and evaluation has historically been based on therapeutics, while early detection relies on screening and diagnostic methods. The evaluation of therapeutic and detection technologies may be intrinsically different. The stages of drug development are more standardized, and therapeutic interventions generate direct outcomes in patients. In contrast, most patient-level effects of detection devices are mediated by subsequent therapeutic decisions. Screening and diagnostic tests generate information subject to interpretation. Furthermore, this information is only one factor in the decision making process. Hence, evaluation of detection technologies is fundamentally an assessment of the value of information.

With the exception of film mammography, new breast cancer detection technologies have been evaluated with diagnostic studies that measure sensitivity (proportion of people with the disease who test positive) and specificity (proportion of people without the disease who test negative). Even if the technologies ultimately are intended to be used in screening, they are not evaluated through screening studies that measure health outcomes. Adoption of new technologies for screening prior to assessment of their effect on clinical outcome has been common and problematic for other diseases because data on detection accuracy are not adequate to assess the potential screening value of technologies. The ideal endpoint for assessing screening technologies is reduction in disease-specific mortality, but clinical trials necessary for measuring those endpoints are large, lengthy, and costly. Surrogate endpoints for mortality are difficult to define because the net effect of new detection technologies could be either positive (more accurate detection, leading to lower breast cancer mortality) or negative (capable of identifying more lesions, but not changing disease-specific mortality, and thus leading to greater morbidity and costs).
Technology Adoption

After the hurdles of FDA approval, insurance coverage, and reimbursement have been cleared, the adoption of breast cancer detection technologies will ultimately depend on whether women and their health care providers find them acceptable. Much is already known about the adoption of mammography, and this knowledge may prove instructive for other technologies. Experience suggests that education, outreach, and access to facilities are all essential.

Use of screening mammography has increased greatly in the last decade, but many women still do not get screened, and many others do not undergo screening at the recommended intervals. Studies indicate that physician recommendation is the single most influential factor in whether women are screened.

Access to screening facilities can be difficult for women who lack health insurance. The National Breast and Cervical Cancer Early Detection Program was established through the Centers for Disease Control with the goal of providing screening exams for uninsured women. The program has grown since it was launched 10 years ago, but still only reaches about 12–15% of eligible women nationwide. New federal legislation that would provide Medicaid coverage for treatment of breast cancer detected through the program was recently passed, but state participation is pending.

As more women adopt the practice of routine screening and the number of women eligible for screening mammography increases (due to an aging population), demand for trained mammographers and screening facilities will increase. There are reports that too few specialists are being trained to fill the current and future needs, but quantitative data are lacking. There are also concerns that the reimbursement rate for mammography is too low to cover the procedure’s actual costs (including costs of complying with federally mandated quality standards, which are unique to mammography), and that this situation could lead to a reduction in screening services.

When mammography was introduced, it was a “void-filling” technology, and thus had no competition during the dissemination process. New technologies face a much different scenario. Evaluation will likely include comparison to mammography, and adoption will require competition with other technologies that are currently available.

Recommendations

The committee made recommendations to improve the development and adoption process for new technologies (1–5); and to make the most of technologies currently available for breast cancer detection (6–10).

1. **Government support for development of new breast cancer detection technologies should continue to emphasize research on the basic biology and etiology of breast cancer and on creation of classification schemes for breast lesions based on molecular biology.** A major goal is to determine which lesions identified by
screening are likely to become lethal and thus require treatment. This approach would increase the potential benefits of screening while reducing the potential risks.

- Research should focus on development of biologic markers and translational research to determine appropriate use and application of the markers, including functional imaging.
- Funding priorities should include specimen banks, purchase and operation of high-throughput technologies, and bioinformatics.

2. Breast cancer specimen banks should be expanded and researchers access to patient samples should be enhanced.

- Health care professionals and breast cancer advocacy groups should educate women about the importance of tumor banks and encourage women to provide consent for research on specimens.
- Stronger protective legislation should be enacted at the national level to prevent genetic discrimination and ensure confidentiality of genetic test results.
- The National Cancer Institute should devise strategies to facilitate researcher access to patient samples in specimen banks.

3. Consistent criteria should be developed and applied by the Food and Drug Administration for approval of screening and diagnostic devices and tests.

- Guidance documents for determining “safety and effectiveness,” especially with regard to clinical data, should be articulated more clearly and applied more uniformly.
- Given the complexity of assessing new technologies, FDA advisory panels could be improved by including more experts in biostatistics, technology assessment, and epidemiology.

4. For new screening technologies, approval by the FDA and coverage decisions by the Health Care Financing Administration (HCFA) and private insurers should depend on evidence of improved clinical outcome. This pursuit should be streamlined by coordinating oversight and support from all relevant participants (FDA, NCI, HCFA, private insurers) at an early stage. This approach should prevent technologies approved for diagnosis from being used prematurely for screening in the absence of evidence of benefit. Technology sponsors generally lack resources and incentive to undertake large, long-lasting, and expensive screening studies, but a coordinated approach would make it easier to conduct clinical trials to gather outcome data.

- Detection technologies should be approved by FDA for diagnostic use based on evidence of accuracy (sensitivity and specificity). In the case of “next generation devices,” technical advantages such as patient comfort or ease of data acquisition and storage could be considered in determining approval.
- If a new device, approved for diagnosis, shows potential for screening (based on evidence of accuracy), and the developers wish to pursue a screening use, an investigational device exemption should be granted for this use and conditional coverage should be provided for conducting large-scale screening trials to assess clinical outcomes.
- Trials should be designed and conducted with input from the FDA, NCI, HCFA, the Agency for Healthcare Research and Quality (AHRQ), and breast cancer advocacy organizations.
The committee made several recommendations for improving the development and adoption process for new technologies.

The committee also made several recommendations to optimize the benefits of proven technologies for breast cancer detection.

- HCFA and other payers should agree to cover the cost of tests in approved trials, while the National Cancer Institute (NCI) and the technology’s sponsors should take responsibility for other trial expenses. Participation by private insurers would be particularly important for assessing new technologies in younger women who are not yet eligible for Medicare coverage. Although this expense may seem burdensome to private insurers, the cost of providing tests within a clinical trial would be much less than the costs associated with broad adoption by the public (and associated pressure to provide coverage) in the absence of experimental evidence for improved clinical outcomes.

- Trial data should be periodically reviewed and results should determine whether FDA approval is granted and coverage is extended to screening use outside of the trials.

- The ideal clinical endpoint is reduced disease-specific mortality. However, given the length of time required to assess that endpoint, and the fact that early detection by screening mammography has already been proven to reduce breast cancer mortality, a surrogate endpoint for breast cancer detection is appropriate in some cases. As a general rule, a screening technology that consistently detects early invasive breast cancer could be presumed efficacious for the purposes of FDA approval. Detection of premalignant or preinvasive breast lesions, however, cannot be assumed to reduce breast cancer mortality or increase benefits to women, and is not an appropriate surrogate endpoint for FDA approval, given our current lack of understanding of these lesions.

5. The National Cancer Institute should create a permanent infrastructure for testing the efficacy and clinical effectiveness of new detection technologies as they emerge. The NCI Breast Cancer Surveillance Consortium and the American College of Radiology Imaging Network (ACRIN) may provide model platforms for this purpose.

6. HCFA should analyze current Medicare and Medicaid reimbursement rates for mammography, including a comparison to other radiological techniques, to determine whether they adequately cover the total costs of providing the procedure. The analysis should include costs associated with the requirements of the Mammography Quality Standards Act. External and independent experts should be involved in the analysis.

7. The Health Resources and Services Administration (HRSA) should undertake or fund a study to analyze trends in specialty training for breast cancer screening among radiologists and radiologic technologists, and examine factors affecting the decision of practitioners to enter or remain in the field. If trends suggest a shortage of trained experts, HSRA should seek input from professional societies like the American College of Radiology and the Society of Breast Imaging in making recommendations to reverse the trend.

8. Until health insurance becomes more universally available, Congress should expand the Centers for Disease Control and Prevention (CDC) screening program to reach a higher fraction of eligible women, and state legislatures should participate in the federal Breast and Cervical Treatment Act by providing funds for cancer treatment for eligible women. CDC should reach 70% of eligible women (as opposed to the current 15%), based on the goals of the U.S. Department of Health and Human Services’ Healthy People 2010.

9. The National Cancer Institute should sponsor large randomized trials every 10 – 15 years to reassess the effect of accepted screening modalities on clinical out-
come. Trials would compare two currently used technologies with different sensitivities. Breast cancer-specific mortality would be the principle outcome under evaluation. Because detection and treatment are both continually evolving, the benefit of a screening method may change over time.

10. The National Cancer Institute, through the American College of Radiology Imaging Network or the Breast Cancer Surveillance Consortium, should sponsor further studies to define more accurately the benefits and risks of screening mammography in women over age 70. As the age distribution of the United States continues to shift toward older ages, this question will become increasingly important.

For More Information . . .

Copies of Mammography and Beyond: Developing Technologies for the Early Detection of Breast Cancer are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at www.nap.edu. The full text of the report is available on line at http://books.nap.edu/catalog/10030.html.

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