

Current Status of Full-Field Digital Mammography¹

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Screen-film mammography has been studied extensively for the past 30 years, and because of many large randomized screening trials, it is known to reduce breast cancer mortality by approximately 18%–30% (1,2). The decline in the rate of breast cancer death in the past few years may be due in part to the widespread use of this imaging test (3,4). However, while standard screen-film mammography is very good, it is neither perfectly sensitive nor highly specific. Dense breast tissue and diffuse involvement of the breast with tumor tend to reduce the sensitivity of screening mammography (5–7). Approximately 10%–20% of breast cancers that are detected at self-breast examination or physical examination are not visible at screen-film mammography (6,8,9). In addition, when lesions are detected at mammography and biopsy is recommended by experienced radiologists, only 5%–40% of lesions prove to be malignant (10–12). Clearly, there is room for improvement in both breast cancer detection and lesion characterization.

A major limitation of screen-film mammography is the film itself. The film serves as the medium of image acquisition, storage, and display. Breast cancer is often similar in

x-ray absorption to surrounding normal dense breast tissue. Digital detectors offer improved detection because of improved efficiency of absorption of the incident x-ray photons, a linear response over a wide range of incident radiation intensities, and low system noise (13,14). Thus, digital mammography has the potential to improve breast cancer detection and breast lesion characterization (15).

Also, once a screen-film mammogram is obtained, its contrast cannot be substantially altered. Contrast loss due to film underexposure, especially of dense glandular tissues, cannot be regained through film display. Radiologists cannot manipulate the image directly. Improvements in image display involve either acquiring more images with altered exposure factors, magnification, or focal compression (thus exposing the patient to more radiation) or looking at the images with a hot light or magnifying glass.

Digital acquisition systems directly quantify x-ray photons and decouple the process of x-ray photon detection from image display. Digital images can be processed with a computer and displayed in multiple formats (eg, on film or a monitor), and such contrast manipulation can affect lesion conspicuity. Image processing has been shown to improve visualization of details within medical images in at least one other application (16). Because the steps of image acquisition and display are separated, each can be optimized. In addition, image storage, transmission, and retrieval can be improved, and software to assist the radiologist in interpreting the images can be used.

This article will detail information that is currently available about the four clinical full-field digital mammography detectors that are currently undergoing testing for U.S. Food and Drug Administration (FDA) approval. These are the Fischer Imaging SenoScan (Fischer Imaging, Denver, Colo), Fuji Medical Systems Computed Radiography for Mammography (Fuji Medical Systems USA, Stamford, Conn), General Electric (GE) Senographe 2000 D (GE Medical Systems,

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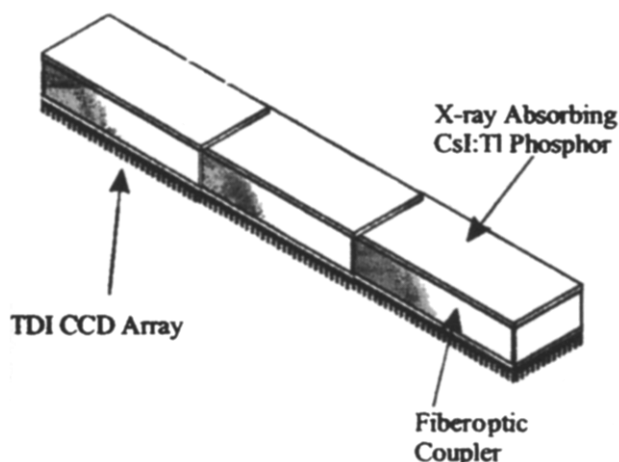


Figure 1. Fischer Imaging SenoScan digital mammography scanning-slot digital mammography system. TDI CCD = time-delay integration, charge-coupled device.

Milwaukee, Wis), and Trex Digital Mammography System (Trex Medical, Long Island, NY). These are the systems that will be available for purchase in the next few years. Other systems are under development, but there is insufficient information in the literature at this time to describe them in this article.

TECHNICAL INFORMATION

Overview

All four of the full-field digital mammography systems are based on the absorption of x rays by a phosphor material with subsequent conversion of the absorbed energy to electronic charge. The charge signal is then digitized and stored as a matrix in computer memory to represent the image.

Fischer Imaging

The system by Fischer Imaging uses a thallium-activated cesium iodide (CsI:Tl) phosphor and fiberoptic coupling to a charge-coupled device. Optical demagnification is not used. The x rays are collimated into a fan beam that matches the size and shape of the rectangular detector array. Image acquisition is carried out by scanning the detector in synchrony with the x-ray beam laterally across the breast. The detector (Fig 1) is sufficiently long to cover the breast in the antero-posterior direction but is only about 1.4 cm wide in the scanning direction. Acquisition takes place with a time-delay integration mode in which charge is accumulated in storage wells in the charge-coupled device and then shifted down charge-couple device columns from row to row at the same rate and in the opposite direction as the detector and x-ray beam move across the breast. The detector element is ap-

proximately 54 μm in standard resolution mode with 12-bit-per-pixel digitization. A high-resolution mode provides a limited field of coverage with a detector element of 27 μm .

Fuji

The current system is based on the original Fuji Computed Radiography product (Fuji Medical Systems USA, Stamford, Conn), introduced in 1981, with subsequent advances in imaging plate technology and image processing. The detector is a flexible plastic sheet coated with a photo-stimulable x-ray absorbing phosphor material, typically barium fluorobromide. The imaging plates, available in standard mammographic cassette sizes, are loaded in cassettes for exposure in standard screen-film Bucky trays. In response to absorption of x rays, electronic charges are stored in "traps" in the material of the phosphor where they remain stable for some time. After exposure, the image is read by precision scanning of the imaging plate by a laser beam (Fig 2). The red laser light discharges the traps, causing stimulated emission of blue light. The blue light is collected by an efficient light guide and detected by a photomultiplier tube. The resulting signal is logarithmically amplified, digitized, and processed for film or soft-copy display. The imaging plate is erased by exposure to white light in the image reader for reuse. The resultant image has a pixel size of 100 μm with a digitization precision of 10 bits after logarithmic compression.

GE Medical Systems

The GE system incorporates a large area matrix of photodiodes on an amorphous silicon substrate as shown schematically in Figure 3. The entire detector is coated with a layer of CsI:Tl. Each light-sensitive diode element is connected by a thin film transistor switch to a control line and a data line such that the charge produced on the diode in response to light emission from the phosphor is read out and can be digitized. The detector element size is approximately 100 μm , and digitization is performed to a precision of 14 bits per pixel. The imaging plate fits into an enclosure that is physically similar to the Bucky tray on the GE DMR conventional mammography unit (Fig 4).

Trex

The Trex system, which can be used on certain models of Lorad and Bennett mammography units, is based on modules that are similar to the digital detectors used in some stereotactic biopsy imaging systems. Each module consists of a CsI:Tl phosphor layer on the input surface of a fiberoptic taper, providing optical demagnification on the order of

X-ray Exposure

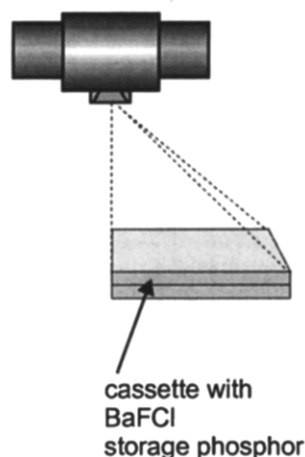
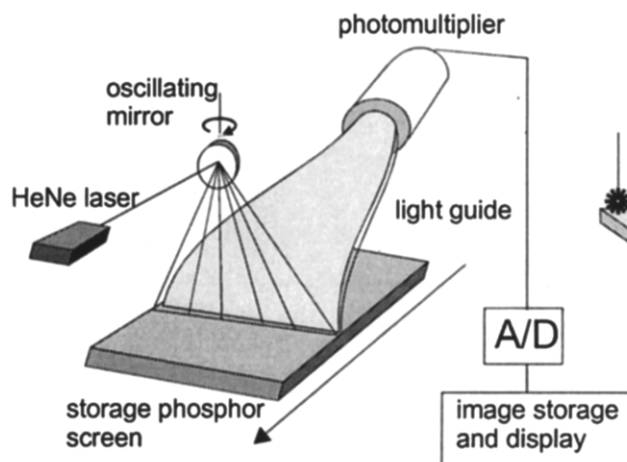


Image Scanner Readout



Erasure

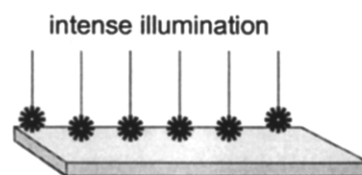


Figure 2. Fuji Medical Systems Computed Radiography system for mammography. A/D = analog to digital.

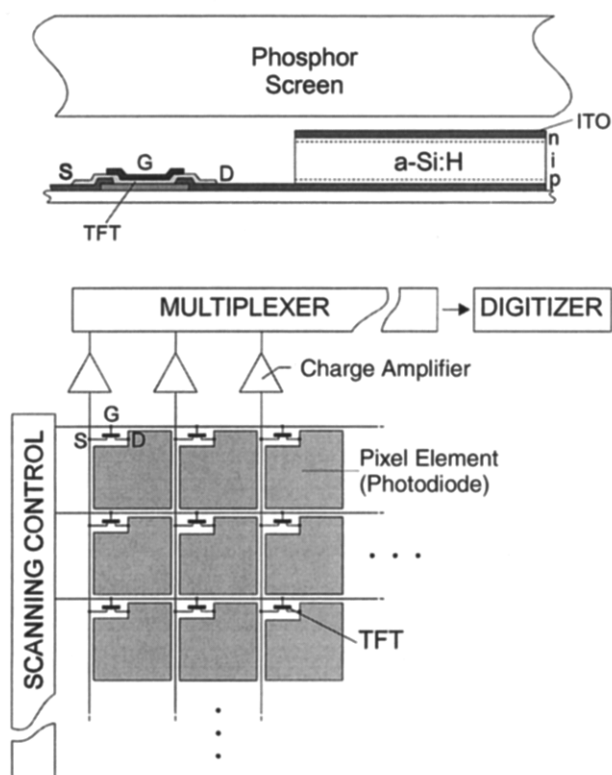


Figure 3. The GE Senographe 2000 D digital mammography system. D = drain, G = gate, ITO = indium tin oxide, S = source, TFT = thin film transistor.



Figure 4. The GE detector (bottom) compared with the Bucky tray on the GE conventional mammography unit (top).

50%. Each taper couples light from the phosphor to an area charge-coupled device array bonded to its exit surface. To image the entire breast, the Trex system uses a 3

× 4 mosaic of these detector modules (Fig 5). The pixel size at the detector is 41 μm pixels, with digitization of 14 bits per pixel.

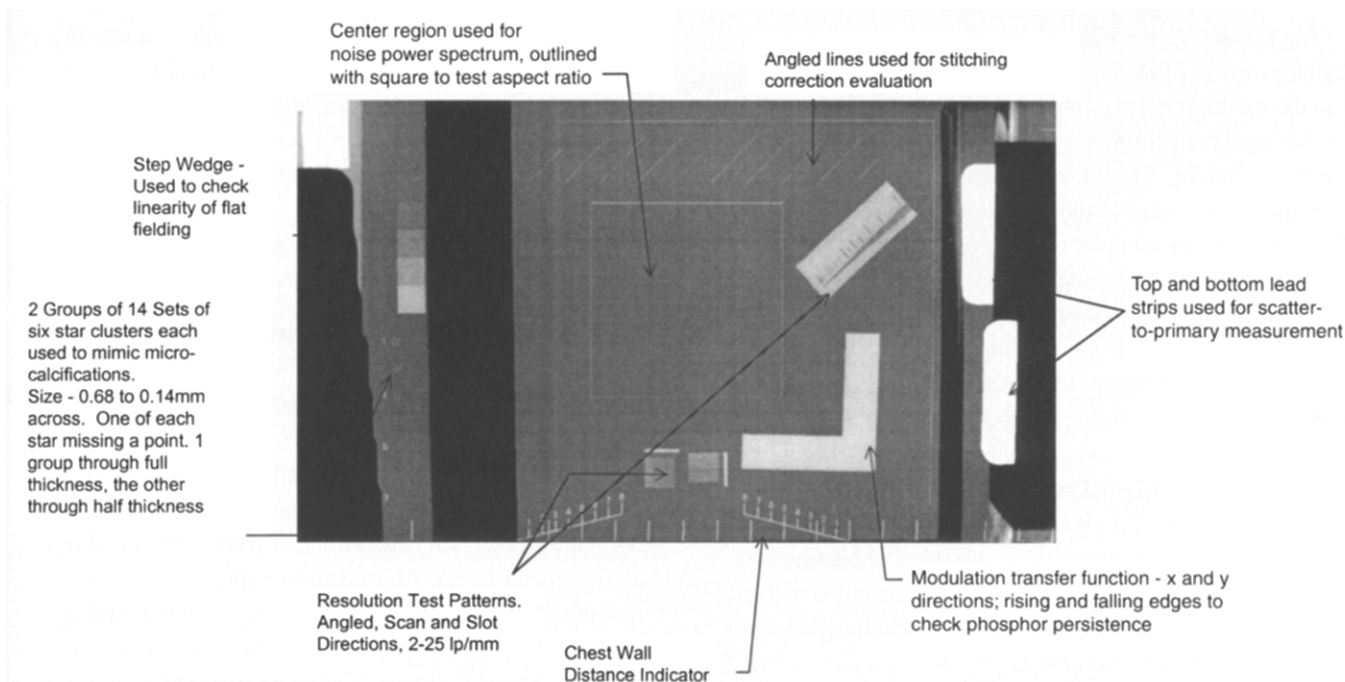


Figure 6. A digital image, acquired with the Fischer SenoScan unit, of the IDMDG digital mammography phantom.

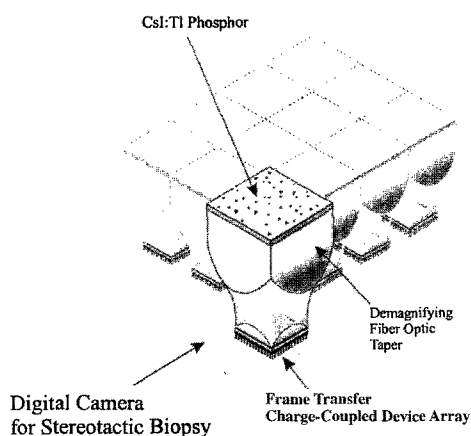


Figure 5. The Trex Digital Mammography System.

Technical Characterization

With funding from the Office of Women's Health of the U.S. Department of Health and Human Services (Washington, DC), the International Digital Mammography Development Group (IDMDG) (Chapel Hill, NC) has completed technical characterization of the Fischer, GE, and Trex machines. This has included measurement of modulation transfer function, noise, patient dose, and geometrical factors such as distortion and tissue coverage. Temporal variation of these quantities has been monitored. Although the modulation transfer function of digital mammography is less

than that of screen-film systems, the detective quantum efficiency of the digital systems is higher, providing improved signal-to-noise ratio and potentially allowing substantial improvement of contrast.

Yaffe and colleagues (17) led the scientific team that completed the technical characterization. In addition, the IDMDG has developed a digital mammography phantom and a quality control program for digital mammography, including some automated quality control techniques. A digital radiograph of the IDMDG phantom is shown in Figure 6. A uniform region provides data to be used for calculation of the noise power spectrum. The phantom includes tools for measuring the limiting spatial resolution, low contrast resolution, and dynamic range as well as tests for stitching and/or scanning artifacts and the amount of tissue missed from the image at the chest wall. A separate test device is provided for measurement of modulation transfer function. A digital mammography quality control manual was developed for the physics group for use in the program. This program includes frequent tests of modulation transfer function, limiting spatial resolution, scatter-to-primary ratio, image nonuniformity, noise power spectrum, and tests that are analogous to those required for screen-film systems under the 1992 U.S. Mammography Quality Standards Act. The IDMDG clinical pilot study described below used this quality control program during patient accrual (17).

The IDMDG's work is continuing under funding from the Department of Defense (DOD). Specifically, determination of optimum radiographic technique for each machine and for each patient breast type for digital mammography is currently ongoing. The choice of filtration material for each machine is also being studied carefully.

Because image contrast is freely adjustable by the viewer, the technique for image acquisition should be optimized to maximize the signal-to-noise ratio for a given radiation dose. Preliminary work indicates that the optimum spectrum may be substantially different than those used for screen-film mammography, and these results are expected to hold for any system that uses a CsI phosphor detector (18).

Niklason et al (19) and Hendrick et al (20) have carefully studied the advisability of using a radiographic grid for the GE system. Using contrast detail and other phantoms and measuring scatter fraction and signal-to-noise ratios with and without grids, they concluded that a conventional antiscatter grid would be beneficial for breast thicknesses greater than 5 cm. Use of a conventional grid for breasts with thickness less than 5 cm resulted in a loss of signal-to-noise ratios (for fixed dose) and did not improve low-contrast lesion detection. Niklason et al suggested that use of a grid with higher primary transmission would be beneficial for a wider range of breast thicknesses. Because these results depend more on the imaging geometry than on the detector technology, they should similarly apply to the Trex and Fuji systems and to any large-area detector system. Grids are not necessary for the Fischer system given the scatter rejection already available through the scanning-slot detector configuration itself.

Kimme-Smith et al (21), with DOD funding, have developed a phantom designed to be read automatically and tested a version of it on the Trex, GE, and Fischer systems. The phantom differs from the IDMDG phantom in that it is designed specifically to allow determination of the signal-to-noise ratio and calcification conspicuity at different locations in the image field. In their preliminary work, Kimme-Smith et al observed variation of performance at different locations in the image plane, suggesting that nonuniformity of detector performance should be monitored as part of a quality control program.

Technical Characterization Specific to the Fuji Detector

The Fuji system was evaluated for mammography in 1994 (22). While the modulation transfer function of the digital system was found to be lower than that of Fuji's screen-film product, the detective quantum efficiency was similar and was maintained over a wider range of exposure.

Contrast-detail performance was superior to the screen-film product. Cowen et al (23) have devised a quality control phantom for the Fuji system. In addition, the company has developed both a quality control program for digital mammography that is based on the Mammography Quality Standards Act and includes use of the American College of Radiology mammography phantom and recommended radiographic techniques that include the use of a radiographic grid.

Technical Characterization Specific to the GE Detector

Hendrick and Landberg (unpublished data) have developed a quality control program and manual for the GE system similar to the program developed by the IDMDG. This group has also used contrast-detail phantoms to compare the low-contrast detection capabilities of the GE digital system with optimized screen-film mammography for a range of breast thicknesses and tissue compositions. They found that low-contrast detection of the 100- μ m GE detector with a grid was superior to screen-film mammography with a grid at matching breast doses ($P < .01$) (20). However, this study did not compare digital to screen-film mammography for the detection of calcifications.

Technical Characterization Specific to the Trex Detector

Feig and colleagues (unpublished data), with National Cancer Institute funding, have evaluated the image quality and conspicuity of normal anatomic features for 324 Trex digital mammograms compared with screen-film mammograms of the same women. All digital mammograms were found to have better and more uniform exposure of the whole breast and improved image contrast. Sharpness of anatomic features and lesions was better in all digital mammograms of women with fatty breasts and was better in 40% of women with dense breasts. Conspicuity of calcifications was better in 25% of digital mammograms and equal in the other 75%.

IMAGE[®]DISPLAY FOR DIGITAL MAMMOGRAPHY

Image Communication

The first step in the display of digital images is the communication of the digital study from the scanner to the presentation device, whether film printer or soft-copy workstation. The mechanism for communicating the image and associated data has recently been standardized and is the Digital Imaging and Communication in Medicine (DICOM) DX (digital x ray) SOP (service-object pair) class, specifically the mammography submodule (24).

The DICOM DX standard also provides definitions for two states of mammography image data: "for processing" and "for presentation." "For processing" refers to the original, or raw, data as acquired on the detector, and "for presentation," the image after it has been processed for display. The device-independent display of digital mammograms is also defined in DICOM as the Grayscale Display Function Standard and the associated hard-copy (film print) and soft-copy (soft-copy presentation state) standards. While standards now exist for the proper display and communication of digital mammography studies, much work remains to be done by commercial vendors to support these standards completely. It is important that digital mammography devices and the accompanying display systems support the DICOM DX module, the display function standard, and the appropriate hard-copy and soft-copy presentation standards, so that digital mammograms can be readily transferred and read across various commercial platforms.

Image Presentation

There are currently two ways digital mammography studies are presented: hard copy (laser-printed film) and soft copy (cathode ray tube displays). Each of these display types has advantages and disadvantages for digital mammography.

Hard copy (film).—Laser printers for digital mammography are available from several vendors. These printers support spatial resolutions comparable to that of screen-film mammography (up to $4,800 \times 6,400$ -pixel matrix size) with the reproduced size capable of matching the acquisition resolutions of current scanners (down to $41 \mu\text{m}$ spot size). The gray-scale range is roughly similar to that of mammography film, with laser-printed films achieving maximum optical density of 3.5–4.0, while mammography films can achieve maximum optical density slightly over 4.0. Laser-printed films generally are not subject to the same level of processor variability or processor artifacts that are present with single-emulsion screen-film mammograms. Furthermore, laser-printed films allow radiologists to use the same reading protocols currently used in interpreting screen-film images. Films can be hung on a multipanel viewer with standardized layout, and a "hot light" and magnifying lens can readily be used. This takes advantage of the substantial training and familiarity that radiologists have in interpreting screen-film mammograms.

The disadvantages of using laser-printed film are cost and the availability of only one presentation format per sheet of film. The costs include the time, staff, and supplies required for printing and development. Furthermore, if more than one processed version is needed to obtain the maximum amount

of information from a mammogram, more than one version would have to be printed. This would be impractical, especially in a screening setting where speed and efficiency are essential to keep costs low.

Soft copy (cathode ray tube displays).—Currently, only cathode ray tube technology supports the requirements of soft-copy display for digital mammography. The best high-quality cathode ray tube technology—100–150 foot-lambert luminance, $2,048 \times 2,560$ -pixel matrix—is limited compared with film. The spatial resolution is less than one-quarter that of film resolution, and the luminance range is substantially lower. However, both of these factors can be mitigated. Full spatial resolution is possible through "roam and zoom" techniques, but this must take place seamlessly so that reading on a monitor is similar to reading mammograms on film with a magnifying glass. Furthermore, the luminance difference may not be that important. Two studies (25,26) have demonstrated that mammography feature detection performance does not degrade when soft-copy display luminance ranges are used instead of mammography light-box ranges. However, larger scale performance studies evaluating the effect of display characteristics on the detection and diagnosis of different mammographic features are required.

The advantage of soft copy is its flexibility. A large number of presentations of an image can be available at the push of a button. This allows application of image processing specific to lesion type or mammographic task (screening vs diagnosis). The digital image can be adjusted online to permit immediate evaluation of questionable areas.

While soft-copy presentation holds the greatest promise for realizing the full advantage of digital mammography, currently available commercial implementations are lacking. Current systems are not fast enough and do not provide support for evaluation of the current examination along with previous images for comparison or allow side-by-side comparison of extra views obtained in a diagnostic work-up. In addition, the user interfaces are awkward and not tuned to the specific tasks of screening and diagnostic readings. Longer interpretation times over those expected with printed film display are likely.

At least two noncommercial digital mammography workstations that apparently overcome these limitations have been displayed at the Radiological Society of North America meetings in Chicago, Ill (27,28). Clinical testing of systems at the University of North Carolina, Chapel Hill (E.D.P), and University of California, San Francisco (E.A.S.), is under way, funded by two separate DOD grants.

Image Processing for Display

Image processing is critical for the success of digital mammography, as it is for all digital imaging systems. In addition, mammography requires specific processing to achieve images suitable for different mammography reading purposes. Recent results of an IDMDG preference study suggest that different presentation formats are appropriate for different clinical tasks (screening vs diagnosis) and for the diagnosis of different lesion types (calcifications vs masses). In addition, the type of image processing preferred by radiologists differed by machine type (Fischer vs GE vs Trex) (29).

The algorithms studied were manual intensity windowing, histogram-based intensity windowing, mixture model intensity windowing, contrast-limited adaptive histogram equalization, MUSICA (Agfa division of Bayer Corp, Ridgefield, NJ), unsharp masking, peripheral equalization, and Trex processing. These choices were based partially on results of preliminary laboratory studies (30–34). Not all potentially useful algorithms could be included in this study.

Given results of these and other laboratory studies (23, 35–37), the diagnostic accuracy of digital mammography will depend not only on the acquisition device itself but also on the processing method used for image display. If poor choices are made, diagnostic accuracy might be worse than that of screen-film mammography. It is extremely important to determine what image processing methods will be appropriate both for screening and the diagnostic evaluation of calcifications and masses.

Computer-aided Diagnosis

Computer-aided diagnosis (CAD) is the detection of a potential abnormality or the diagnosis of an abnormality by means of computer analysis of the mammogram. Several groups (38–41) have demonstrated improved radiologist performance in lesion detection and characterization when a CAD system is used with digitized screen-film mammograms. CAD is currently being extended to full-field digital mammography.

Specifically, GE has established an exclusive agreement with R2 Technologies (Los Altos, Calif), a CAD company, to apply their algorithms to its soft-copy workstation. Likewise, Fischer and Trex are working with other companies to apply CAD to their products. A CAD product also has been developed and is being tested by Fuji. Preliminary results were reported at the Fourth International Workshop on Digital Mammography (42, pp 87–94, 201–204). The investigators reported evaluation of 1,212 digital mammograms that showed 240 cancers. The CAD system showed 90.5% sensitivity with 1.3 false-positive results per each image. This

study involved only Japanese women. Fuji plans further evaluation of this product in a North American population.

CAD seems best suited for application to soft-copy presentation methods because this display method allows dynamic interaction with the images so that computer interpretation can be displayed in conjunction with the images. In addition, it is conceivable that local image processing can be tailored and applied instantaneously to the lesion types detected with the computer algorithms. Different types of CAD, or different settings of CAD, may be used for different mammographic tasks. It is important for CAD techniques to be demonstrated on digital mammograms and to achieve sensitivity and specificity levels that make the techniques clinically useful. This will require testing algorithms on digital mammogram databases and improvements in the sensitivity and specificity of existing systems.

CLINICAL EVALUATION

Industry-sponsored Clinical Trials

On June 19, 1996, the FDA published *Information for Manufacturers Seeking Marketing Clearance of Digital Mammography Systems* (43), which outlined a requirement that manufacturers conduct a clinical trial designed to show agreement between screen-film mammography and digital mammography if devices were to become FDA-approved through the 510(k) or premarket approval mechanism. Manufacturers were instructed to discuss the proposed investigational plans with the FDA's Center for Devices and Radiological Health. The FDA guidance document specifically indicated that the probability of a positive digital mammogram should be greater than 0.90 if the screen-film mammogram were positive and the probability of a negative digital mammogram should be greater than 0.95 if the screen-film mammogram were negative. In addition, the FDA estimated that 520 women (260 with abnormal screen-film mammograms and 260 with normal screen-film mammograms) would be needed in a trial to achieve such an estimate of agreement. There was no requirement that manufacturers determine truth about the presence or absence of cancer in the patient, only that the screen-film mammogram interpretations and the digital mammogram interpretations agree.

All four manufacturers designed agreement studies, which were discussed extensively with officials at the Center for Devices and Radiological Health. Recruitment to clinical trials was begun shortly thereafter. The trials that were carried out were similar, as would be expected from the FDA-provided blueprint.

Table 1
Institutions Involved in Office of Women's Health Clinical Trial

Institution	Location	Machine Type	Principal Investigator
University of Pennsylvania	Philadelphia, Pa	GE	Emily Conant
Massachusetts General Hospital	Boston, Mass	GE	Dan Kopans
University of Toronto	Toronto, Ont	Fischer	Rene Shumak
Mount Sinai Hospital	Toronto, Ont	Fischer	Roberta Jong
Thomas Jefferson University	Philadelphia, Pa	Trex	Stephen Feig
University of North Carolina	Chapel Hill, NC	Fischer	Etta Pisano
Good Samaritan Hospital	West Islip, NY	Trex	Melinda Staiger
University of Virginia	Charlottesville, Va	Trex	Laurie Fajardo

Specifically, the Fischer trial enrolled 570 women at four institutions (University of North Carolina, Chapel Hill; Thomas Jefferson University Hospital, Philadelphia, Pa; Sally Jobe Clinic, Denver, Colorado; and Brook Army Medical Center, San Antonio, Tex). The cohorts were women with Breast Imaging Reporting and Data System interpretation codes 3, 4, or 5 on the diagnostic mammograms and women with symptoms.

The GE trial enrolled 652 women at four centers (University of Colorado, Denver; University of Massachusetts, Worcester; Massachusetts General Hospital, Harvard University, Boston; and the University of Pennsylvania, Philadelphia). The cohort consisted of women presenting for diagnostic mammography.

The Trex trial enrolled 520 women at three centers (University of Virginia, Charlottesville; University of California, Los Angeles; and Good Samaritan Hospital, West Islip, NY). The cohorts were women with normal screening mammograms and women with abnormal screening mammograms.

In all studies, radiologist readers interpreted the screen-film and digital mammograms of the enrolled patients and measured agreement of these readings. Trex submitted the data obtained with their protocol to the FDA in early December 1997.

Information on a Fuji agreement study protocol is not available, but there are apparently three institutions designated to acquire cases, with the cases to be read at an additional site.

Unfortunately, the FDA's guidelines were flawed in that the level of agreement required between digital mammography and screen-film mammography was not attainable even when screen-film mammograms were compared with each other because of intrareader and interreader variability (44–46). This issue was discussed at a meeting of an advisory panel convened by the FDA on August 17, 1998. On February 8, 1999, the FDA revised their guidance document and

notified the manufacturers that the clinical section was no longer valid. Letters, which have not been made public, were sent to all of the manufacturers indicating that the digital mammography FDA-approval trials must now be based on truth regarding breast cancer status and not direct agreement with screen-film mammography. That is to say, sensitivity and specificity, as measured with a method such as receiver operating characteristic curve analysis, must now be reported.

All manufacturers are now in the process of negotiating protocol revisions with the FDA to meet these new requirements. It is likely that these new efforts will center on reader studies that use a set of mammograms of multiple cases with biopsy-proved lesions. This might involve enrolling additional women or collecting additional cases from the existing databases at participating centers.

Given the vagaries of the FDA approval process and the understandable reticence of the manufacturers in sharing their plans with their competitors, it is impossible to predict when the FDA will approve the new protocols, when data from those protocols will be submitted to the FDA, or when the FDA will issue 510(k) approval of the devices.

Federally Funded Clinical Trials on Digital Mammography

Two federally funded clinical trials have opened to date. One of the trials compares digital mammography with screen-film mammography for the diagnostic mammography population. The other trial compares the GE digital mammography system with screen-film mammography for the screening mammography population.

The diagnostic mammography trial, funded by the Office of Women's Health, was run under the auspices of the IDMDG and enrolled 210 women at eight centers. Table 1 lists the centers involved in this study, the principal investigator at each site, and the type of digital mammography unit used at that site.

Table 2
Institutions Involved in DOD Clinical Trial

Institution	Location	Machine Type	Principal Investigator
Johns Hopkins University	Baltimore, Md	Trex	Laurie Fajardo
University of Pennsylvania	Philadelphia, Pa	GE	Emily Conant
University of Toronto	Toronto, Ont	Fischer	Rene Shumak
University of North Carolina	Chapel Hill, NC	Fischer	Etta Pisano
Good Samaritan Hospital	West Islip, NY	Trex	Melinda Staiger
University of California, Los Angeles	Los Angeles, Calif	Trex and GE	Lawrence Bassett

Two patient cohorts were enrolled, group A and group B. Group A consisted of all consecutive women with mammographically dense breasts who presented to the participating mammography clinics for problem-solving mammography and who were scheduled to undergo either open or percutaneous large-core needle breast biopsy within the 12 weeks after the eligibility mammogram was obtained. Women with palpable lesions, nonpalpable lesions, or both were included in this group. Group B consisted of a random sample of women with mammographically dense breasts who presented to the participating mammography clinics for problem-solving mammography, who were not scheduled to undergo biopsy, and who were recommended for 1-year follow-up.

Accrual to this trial has recently been completed. The cases are currently being prepared for a radiologist reader study. Eighteen radiologist readers will interpret images, either in screen-film format, manufacturer's printed digital format (default format), or digital processed format with either Musica or histogram-based intensity windowing image processing. Readers will score all cases with a six-point scale, and analysis will be done with a receiver operating characteristic curve.

This study will serve as a pilot study for another larger clinical trial funded by the DOD. An additional 1,075 women in essentially the same patient cohorts will be enrolled at six centers. Table 2 shows the institutions and investigators involved and the type of digital mammography equipment that will be used at each site. A larger reader study of all 1,275 cases will take place at the end of accrual.

Both of these studies rely on the presence of physical examination findings or an abnormal screen-film mammogram to select eligible patients. This may cause an underestimate of the effectiveness of digital mammography because enrollment of a patient with cancer to the trial depends on detection of the cancer with another modality.

The only other federally funded clinical trial currently open is a screening study that uses only GE digital mam-

mography equipment and is funded by the DOD. This study will ultimately enroll 15,000 women older than 40 years presenting for screening mammography at two centers, University of Colorado Health Science Center, Denver (UCHSC), and the University of Massachusetts, Worcester. To date, approximately 4,000 women have been enrolled (John Lewin, UCHSC, written communication, February 26, 1999). This study is unique in that the work-up of lesions proceeds based on the findings of either digital or screen-film mammography so that cancers can be detected with either modality.

Interim data analysis revealed approximately equal sensitivity of screen-film and digital mammography.⁶ However, digital mammography had a significantly ($P < .001$) lower recall rate and a higher true-positive biopsy rate than screen-film mammography in this population (McNemar χ^2 test) (47). All digital cases were read with soft-copy display, and this might account for the reduced false-positive rate for digital versus screen-film mammography because immediate manipulation of the image allowed for some online assessment of areas of concern that would ordinarily have required another patient visit and additional mammographic views. However, results reported to date are preliminary and based on only a limited number of cancers. More precise estimates of sensitivity, specificity, and positive and negative predictive values of GE digital mammography compared with screen-film mammography for the screening population will be obtained at completion of the entire study.

Telemammography

Digital mammographic images can be readily transmitted electronically for remote interpretation and consultation. Dudding et al (48) did the earliest work in this area and demonstrated the feasibility of transmitting digital mammograms by means of satellite between two facilities. Image transmission time was 1 minute per image, and data loss was minimal even with adverse weather conditions.

More recently, Yaffe has experimented in transmitting Fischer digital mammography data between two sites in Toronto by means of a T1 satellite protocol (M.J.Y., unpublished data, 1999). He ultimately plans to transmit digital mammography and breast ultrasound clinical data from a remote van in rural Ontario to Toronto for expert interpretation. The Canadian Network for the Advancement of Research, Industry, and Education funded this study.

Huang and Sickles are conducting two ongoing studies that will ultimately enroll 500 women each. The studies are using two Fischer SenoScan units at two separate University of California, San Francisco, clinical sites (E.A.S., unpublished data, 1999). The "telemanagement" study of the two studies seeks to measure the difference in diagnostic accuracy of an expert breast imaging radiologist interpreting digital mammograms of patients presenting for diagnostic mammography at a remote location compared with that of a general radiologist interpreting screen-film mammograms of the same patients on site. Both radiologists manage the patient's work-up in real time based on the available images. Interestingly, use of the Huang-Sickles nonproprietary mammography workstation has allowed the digital images to become available for remote interpretation consistently faster than the screen-film images have become available for local interpretation.

The "teleconsultation" study is constructed to prove the usefulness and feasibility of remote consultation by general radiologists with expert breast imagers. This involves a real-time viewing and interaction with the same set of images at two sites as the radiologists speak by telephone.

Tomosynthesis and Three-dimensional Breast Imaging

Digital mammography also allows multiple images to be combined into three-dimensional images. For tomosynthesis, special hardware that provides precise motorized x-ray tube motion and allows the image to be focused within a lesion permits blurring of the planes above and below the lesion so that more detailed information about lesion surface characteristics and associated features can be gleaned from the image. Niklason et al (49) have published preliminary specimen tomosynthesis images acquired with a specially adapted GE digital mammography device. The GE system makes seven to 10 low-dose images of the breast as the x-ray tube moves above the woman. The total radiation from the sum of these exposures is similar to that of a single conventional mammogram. Tomograms from any level in the breast may be reconstructed from the low-dose images.

The DOD has recently funded a clinical trial to evaluate the GE tomosynthesis product for patients recommended to undergo biopsy. The cross-sectional and lesion edge detail that potentially can be achieved with such a system might substantially improve diagnostic accuracy. The device itself is being constructed under the supervision of Beale Opsahl-Ong of GE-CRD, and accrual to this trial will commence later in 2000 with approximately 400 women to be enrolled at Massachusetts General Hospital.

Another potentially useful application is stereoradiography of the breast, also called stereomammography. In this technique, two images of the breast are taken at slightly different angles, typically 2°–5° apart. The two images can be rendered on a soft-copy display system so that the observer can fuse the images, thus giving the perception of the relative depths of structures within the image. This may reduce obscuration by overlying structures and eliminate false-positive findings. Stereomammography also may be useful for interventional procedures. Maidment et al have been funded by the DOD to determine appropriate technical factors (angle and dose) for this technology and to compare this technology to tomosynthesis. A clinical trial was planned for late 1999.

Further evaluation of the usefulness of evaluating three-dimensional data obtained from limited projections of the breast is ongoing at Thomas Jefferson University Hospital under two other DOD grants to Maidment et al. These studies are examining the efficacy of limited-view binary three-dimensional reconstructions of breast calcifications. In this technique, three to seven views of the breast are obtained and calcifications are segmented from the background. These calcifications are then paired between views, and a three-dimensional model is obtained. In a preliminary retrospective interpretation study involving 44 patients, the number of lesions that required biopsies was reduced by over 50% (50,51).

Dual-Energy Mammography

Dual-energy mammography is another technology that becomes practical once the image data are digital. With this technique, two exposures of the breast are made, one at typical mammographic exposure energy between 20 and 30 kVp and one in a higher range, such as 40–80 kVp. Alternatively, two stacked detectors can be used with a single exposure, with the first detector preferentially absorbing low-energy x rays while the second detector preferentially absorbs high-energy x rays. Since there is information in both images about the atomic

number and density characteristics of the tissue through which the x-ray beam traversed, a weighted subtraction of one image from the other can be done and additional information about breast tissue composition can be obtained. Specifically, it may be possible to show just the regions of the breast that contained calcium, perhaps rendering calcifications more obvious, especially in dense breast tissue. Johns and colleagues (52,53) performed initial work on this subject. Boone and colleagues (54,55), with DOD funding, are evaluating computer simulations of dual energy and building a dual energy mammography system based on thin-film transistor array technology similar to that in the GE system.

Digital Subtraction Mammography

At least some of the sensitivity of both breast magnetic resonance (MR) imaging and sestamibi scintigraphy in dense breast tissue is due to differential blood flow to breast cancers compared with background normal breast tissue. Presumably, digital mammography should be able to depict subtle differences in contrast uptake by tumors compared with background tissue by allowing a subtraction of a precontrast from a postcontrast image after the injection of intravenous contrast material. In addition, digital mammography offers much higher spatial resolution than the other technologies. It potentially will allow visualization of small arteries that would not be visible with MR imaging or sestamibi scintigraphy. Since even very small cancers develop an arterial supply through angiogenesis, it may be possible to detect cancers at a smaller size than those currently detected with screen-film mammography. Digital subtraction mammography may also be able to demonstrate more accurately the extent of breast cancer, especially in women with dense breasts or in women with invasive lobular carcinoma.

Niklason and colleagues (56) have done preliminary work on technique optimization and low-contrast detection limits of enhancing lesions and vessels in digital subtraction mammography and published images revealing the ability of the GE full-field digital system to depict small capillary beds in an *in vivo* rabbit model with digital subtraction angiography. A small Breast Cancer SPORE (Specialized Program of Research Excellence) developmental grant to Pisano will be funding additional technical investigation and a clinical study of digital subtraction mammography at the University of North Carolina. This will include investigation on the timing and number of images and dose of injection of intravenous contrast agents for use in breast imaging.

FUTURE RESEARCH IN DIGITAL MAMMOGRAPHY

Basic Technical Issues

The existing four detector technologies have all been applied clinically and have shown improved contrast-detail performance compared with conventional screen-film mammography (17,21). Therefore, the detector is probably no longer the limiting factor in the development of clinically acceptable digital mammography. Nevertheless, there are opportunities for improvement in detector performance. These are likely to come about both by improvements in existing flat-panel detectors and by use of direct-conversion materials in which the absorption of x rays directly yields charge that can be measured and digitized. A number of new detector materials for this purpose are under investigation, including amorphous selenium, cadmium zinc telluride, and lead iodide. By eliminating an intermediate stage of x ray to light conversion, the noise characteristics of these new detector materials potentially can be improved beyond what is possible with phosphors. In addition, because these detectors produce a signal in electronic form, which can be easily collected by an electric field, lateral spread of the signal can be minimized, thereby opening the possibility of extremely high spatial resolution and greater efficiency in the use of incident x rays.

Studies also are needed to evaluate the real clinical requirements of any detection system for mammography because the requirements in both spatial and contrast resolution are not yet known. Do the different tasks in mammography—screening, diagnosis, and interventional procedures—require different detector element sizes, different bit depths, or both? Results of some preliminary work with the Fuji system suggest that microcalcification detection and characterization performance will not differ between digital and screen-film mammography (57).

Furthermore, x-ray beam characteristics might be further optimized for use with the digital detectors. Some preliminary work has shown that detective quantum efficiency performance of both screen-film and digital mammography could be improved if the x-ray spectrum were more monoenergetic (58,59). In addition, phase contrast x-ray imaging, which takes into account the variations in the speed of electromagnetic radiation of different tissues, and diffraction-enhanced mammography, which allows visualization of the diffraction component of the x-ray beam, deserve further exploration (60,61).

Display Issues

Currently available commercial soft-copy display systems are inadequate for real clinical demands, mainly because of

the awkwardness of the user-computer interface. Further work must be done to optimize the computer-human interaction, especially regarding the mental model used to arrange the images for interpretation, and to improve navigation among the images by the reader. In addition, computer systems should be optimized so that all interactions occur instantaneously in real time, including the loading of the image on the soft-copy display study and the reviewing of large images on multiple display screens.

In addition, investigation of improved display technology is needed. Liquid-crystal displays and plasma screens may offer improved performance if they can be adapted for digital mammography.

Further work should be done on the development and evaluation of image processing algorithms for use with digital mammograms. The algorithms to be used for each clinical task should be tested through reader interpretation studies and pathologically proved cases.

CAD algorithms should be adapted for use with full-field digital mammography. Ideally, such algorithms should be integrated with soft-copy display systems so that appropriate image processing for the computer-detected lesions can be applied instantaneously and locally in the region of interest.

Telemammography

Devising the optimum system configuration for centralized storage and retrieval of digital mammograms should be a priority. Such a system would allow rapid comparison with old images, potentially from any prior examination facility, with the patient's permission. Issues of the logistics of handling such large data files, image compression, and patient privacy must be resolved.

The development and testing of appropriate soft-copy devices for remote interpretation, management, and consultation should be a priority.

Three-dimensional Breast Imaging, Dual-Energy Mammography, and Digital Subtraction Mammography

The ongoing study of three-dimensional breast imaging at Massachusetts General Hospital and Thomas Jefferson University Hospital will serve as pilot studies for the assessment of these technologies. Clearly, if this work is successful, larger studies involving more clinical centers will be needed to assess the usefulness of these methods in the diagnostic setting.

In addition, exploration of the use of tomosynthesis and other methods in a screening setting is of interest. These techniques, paired with CAD for screening, might be useful

in reducing the need for return visits after an abnormal screening mammogram. For example, any woman with a CAD-detected mass or cluster of calcifications at screening could immediately undergo tomosynthesis or three-dimensional imaging, allowing immediate further diagnostic work-up.

Both dual energy mammography and digital subtraction mammography are areas ripe for further investigation and development. Digital subtraction mammography issues requiring investigation are the use of evaluation of uptake and washout curves for intravenous contrast material, technical optimization of beam quality, and radiation dose required. Clinical studies will be required to determine what patient groups will benefit most from these techniques.

Clinical Issues

The Office of Women's Health study that will be completed shortly, along with the DOD study just started, will evaluate the effect of digital versus screen-film mammography in the diagnostic mammography patient population. By enrolling a large number of patients who underwent biopsy and who have dense breasts, the power of the Office of Women's Health study has been maximized to allow detection of a relatively small difference between digital and screen-film mammography in this setting. Once the Office of Women's Health study is completed, more precise power calculations based on actual radiologist performance in interpreting digital mammograms will be available. Initially, the biostatistician working with the IDMDG estimated that enrollment of 2,500 women would be needed to reliably show a 0.10 difference in the area under the curve in a receiver operating characteristic curve analysis comparing digital to screen-film mammography. These estimates will be revised after the Office of Women's Health reader study is completed. It is possible that the current enrollment of 1,275 women will be adequate to detect differences that may exist between digital and screen-film mammography in this setting. However, enrollment of more than 2,500 women may be needed for differences to be detectable.

A second study, a full-fledged screening trial, is under way only for one manufacturer, GE. Obviously, digital mammography will have to prove its value in the screening setting, as well as the diagnostic setting, if it is to replace screen-film mammography. The cost of such trials, given the many thousands of patients required, is huge.

It could be argued that a future screening trial should include all available equipment from all manufacturers to allow a generic statement to be made about the diagnostic accuracy of digital versus screen-film mammography. However,

mixing images acquired with the various digital mammography units into one study could confound the results, especially if one or more of the systems performs substantially differently than the others. At minimum, to detect machine-type differences in the outcome of a large screening study that included more than one machine type, a large number of cases acquired with each piece of equipment would have to be included. The numbers of cases per machine type would have to be determined by careful power calculations based on preliminary work and the available literature.

Alternatively, a single large trial could be performed with rigorous quality control standards that all devices would have to meet. In this way, much like the Mammography Quality Standards Act set standards for all types of screen-film mammography systems, similar standards could be set and followed so that the machine differences would be reduced. However, the differences between machines might not be large enough to justify a very large trial, one large enough to detect small differences between machines. Running individual screening trials for each device is yet another strategy, but this would be the most expensive option.

Two other potential confounders for all clinical digital mammography trials are the display method (soft copy vs film) and image processing algorithms applied to all images. Selecting the appropriate image processing for display of digital mammograms is important and may greatly affect the outcome of all clinical trials involving digital mammography. Selection should be done scientifically and not for aesthetic reasons, or because the resulting images resemble the screen-film mammograms with which radiologists are familiar and comfortable. Aiming for familiarity and comfort may squander some of the potential improvement in diagnostic accuracy available with digital mammography. A possible answer to the effect of these issues on clinical trials is to allow the manufacturers to determine their preferred method of display and processing. Whatever is selected should be standardized across all readers within any trial.

Finally, in prior breast cancer screening trials, mortality from breast cancer has served as the most important outcome measure. This is probably not possible or realistic for digital mammography. The window of opportunity for performing such a study is narrow. Once digital mammography is approved by the FDA, it may become rapidly and widely available. Screening trials in which patients were randomly assigned to either digital mammography or screen-film mammography would be confounded by crossover of patients between the two systems and non-compliance of the patient with the randomization assign-

ment. Surrogate end points, such as those selected in the UCHSC/University of Massachusetts Medical Center screening study (sensitivity and specificity, positive and negative predictive values, and receiver operating characteristic curve differences) seem practical and realistic for future digital mammography screening trials.

The issue of cost-effectiveness of this new technology compared with standard screen-film technology is an important one (62). Because of the software and hardware involved, digital mammography will cost more to provide than screen-film mammography, even with the predicted reduction in costs due to filmless operations. At a minimum, it must outperform current technology if it is to be widely adopted. Digital mammography will not be an attractive alternative to screen-film mammography if it is only equivalent in diagnostic accuracy. We believe that the extra tools that digital mammography more readily allows (eg, tomosynthesis, digital subtraction mammography, and CAD) must be developed and exploited for digital mammography to have added value to patients and physicians.

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