AD_____

Award Number: DAMD17-02-1-0295

TITLE: An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall

PRINCIPAL INVESTIGATOR: David J. Getty, Ph.D.

CONTRACTING ORGANIZATION: BBN Technologies Solutions LLC
Cambridge, Massachusetts 02138

REPORT DATE: August 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 2003	Annual (1 Aug 2002 - 31 Jul 2003)

4. TITLE AND SUBTITLE
An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall

5. FUNDING NUMBERS
DAMD17-02-1-0295

6. AUTHOR(S)
David J. Getty, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
BBN Technologies Solutions LLC
Cambridge, Massachusetts 02138

E-Mail: getty@bbn.com

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Original contains color plates: All DTIC reproductions will be in black and white.

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)
The goal of this project is to evaluate stereoscopic digital mammography, compared to standard, non-stereo digital mammography, for the earlier detection of breast cancer and reduced rate of patient recall for further workup. During the project, approximately 2000 women at elevated risk for development of breast cancer will receive stereo mammograms at the Emory Breast Clinic.

In the first year of the project, we built a high-resolution (2304 x 1800 pixels) stereo display workstation that will be used during the project, and we wrote a software application that will be used by the participating mammographers to control various aspects of the displayed stereo mammograms as they interpret mammographic cases. We also wrote software to calibrate the grayscale on the high-resolution grayscale monitor to comply with the DICOM standard. The stereo workstation was shipped to Emory University near the end of the first project year.

Working with project staff at Emory University, we developed the set of data forms that will be used to collect study data on patients enrolled into the project.

14. SUBJECT TERMS
Stereoscopic digital mammography, breast cancer detection, reduced rate of recall, focal abnormality detection

15. NUMBER OF PAGES
55

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

INTRODUCTION

The objective of this project is to evaluate stereoscopic digital mammography, compared to standard, non-stereo digital mammography, for early detection of breast cancer and for reduced rate of patient recall. We hypothesize that by viewing the internal structure of the breast in depth, a mammographer will be able to detect subtle lesions in the breast earlier and with greater accuracy. When seen directly as a volumetric structure, a benign lesion may be more confidently dismissed without further workup. We also believe that the stereo mammogram will reduce false positive detections of apparent lesions, chance superimpositions of normal tissue that in the standard non-stereo mammogram resemble a volumetric focal abnormality. In the stereo mammogram, the otherwise superimposed tissue is seen as separated in depth. As a result, we believe that fewer patients will need to be recalled for further workup of what turn out to be false positives. Over the remaining four years of the project, approximately 2000 women who are at elevated risk for development of breast cancer, because of personal or family history, will be enrolled in the project and given stereoscopic digital mammography screening examinations. The mammographic images will be interpreted both in a stereo reading and a standard non-stereo reading, by different mammographers. The reading data will be analyzed to determine the comparative rates of true lesion detection and cancer diagnosis, and of the rates of recall for further workup.

BODY OF REPORT

1. Overview of Year 1 Progress

Over the past first year of the project, that began on August 1, 2002, we have completed almost all of the work in Tasks 1 and 3 that was planned for Year 1 of the project. This work is described in the sections of the report that follow. Several small parts of Tasks 1 and 3, that require the assistance of the Emory project staff, remain uncompleted because we have not received authorization from the Army to set up the subcontract with Emory.

The subcontract has been held up, pending final human subjects approval of the Research Protocol, Subject Consent form, and other subject data collection forms by the Emory IRB and the Army HSRRB (Human Subjects Research Review Board). At this point, we have gone through a number of cycles of alternately submitting materials to the Emory IRB and the Army HSRRB. In the typical cycle, we have submitted materials to the Emory IRB, gotten back a list of requested modifications, made the changes and resubmitted the materials, and then received approval. We would then send the materials to the Army HSRRB who would develop another list of requested modifications. We would make these changes and resubmit the materials, in time getting their approval. Since the materials were now different from those approved by the Emory IRB, we were required to resubmit the materials to Emory for review.

The problem of getting approval by both groups has been exacerbated by the fact that the original human subjects reviewer assigned by the Army to our project was changed part way through the process. The newly assigned reviewer had a substantial number of requested modifications that were new and different from those requested by the original reviewer. This required another cycle of modification and review. In addition, the HIPAA regulations came into effect during the year. This provoked a series of changes to the Subject Consent form, and another cycle of approvals.

As a result, we have only very recently obtained approval of all the materials by the Army HSRRB, with approval by the Emory IRB expected shortly. As soon as the subcontract is in place with Emory, we will endeavor to finish those remaining uncompleted parts of Tasks1 and 3, with Emory's help, within two months. The uncompleted parts of Tasks 1 and 3 will be discussed at appropriate points later in the report.

We had planned to start enrolling patients and acquiring stereo mammograms at the beginning of Year 2 of the project (August 1, 2003). We anticipate now that the delay in establishing a subcontract with Emory will push the start of enrollment until late October. This will almost certainly reduce the number of patients enrolled in the study during Year 2 of the project, although we will do our best to increase the rate of enrollment to make up for the lost time.

2. Development of the Stereoscopic Display Workstation and Controlling Software Programs (Task 1)

During the first year of the project we built two copies of the stereo display workstation, one of which is shown in Figure 1. One workstation will remain at BBN during the project and the other will be located at the Emory Breast Clinic at Emory University, to be used by the mammographers participating in the project. During this first year, we developed three programs for the workstation: (1) a program for use by us, as developers, to control the stereo display, (2) a second program for use by radiologists to control the display, and (3) a third program to enable us to calibrate the displayed grayscale luminance of the image display monitor to match the standard DICOM grayscale curve.

Figure 1. Stereoscopic display workstation.

2.1 Acquisition and display of a stereo mammogram.

A stereo mammogram consists of two x-ray images of the breast taken sequentially from slightly different points of view. As illustrated below in Figure 2, the x-ray source is rotated by about 6 degrees between exposures while the position of the breast remains fixed in the compression device. A digital x-ray detector captures each x-ray image directly and stores it as a data file on a computer. In our prior research, stereo mammograms were acquired on a pre-clinical version of the GE full-field-of-view digital mammography unit (GE Senographe 2000D), located at that time at the University of Massachusetts Medical Center.

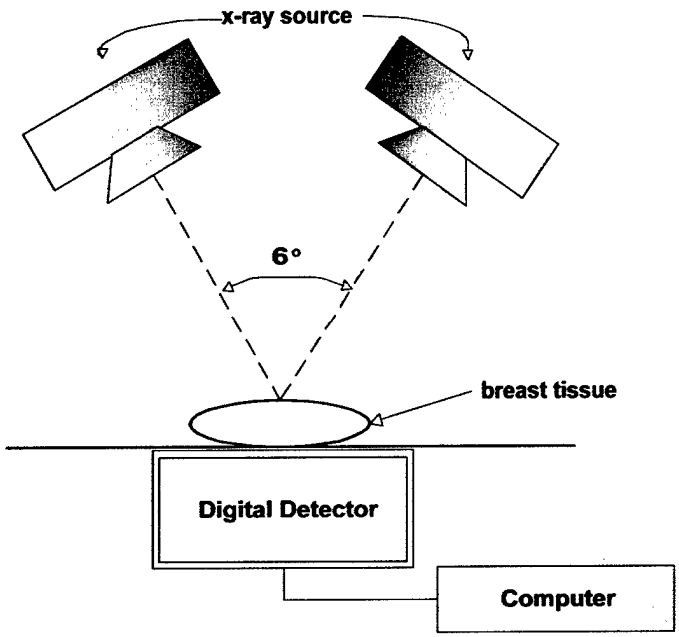


Figure 2. Acquisition of a stereoscopic digital mammogram.

An example of a stereo pair of digital mammograms of a benign mass is shown in Figure 3. Although the two views look very similar, there are subtle differences in the two images resulting from their having been captured from slightly different points-of-view. When one image is presented in isolation to each eye, the visual system is able to fuse the two images into a single image seen in depth (also possible to experience here crudely by crossing your eyes and concentrating on the middle image).

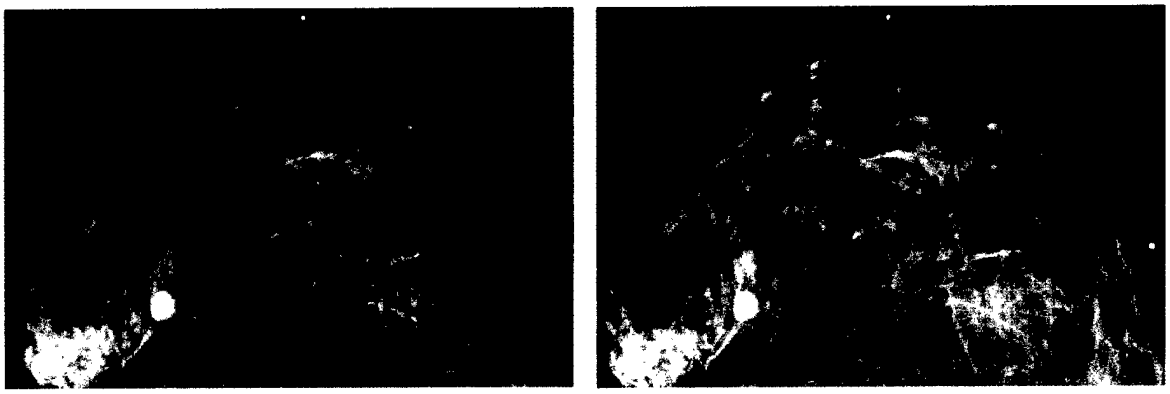


Figure 3. Stereoscopic pair of digital mammograms of a benign mass.

To see a stereo mammogram on the stereo display workstation, as illustrated in Figure 1, the user wears special stereo-viewing glasses (StereoGraphics' CrystalEyes) and views the two images on a high-resolution MegaScan monochrome monitor that presents them alternately in rapid succession—at a 120 Hz. refresh rate. The stereo-viewing glasses are synchronized to the display by an infrared beam and alternately block each eye's view of the display—effectively routing each image to only one eye. The viewer's visual system fuses the two images into a single in-depth image that shows the internal structure of the breast in depth. The software that we have developed permits the user to control many aspects of the displayed stereo image, including brightness and contrast (grayscale windowing), black/white reversal, and depth inversion.

2.2 Components of the stereo display workstation

The stereo display workstation consists of the following hardware components:

- PC computer with 512 Mb of memory, a large hard disk and a standard system color monitor and keyboard,
- Dome/Planar PCI MD8 image display controller, with stereo modifications,
- MegaScan high resolution grayscale medical monitor adapted for stereo display,
- StereoGraphics E-PRO infrared emitter,
- StereoGraphics CrystalEyes-3 stereo LCD glasses,
- Logitech Mouseman Wheel optical, 4-button mouse,
- PI X-Keys programmable keypad, 20 keys, PS/2 interface.

2.3 Display control program for use by the developers.

The first piece of software we wrote was a display control program for our own use as we developed the display system. The functionality included means of reading stereo image pairs into the display and means to control a number of aspects of the appearance of the displayed stereo image. The Main screen of the program is shown in Figure 4.

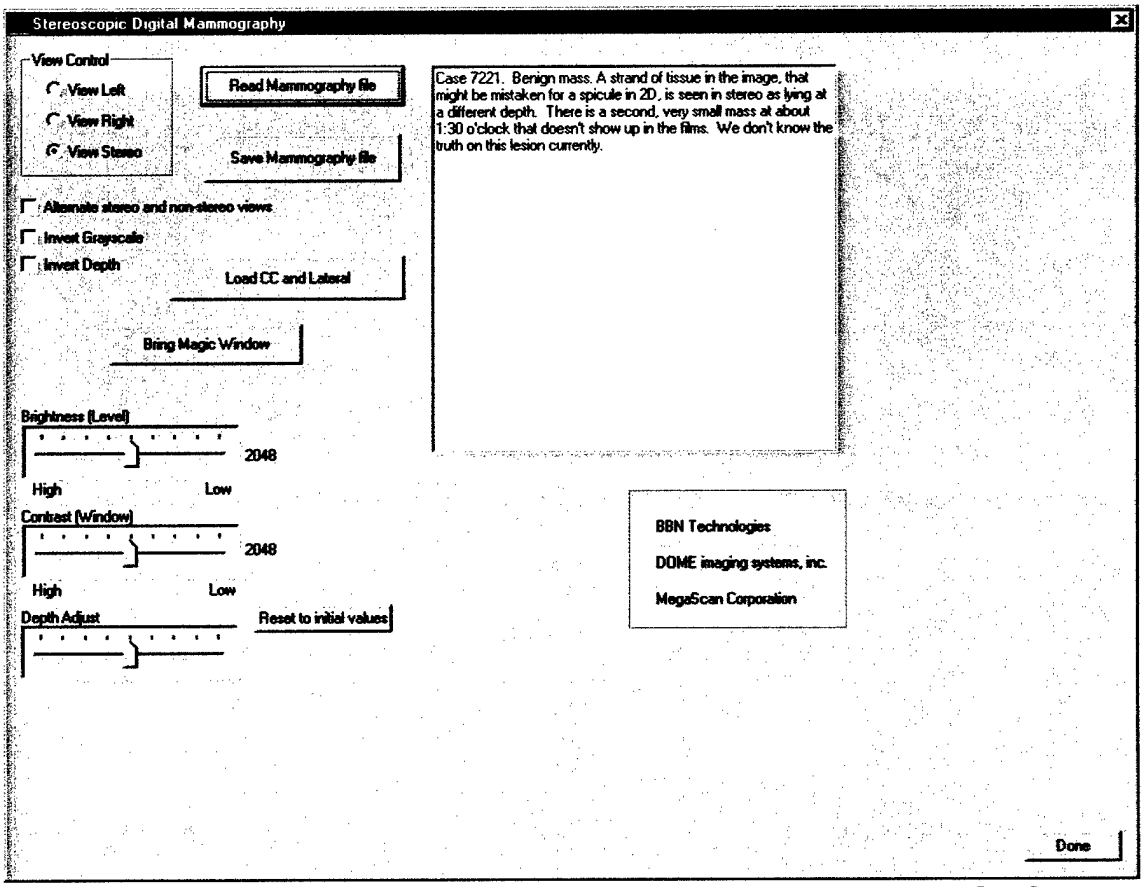


Figure 4. Main screen of the display control program used by the developers

Stereo mammographic image file pairs are identified to the program by special stereo specification files with a ".mamo" filetype. The specification file contains multiple lines of text that indicate the names of the left- and right-eye image files, the default brightness (window level) and contrast (window width) values to use in creating the array of grayscale values to load into the MD8 lookup table (LUT), and, optionally, a paragraph of descriptive text about the images. Clicking the "Read Mammography file" button brings up a standard Windows directory window that displays available "mamo" files, permitting the user to choose one for display. Selecting one causes the program to load the two images of the stereo pair into the appropriate frame buffers on the MD8 card, computes the array of LUT values from the specified brightness and contrast values and loads them into the LUT, and displays the descriptive text, if present, in the text window on the Main screen. The user can save changes to the descriptive text and the current grayscale windowing values as a new default by pressing the "Save Mammography file" button. It should be noted that the stereo image pair is displayed with the chest wall at the bottom of the displayed image and the breast nipple pointing towards the top of the image, as if the patient were lying on her back. This represents a 90-degree rotation from the displayed orientation on the non-stereo GE digital mammography workstation. This orientation of the displayed stereo image is dictated by the direction of movement of the x-ray tube in the patient's frontal plane and cannot be changed.

Standard mammography screening exams consist of 4 images: CC and MLO views of both Right and Left breasts. Thus, a stereo screening exam will consist of 8 images. Stereo images comprising a full screening exam are identified to the program by special exam specification files with a ".ccl" filetype. The contents of the file are similar to the "mamo" filetype described above, with the addition of lines of text naming each of the 8 images: Left- and Right-eye images of each of the 4 views: L-CC, L-MLO, R-CC, R-MLO. The user can select an exam for display by clicking the "Load CC and Lateral" button. This causes the program to create two Overview images comprising a stereo pair, one consisting of the 4 views intended for the Left eye, the other the 4 views intended for the Right eye. Each image is inserted into the Overview image at half resolution. The layout of the Overview image is shown in Figure 5. The Right and Left breast CC views (and the two MLO) views are shown "back-to-back," with the chest wall at the horizontal centerline.

R-CC	R-MLO
L-CC	L-MLO

Figure 5. Layout of the 4 views in the Overview image

The View Control radio buttons permit the user to switch between stereo and non-stereo viewing (either the left- or right-eye view) of the images, for comparison. Choosing a non-stereo viewing mode causes a single image to be displayed to both eyes, while the display controller remains in "stereo" display mode. As a result, the user's stereo glasses remain in the stereo shuttering mode even though a non-stereo image is

seen. This is done to prevent changes in apparent brightness of the display when switching between stereo and non-stereo viewing modes.

There is also a checkbox that when clicked alternates between stereo and non-stereo views, cycling to the alternate mode every 5 seconds. Another checkbox inverts the displayed grayscale, by complementing each grayscale value in the LUT. The result is that white pixels on the display become black, and vice versa. A third checkbox inverts depth within the displayed volume, as if one had reached into a glove and pulled it inside out. Portions of the breast that had been in the background are now seen in the foreground, and vice versa. This transformation is accomplished in the program by simply swapping the Left- and Right-eye images.

It is also possible to move the location of the displayed volume relative to the surface of the display screen. Using a slider on the Main screen ("Depth Adjust"), the user can continuously move the volume so that, at one extreme, it is seen as being contained entirely within the monitor or, at the other extreme, so that it is seen as lying entirely in front of the monitor surface. From experience, we've found that users differ in their preference for where the volume is located. Initially, most users prefer the volume to be located within the monitor; with experience, many come to prefer the volume in front of the monitor. One advantage of placing the volume in front of the screen surface is that one person can point with a finger or a pencil to a location of interest within the volume and share the pointed-to location with other users who are also viewing the display. This transformation is accomplished in the program by horizontally shifting the two images relative to one another.

Another pair of sliders, "Brightness" and "Contrast," allow the user to continuously change the brightness and contrast of the displayed stereo image. Moving one of these sliders causes the program to recalculate the 256 entries in the MD8 card's LUT that control the brightness and contrast.

There is a second, more powerful and more convenient, means of controlling brightness and contrast available to the user. Pressing the button labeled "Bring Magic Window," or pressing the Thumb button on the mouse, causes the program to bring up a new full-screen window, shown in Figure 6.

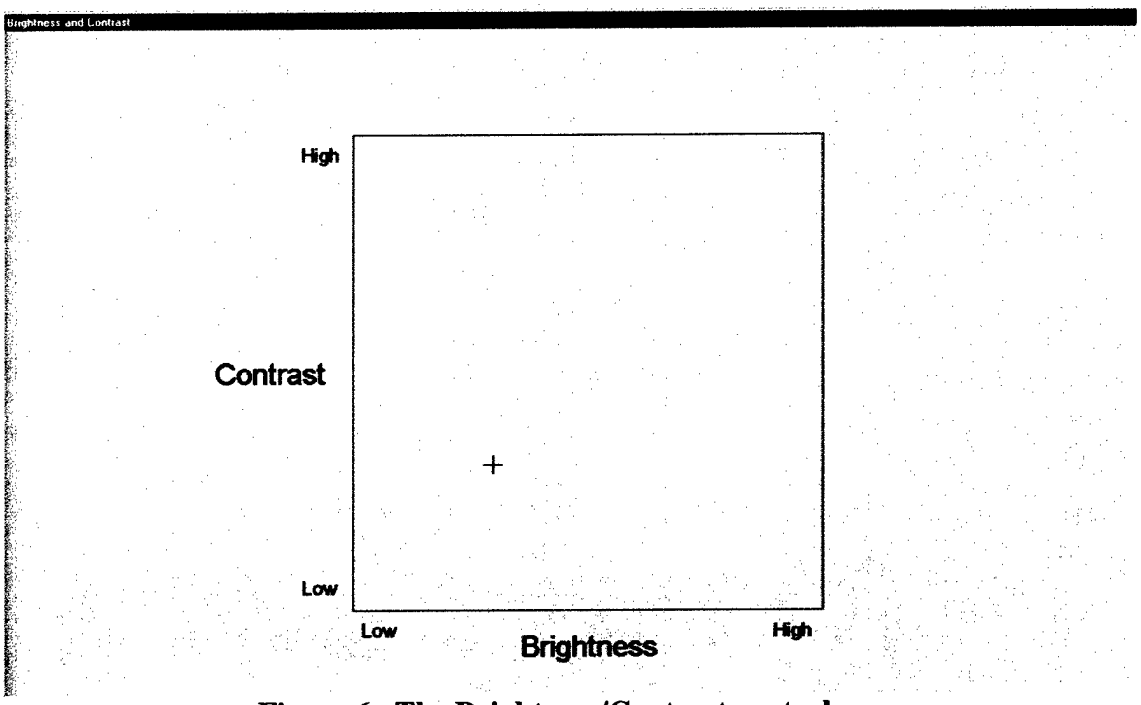


Figure 6. The Brightness/Contrast control screen.

The square in this window represents the 2-dimensional Brightness (x-axis) and Contrast (y-axis) space. The current values for Brightness and Contrast are indicated by the location of the black cross-hair in the space. If the user presses the Left mouse button, the cross-hair changes to the standard mouse pointer and movements of the mouse move the pointer within the square, changing brightness and contrast in accordance with the movement. A significant advantage of this method of control is that both brightness and contrast can be modified simultaneously, through diagonal movements of the mouse, or only brightness can be changed (horizontal movement) or only contrast can be changed (vertical movement). A patent is pending on this method of control. Successive presses of the Left mouse button toggle the two states of brightness/contrast control: (1) freezing the control so that mouse movements have no effect (cross-hair indicator) and (2) un-freezing the control, permitting changes (mouse pointer). The white boxed "X" shown in the square indicates the default settings for brightness and contrast read from the stereo image specification file when the stereo image was opened.

While in the Brightness/Contrast Control mode, the other mouse buttons are active and perform specific functions. The Right mouse button inverts the grayscale (black becomes white, white becomes black). The Middle mouse button inverts depth within the displayed volume, as described previously. Finally, pressing the side Thumb button exits the Brightness/Contrast Control mode, returning the user to the Main screen.

The remaining button on the Main screen, "Reset to initial values," causes the program to reset brightness and contrast to the default values that were initially read from the stereo image specification file.

2.4 Display control program for use by radiologists

The second piece of software produced during this first year of the project is a program to control the stereo display, intended for use by participating radiologists. This program is based on the program described above in Section 2.3. Based on our experience with the first program, we designed this second program to include all of the important functionality needed by the radiologist, including modifications to several controls to improve their usability. We have simplified and improved the design of the Main screen, shown in Figure 7, to make the program more intuitive and easier to use.

A primary change in this program is the method of reading stereo mammography cases. All of the stereo mammograms we acquired in our previous research were unprocessed CC views captured on a pre-clinical version of the GE Senographe 2000D at the University of Massachusetts Medical Center. Stereo image pairs were saved as TIFF image files, each image being 2304 by 1800 pixels in size. In the current project, the images will be acquired on a more recent clinical version of the GE digital mammography unit. Image files are saved in the DICOM format, with a number of specialized tags added to the DICOM header by GE to document x-ray imaging parameters. In addition, GE has modified the image size; it is now 2294 by 1914 pixels in size. Rather than re-engineer the Dome MD8 board and the MegaScan monitor to accommodate the altered image size, we will remove the top 114 lines of each image to reduce the height to 1800 lines. (In fact, an additional 18 lines will be removed to reduce the height to 1782 lines, needed by the MD8 card for vertical retrace). For all but the largest breasts (which will be excluded from the study), this height reduction will not result in the loss of any imaged breast tissue.

GE stores the images for a particular patient in a hierarchical file structure, with raw images in one subdirectory and processed images in another subdirectory. Since the Emory Breast Imaging Clinic currently uses only the processed images when interpreting cases, we will do the same in the stereo reading. Because we do not yet have approval from the Army to acquire stereo mammograms on patients, we do not have, at present, any samples of stereo mammograms acquired on the Emory GE system to guide and test our software to read the 8 images (4 stereo pairs) that comprise a subject's screening exam. We anticipate that the stereo images for each subject will be read from the Emory PACS system and written onto a CD-ROM, most likely with only a single case written per CD.

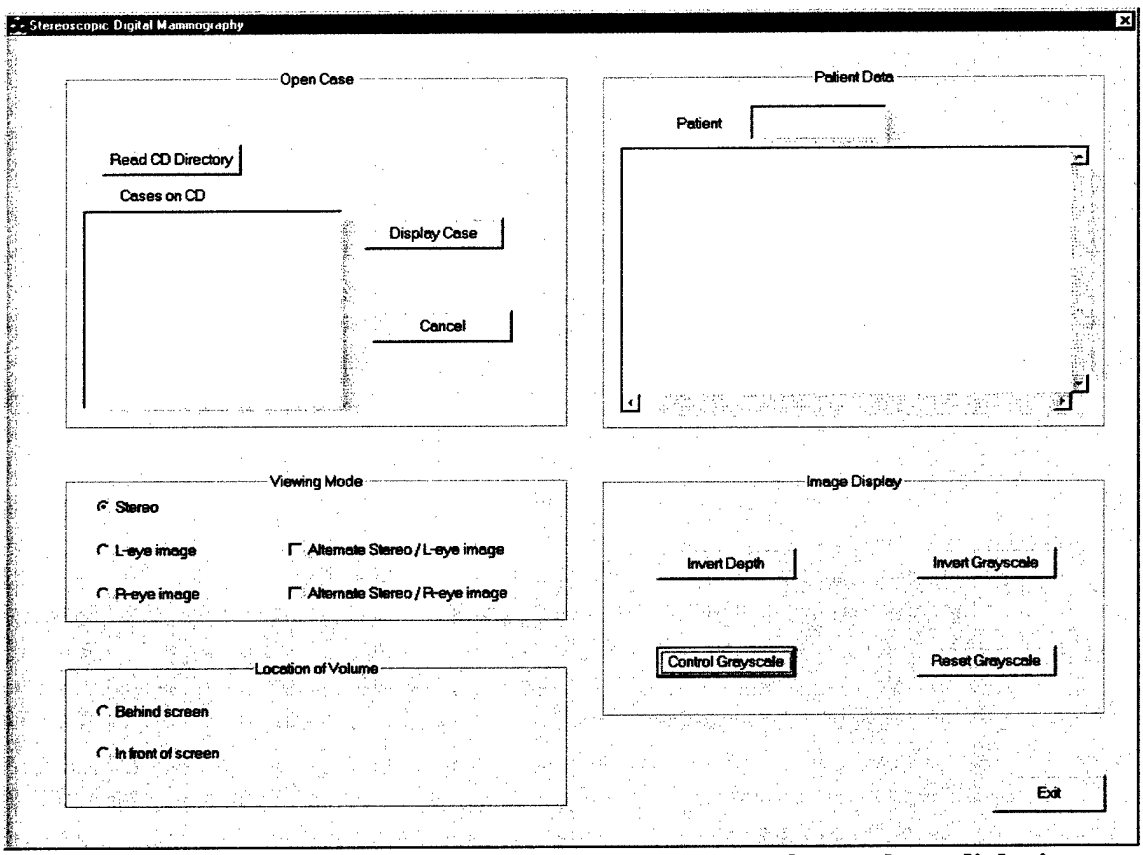


Figure 7. Main screen of the display control program for use by radiologists.

In order to view a case on the stereo display workstation, the radiologist will insert the CD-ROM into the PC's CD reader. If the display control program is running, the CD directory will be read automatically and the set of different patient cases on the CD will be shown in the "Cases on CD" window. (The "Read CD Directory" button will also cause the CD's directory to be read). If the user highlights a case, pertinent information about the patient will be read from the DICOM headers of the image files (e.g., patient ID, patient age, and image acquisition parameters) and displayed in the "Patient Data" area on the right side of the screen. Double-clicking a selected case, or pressing the "Display Case" button, will cause the program to read the set of 8 images from the CD-ROM, create the stereo pair of Overview images (CC and MLO views of both breasts), described earlier, and display the Overview in stereo for the user. Once the images are read from the CD-ROM and the Overview created, the user can switch rapidly among single views and the Overview.

The radiologist can switch among views using a small (programmable) keypad, which is visible in Figure 1 to the right of the mouse. The available keys are shown in Figure 8. Pressing any of the single view keys (R CC, R MLO, L CC, L MLO) brings up that single view on the display at full resolution. Pressing the "All Views" key brings up the Overview image. Pressing the "Next View" ("Prev. View") brings up the next (previous) image in a standard sequence:

All Views => R CC => R MLO => L CC => L MLO => All Views.

The reading of a stereo case in the study will take place in two phases. In Phase I, the radiologist will have only the R MLO and L MLO views available for viewing. The Overview will also be available but will be populated only with the two MLO views. After completing the interpretation of the stereo MLO images, and filling out the appropriate study data forms, the radiologist will press the "Next Phase" key to enter Phase II of the reading. In this phase all 4 views will be available and the Overview will be populated with all 4 views. The radiologist will then fill out a second set of study data forms. The purpose of the two-phase reading is to determine whether a single stereo view—namely, the MLO view—is sufficient for screening by itself, or whether the CC view is needed as well. Detection accuracy in both phases of stereo reading will be compared to that of the standard non-stereo reading of the digital mammograms.

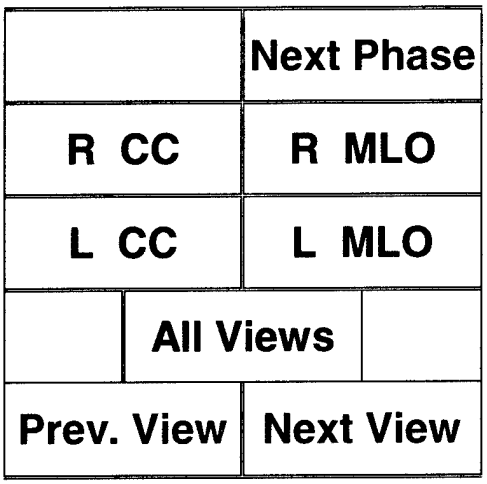


Figure 8. Layout of keys on the keypad.

The default "Viewing Mode" is stereo viewing, but the radiologist can click on radio buttons to see either the L-eye view alone or the R-eye view alone. Checking the adjacent checkbox will cause the display to alternate between a stereo view and a non-stereo view of the current image, switching every 5 seconds.

The radiologist can choose, using the "Location of Display" radio buttons, to have the displayed breast volume appear entirely behind the screen surface within the body of the monitor (the default), or entirely in front of the screen.

Other buttons on the Main screen control several aspects of the displayed image. "Invert Depth" will invert depth within the image—foreground becomes background and background becomes foreground. This permits the radiologist to bring a suspicious area seen as deep in the breast image, behind other tissue, into the foreground for easier inspection. Repeated presses toggle the state of depth inversion. As in the earlier program, pressing the Center key on the mouse will also invert depth.

Pressing the "Invert Grayscale" button complements the contents of the LUT, so that black becomes white and white becomes black in the displayed image. This button, and also the Right key on the mouse, toggles the state of the displayed grayscale.

Pressing the "Control Grayscale" button (or pressing the Thumb button on the mouse) brings up a second screen—the Brightness/Contrast Control screen, shown previously in Figure 6. The simultaneous control of brightness and contrast in the displayed image is the same as described in the earlier program above.

Pressing the "Reset Grayscale" button will reset brightness and contrast back to their initial values. We expect that the initial default brightness and contrast values will be the same for all cases. This is because we believe that the grayscale distribution of pixels in the processed GE images is normalized to be the same across images. We will confirm this once we have a sample of images from Emory.

2.5 Monitor luminance calibration program

The DICOM Standard (Part 3.14) specifies a standard grayscale function that relates image pixel grayscale values to displayed luminance levels. The purpose of the Standard is to ensure that a given medical image looks the same on different monitors, and to perceptually linearize the monitor luminance such that each incremental step in the grayscale pixel value, from 0 to 255, results in an increment in luminance that is a constant number of perceptual *jnds* (just-noticeable-differences) in size.

Using a Tektronix J17 photometer with a J1803 luminance probe, we have set the minimum luminance of the MegaScan monitor to 0.96 cd/m2 and the maximum luminance to 350.05 cd/m2, measured from the central square of the DICOM luminance test pattern. In this test pattern, a variable intensity central square occupies 10% of the screen surface, and the surrounding area has a luminance value that is 20% of the monitor's maximum. We have created a DICOM luminance test image with a central square that is 676 pixels on a side (the area corresponding to 10% of the total displayed pixels). We have set the grayscale value of the central pixels in the image to 200; that of the surround pixels to 100. Actual screen luminance is then determined by the contents of locations 100 and 200 in the MD8 LUT.

We have written a program to help us in the process of determining the digital driving values to be loaded into the MD8 LUT in order to optimize the monitor's luminance function, minimizing the departures from the DICOM grayscale function. The Calibration program screen is shown in Figure 9. The program is able to communicate with the Tektronix photometer via a serial communications line. The program can request, and receive, a series of luminance readings from the meter. The user can load the test image by clicking the "Load test image" button and choosing the test image file from a directory window. The program loads the same test image in both frame buffers of the MD8 card and enables stereo display mode. This is done so that the subsequent luminance measurements will reflect the same conditions present when a user views a true stereo image.

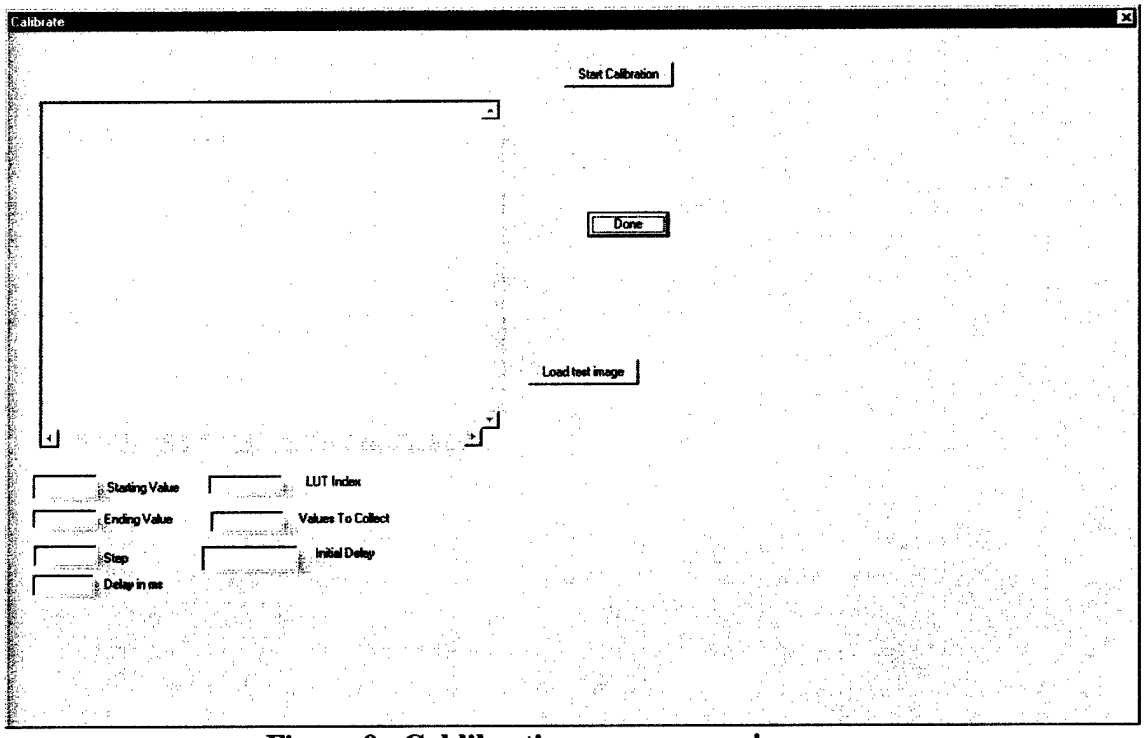


Figure 9. Cablibration program main screen.

The program enables us to set the digital driving value for any of the 256 locations in the MD8 LUT to any value in the range 0 to 1023. This 10-bit range reflects the fact that the MD8 display card has a 10-bit D-to-A converter. To set a single location in the LUT,

- the digital driving value is entered in both "Starting Value" and "Ending Value",
- "Step" is set to 1,
- "Delay" is set to 0,
- the LUT location is entered in "LUT Index,"
- "Values to collect" is set to 1,
- and "Initial delay" is set to 0.

The user then presses the "Start Calibration" to load the LUT location.

Our goal is to set the digital driving value of the central square of the test image to each value between 0 and 1023 and to measure the corresponding screen luminance. We first set the digital driving value of location 100 such that the displayed luminance of the test image background is 20% of maximum (in this case, 70 cd/m2). The program then sets the digital driving value of location 200 ("LUT Index") to successive values between 0 ("Starting Value") and 1023 ("Ending Value"). After loading the LUT with each new value, the program pauses for a user-determined number of milliseconds ("Delay in ms") to permit the monitor circuitry to stabilize and then requests a series of luminance readings (the number entered by the user in "Values to Collect") from the Tektronix photometer. These readings are stored in memory and displayed in the window of the Calibration screen. The user can specify any range of grayscale to scan ("Starting Value" and "Ending Value") and the step size of the successive grayscale values ("Step"). The user can also specify an initial delay before beginning the scan ("Initial Delay"). This is useful for darkening and exiting the room before the scan begins. When the series of

measurements is complete, the user can copy the data to the Windows clipboard and import it into an Excel spreadsheet for analysis.

The measured luminance function for the MD8 card driving the MegaScan monitor is shown in Figure 10 as a function of the 10-bit digital driving value loaded into location 200 of the LUT. One can see that the shape of this function does not match the DICOM standard grayscale function shown in Figure 11. In order to correct the LUT entries to best match the DICOM function, we selected that 10-bit digital driving value from the obtained luminance function that came closest to producing the desired DICOM luminance value, for each of the 256 locations in the MD8 LUT. The resulting grayscale function for our corrected system is also shown in Figure 11. We note that our system's corrected luminance function lies so perfectly on top of the DICOM curve that the DICOM curve cannot be discerned in this plot.

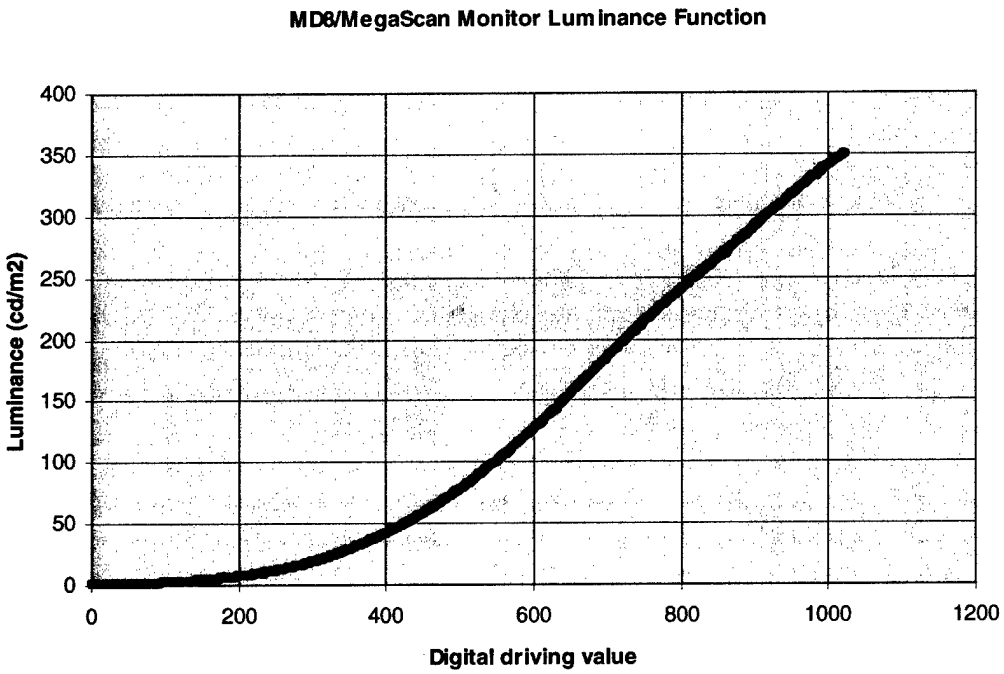


Figure 10. Observed luminance function for the MD8 / MegaScan monitor.

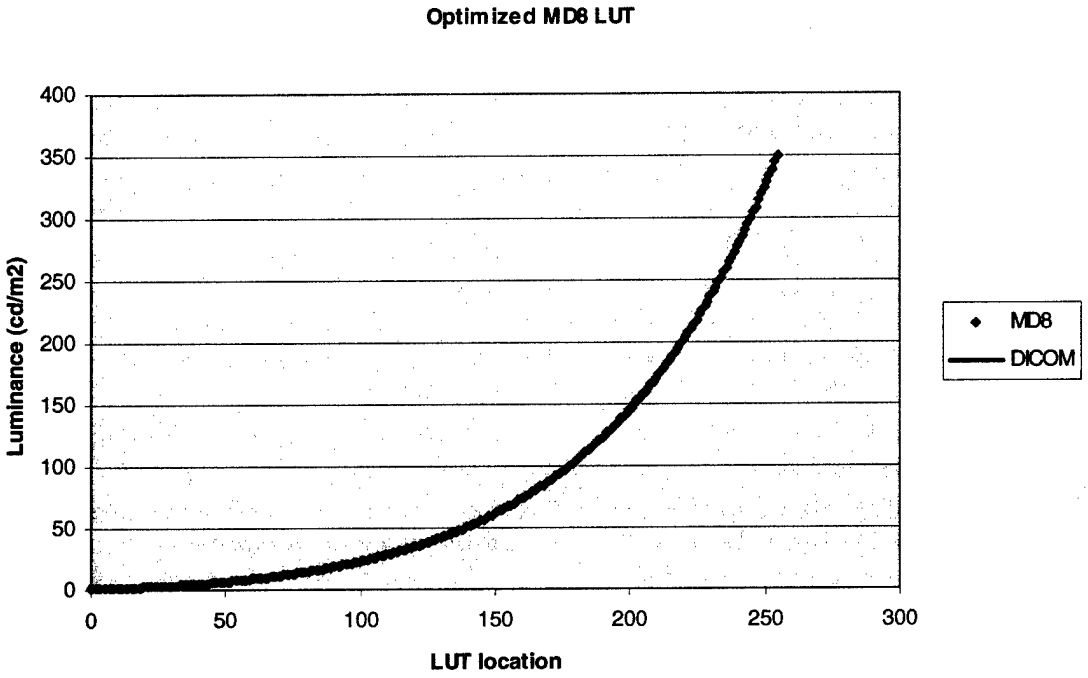


Figure 11. The optimized luminance function of the MD8 / MegaScan monitor. Note: the observed curve lies precisely on top of the DICOM standard curve, obscuring it.

We plan to check the luminance conformance of our two systems to the DICOM standard periodically, and re-calibrate them as needed.

2.6 Investigation of a dual-headed display system

We briefly explored the feasibility of converting our single-headed display system to a dual-headed system. We concluded that it would be possible only if we used two Planar MD8 display cards in the system and were able to synchronize the frame refresh in the two cards. We did not pursue this possibility further when we determined that Planar had discontinued production of the MD8 card and that none remained in stock.

2.7 Remaining uncompleted portions of Task 1

There are two remaining pieces of Task 1 that remain to be completed when Emory is able to help us. The first is to acquire some sample stereo mammograms from the GE Senographe digital mammography unit to be used in the project. These stereo images will be of a breast phantom, and serve two purposes. First, we need to determine whether one can successfully and comfortably view stereo images acquired with a 10-degree separation between the two images. In our prior work, we acquired stereo mammograms with a 6-degree separation. The clinical GE system we will use in this study has a detent that will lock the x-ray tube at an angle of plus and minus 5 degrees from head on. Thus, we can easily acquire stereo images with a 10-degree separation. If this turns out from empirical study to be too large an angle to view comfortably, then we

will have to devise a means of locking the x-ray tube at plus and minus 3 degrees, or use only a 5-degree separation (head-on and a detented offset of 5-degrees).

The second purpose served by the sample stereo mammograms will be to determine the relationship between breast depth in compression (i.e., the height of the compression paddle above the table surface) and offset of a lead "bb", placed on the lower surface of the compression paddle, in the two images of the stereo pair. The height of the compression paddle (in mm) is stored by the GE system in the image file header. When displaying a stereo pair, we need to read this parameter from the header and translate it into a pixel displacement of the two images. This pixel displacement is needed in order to correctly invert depth of the displayed volume when requested by the user.

The second uncompleted subtask is to understand the parameters written into the DICOM header of the image files by the GE system so that we can write the code that will correctly identify and read the 8 image files for a case when the radiologist inserts a CD-ROM into the workstation. The sample stereo mammograms will serve to provide us with examples to develop this code.

3. Preparation of Study Data Forms and Project Database (Task 3)

Although we have not had a subcontract in place with Emory during this past year, Dr. Carl D'Orsi has, nonetheless, been extremely cooperative and helpful in the preparation of the Research Protocol, the Subject Consent form, and the subject data forms to be used in the project. At this time, they have all been approved by the Army HSRRB, and are attached as Appendices to this report:

- Appendix A: Research Protocol
- Appendix B: Subject Consent form
- Appendix C: Enrollment cover letter
- Appendix D: Revocation of permission letter
- Appendix E: Non-stereo reading form
- Appendix F: Stereo-MLO reading form
- Appendix G: Stereo-MLO & CC reading form
- Appendix H: 18-month follow-up call script
- Appendix I: 18-month follow-up call data form

3.1 Remaining uncompleted portion of Task 3

The database has yet to be constructed. Because of the lack of a subcontract with Emory, we were able to develop and obtain approval of the set of study data forms only very recently. The fields to be defined in the database can be determined only when we are certain of the full set of fields on the study data forms. We have decided that the database will be constructed and maintained at BBN since all of the data analyses will take place there. Copies of the study data forms for each enrolled subject will be sent to BBN for entry into the database. We anticipate constructing the database in the statistical database management system, SPSS. This task can be completed within a day or two when we are confident that the study data forms are complete and final.

KEY RESEARCH ACCOMPLISHMENTS

- Assembled two copies of the stereo display workstation from specially designed hardware components, one to reside at BBN and the other to reside in the Breast Imaging Clinic at Emory University.
- Developed a software program for the stereo display workstation for use by the developers in controlling aspects of the workstation.
- Developed a software program for the stereo display workstation for use by radiologists as they interpret cases on the workstation.
- Developed a software program for use in calibrating the luminance function of the stereo workstation to meet the DICOM grayscale standard.
- Wrote the Research Protocol to be followed in the project, and the Subject Consent form to be used in enrolling subjects.
- Developed the set of study data forms to be used to collect and record data for the subject.

REPORTABLE OUTCOMES

PRESENTATIONS

Getty, D. J. (2002). Stereoscopic and biplane digital radiography. Special Refresher Course presentation at the meetings of the Radiological Society of North America, Chicago, December 1-6, 2002.

BOOK CHAPTERS

Getty, D. J. (2003). Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. In H-O Peitgen (Ed.), *Digital Mammography, IWDM 2002, 6th International Workshop on Digital Mammography.* Berlin: Springer, 431-435.

Getty, D. J. (2003). Stereoscopic and biplane digital radiography. Chapter to be published in: E. Samei & M. Flynn (Eds.), *RSNA Categorical Course in Diagnostic Radiology Physics: Advances in Digital Radiography.* RSNA Publications, in press.

CONCLUSIONS

This first year of the project was devoted to preparations for the start of enrollment and stereo mammographic imaging of subjects in the second year. There were four activities contributing to the preparations: (1) creation of the Research Protocol and Subject Consent form, (2) construction of two stereo display workstations, one residing at BBN and the other at the Breast Imaging Clinic at Emory, (3) development of three software programs for controlling and calibrating the stereo display workstation, and (4) the preparation of a set of study data forms for collecting and recording subject data.

Construction of the workstations and development of the software programs all took place at BBN and proceeded as planned. However, we experienced considerable difficulty and delay in getting human subjects approval by the Emory IRB and the Army HSRRB of the several documents and data forms that we developed. These delays were due principally to the necessary, but time consuming, repeated cycling of documents first through the Emory IRB and then the Army HSRRB. This problem was further exacerbated by a change in the assigned Army reviewer midway through the process. And it was further exacerbated by the introduction of HIPAA regulations part way through the process. We obtained approval of the full set of documents from the Army HSRRB only very recently, and expect approval from the Emory IRB shortly—more than a year after we began the process. The Army has not allowed BBN to establish a subcontract with Emory until this approval is obtained. I am grateful to Drs. Carl D'Orsi and Andrew Karellas at Emory for their help in preparing the documents and data forms during the year.

Because of these delays, we will, in all likelihood, not begin enrolling subjects into the study until late in October, 2003. A further contribution to this delay is the fact that the Breast Imaging Clinic will be moving from its current location to a new building at Emory in September.

In spite of these difficulties, we accomplished almost all of the work we had planned for Year 1. We are excited by the prospect of starting to acquire stereoscopic digital mammograms of participating subjects this fall.

REFERENCES

Abbott AH, Netherway DJ, David DJ, Brown T. Craniofacial osseous landmark determination from stereo computer tomography reconstructions. Ann Acad Med Singapore 1990; 19:595-604.

Andre B, Dansereau J, Labelle H. Optimized vertical stereo base radiographic setup for the clinical three-dimensional reconstruction of the human spine. J Biomech 1994; 27:1023-1035.

Doi K, Duda EE. Detectability of depth information by use of magnification stereoscopic technique in cerebral angiography. Radiology 1983; 146:91-95.

Doi K, Patronas NJ, Duda EE, Geldner E, Dietz K. X-ray imaging of blood vessels to the brain by use of magnification stereoscopic technique. Adv Neurol 1981; 30:175-189.

Gautsch TL, Johnson EE, Seeger LL. True three dimensional stereographic display of 3D reconstructed CT scans of the pelvis and acetabulum. Clin Orthop 1994:138-151.

Getty, D. J. Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. In H-O Peitgen (Ed.), *Digital Mammography, IWDM 2002, 6th International Workshop on Digital Mammography.* Berlin: Springer, 2003, 431-435.

Getty, D. J. Stereoscopic and biplane digital radiography. Chapter to be published in: E. Samei & M. Flynn (Eds.), *RSNA Categorical Course in Diagnostic Radiology Physics: Advances in Digital Radiography.* RSNA Publications, in press.

Getty DJ, Pickett RM, D'Orsi CJ. Stereoscopic digital mammography: improving detection and diagnosis of breast cancer. In:Computer Assisted Radiology and Surgery (CARS-2001). Berlin, Germany: Elsevier Science B.V., 2001.

Goodsitt MM, Chan HP, Darner KL, Hadjiiski LM. The effects of stereo shift angle, geometric magnification and display zoom on depth measurements in digital stereomammography. Med Phys 2002; 29:2725-2734.

Goodsitt MM, Chan HP, Hadjiiski L. Stereomammography: evaluation of depth perception using a virtual 3D cursor. Med Phys 2000; 27:1305-1310.

Graf von Keyserlingk D, De Bleser R, Poeck K. Stereographic reconstruction of human brain CT series. Acta Anat (Basel) 1983; 115:336-344.

Greenwell FP. Stereo-radiography of the middle ear. Br J Radiol 1973; 46:159.

Hsu J, Chalberg D, Babbs C, Pizlo Z, Delp E. Preclinical ROC studies of digital stereomammography. IEEE Transactions in Medical Imaging 1995; 14:318-327.

Maidment ADA. Effects of quantum noise on dose and contrast sensitivity in stereoradiography. Medical Physics, in press.

Pearcy MJ. Stereo radiography of lumbar spine motion. Acta Orthop Scand Suppl 1985; 212:1-45.

Rothman SL, Allen WE, 3rd, Kier EL. Stereo roentgenography in craniofacial injuries. A revival of fundamental ideas. Radiol Clin North Am 1973; 11:683-696.

Sekiguchi R, Satake M, Oyama H, Wakao F, Moriyama N. Stereoscopic visualization system for clinical angiography. Stud Health Technol Inform 1996; 29:690-693.

Sexton I, Surman P. Stereoscopic and autostereoscopic display systems. IEEE Signal Processing Magazine 1999:85-99.

APPENDICES

- Appendix A: Research Protocol
- Appendix B: Subject Consent form
- Appendix C: Enrollment cover letter
- Appendix D: Revocation of permission letter
- Appendix E: Non-stereo reading form
- Appendix F: Stereo-MLO reading form
- Appendix G: Stereo-MLO & CC reading form
- Appendix H: 18-month follow-up call script
- Appendix I: 18-month follow-up call data form
- Appendix J: Getty, D. J. (2003). Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer. In H-O Peitgen (Ed.), *Digital Mammography, IWDM 2002, 6th International Workshop on Digital Mammography*. Berlin: Springer, 431-435.

Research Protocol

An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall

1. Investigators

Principal Investigator: David J. Getty, Ph.D.
Division Scientist
BBN Technologies
10 Moulton Street
Cambridge, MA 02138

Tel: 617-873-3751
Fax: 617-873-2794
Email: getty@bbn.com

Co-Investigators: Carl J. D'Orsi, M.D.
Director, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Mary Newell, M.D.
Mammographer, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Kathleen Gundry, M.D.
Mammographer, Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital

Ronald M. Pickett, Ph.D.
Professor of Psychology
University of Massachusetts – Lowell

Medical Monitor: Ernest V. Garcia, Ph.D.
Professor and Vice Chairman for Research
Department of Radiology
Emory University

Research Coordinator: Robin Tarpley, R.N.
Radiology Research Coordinator
Emory University Hospital

Software Engineer: Prakash Manghwani, M.S.
Staff Engineer
BBN Technologies

2. Location of Study

BBN Technologies
10 Moulton Street
Cambridge, MA 02138

Primary Investigator: David J. Getty, Ph.D.
Division Scientist

Breast Imaging Center
Department of Radiology
The Emory Clinic
Emory University Hospital
1365-B Clifton Road, NE
Atlanta, Georgia 30322

Primary Investigator: Carl J. D'Orsi, M.D.
Director, Breast Imaging Center

3. Time Required to Complete

Expected start date: 01-August-2002
Expected completion date: 31-July-2007

4. Objectives

The primary goal of this project is to evaluate stereoscopic digital mammography, in a screening setting, for improved early detection of breast lesions, including breast cancer, and for reducing the rate of recall of patients for workup. We hypothesize that stereoscopic digital mammography, when compared with standard, non-stereo digital mammography, will:

1. Improve the detection of true focal breast abnormalities, including early breast cancer; and
2. Decrease the rate of recall of patients for further workup, by decreasing false positive readings without changing detection sensitivity.

There are three specific aims in this project. The first aim is to further develop the existing stereoscopic display system to improve its usability and efficiency for clinical use. We will observe radiologists using the stereo display and conduct interviews

with them to determine ways to improve the human interface and to usefully augment its capabilities.

The second aim is to enroll approximately 500 women into the study in each of Years 2, 3, 4 and 5 of the project, for a total enrollment of about 2000 women. Women will be enrolled in the study only if they are at high risk for the development of breast cancer. Each woman will receive a screening exam consisting of two stereoscopic digital mammograms of the breast (a cranio-caudal stereo image pair and a medio-lateral-oblique stereo image pair). One randomly-chosen image of each stereo pair will serve the dual purpose of being the standard view for a non-stereo reading condition.

The third aim is to conduct a controlled, paired reading study comparing stereoscopic digital mammography with non-stereo digital mammography for the detection of focal breast lesions and for the rate of recall for workup. Each case will be read independently by two different radiologists, one reading the stereo mammograms and the other reading the non-stereo mammograms. We note that we have chosen to compare stereo mammography with standard digital mammography rather than with film because it is the most direct and appropriate comparison, and because it eliminates the need for additional x-ray exposures to capture the film mammograms. Support for this choice comes from a recently published study that concluded that there was no significant difference between digital mammography (using the same GE Senographe 2000D digital mammography unit that will be used in this project) and film in the rate of cancer detection.

5. Study Population

The target population for this study is women who are at high risk for the development of breast cancer. Approximately 12,000 women receive screening mammograms each year at the Emory Breast Imaging Clinic. Of these, about 10 percent, or approximately 1200 women, are at high risk for development of breast cancer. We seek to enroll approximately 500 of these women at high risk in this study during each of Years 2 through 5 of the project, for a total enrollment of about 2000 patients. A sample of this size is needed to detect a practically significant difference in the rate of lesion detection between stereo and non-stereo viewing. Our reasons for using high risk as a criterion for inclusion are: 1) to maximize the number of lesions and cancers detected in the study, and 2) to provide reasonable justification for the additional x-ray imaging the patients will receive. A high-risk patient who returns for yearly or accelerated screening examinations will be eligible for multiple enrollments in the study.

The protocol for this study will be very similar to that followed in the recently published project comparing full-field digital mammography with screen-film mammography for cancer detection in a screening population. We will use the following inclusion and exclusion criteria to determine eligibility:

Inclusion Criteria

- Patient at high risk for development of breast cancer (any of the following):
    - Personal history of breast cancer, regardless of age,

- Over 40 years of age and first-degree relative (mother, sister or daughter) with either premenopausal or bilateral breast cancer, or more than one first-degree relative with any breast cancer.
- Positive BRCA I or II gene, regardless of age,
- Prior benign breast biopsy that included a pathologic diagnosis of atypical lobular hyperplasia and/or lobular carcinoma in-situ, regardless of age,
- Undergone mantle irradiation to the mediastinum for treatment of lymphoma, regardless of age.

Exclusion Criteria

- Patient does not meet any of the inclusion criteria,
- Patient has had breast augmentation, except for unilateral augmentation done for prior mastectomy,
- Patient has suspected or confirmed pregnancy,
- Patient has large breasts that cannot be entirely imaged on the 19 x 23 cm detector surface of the GE Senographe 2000D digital mammography unit.

6. Protocol Design

This project will use a prospective design in which each case will serve as its own control. The set of digital mammographic images acquired for a patient enrolled in the project will be used in both of the reading conditions being compared: stereoscopic reading of the two views of each breast versus non-stereoscopic, standard reading of the two views of each breast. In the latter, non-stereoscopic reading condition, a single image of each view's stereo pair of images will be randomly chosen for reading.

6a. Subject identification. Each week, the research coordinator will access the already existing clinical history forms and prior mammography reports of patients scheduled to come in for a screening mammogram two or three weeks in the future. The coordinator will identify those patients who are at elevated risk, based on information on the forms, and, thus, are candidates for recruitment into the study.

6b. Description of the recruitment process. The research coordinator will call each scheduled patient that has been identified from the clinical history forms as being at elevated risk. Using a script, the research coordinator will acknowledge and check the risk factors on the forms that are the basis of the elevated risk. The patient will be told that, because she is at elevated risk, she is eligible to participate in a study to evaluate a potentially better method for detecting breast cancer. The stereoscopic mammogram will be described briefly and the woman will be informed that the exam will take about 5 minutes more of her time than a standard screening mammogram and include 2 extra mammographic images of each breast, but with no additional compressions. If she expresses interest in participating in the study, then a cover letter and the Subject Consent form will be mailed to her, in advance of her scheduled screening exam. The study is described in the Subject Consent form. She will be asked to read the material and think about participation, prior to going for the scheduled mammogram.

6c. Description of the informed consent process. Upon arrival for a scheduled mammogram, an eligible woman will be asked if there is a chance of pregnancy (a prominent sign is also displayed at the registration desk of the breast imaging center). Possible pregnancy is an exclusion condition for the study and, in fact, for any screening mammogram. No pregnancy test will be administered. She will then be asked if she received the study description and if she wishes to participate. At this time, any questions the woman has will be answered and, if need be, one of the radiologists involved in the study will also be available. The informed consent will be obtained either by the research technologist or the research coordinator. If the patient agrees, two consent forms will be signed. One will be returned to the patient and the other kept for the study records.

6d. Subject assignment. All of the patients enrolled in the study will be assigned to the same single treatment condition in which two stereo digital mammograms (cranio-caudal and medio-lateral views) will be acquired on the GE Senographe 2000D digital mammography unit. Comparison of the two reading conditions being studied in the project (stereoscopic versus non-stereoscopic reading) will occur in the context of image interpretation by the radiologists.

6e. Subject screening procedures. Eligibility for admission to the study will be determined on the basis of a prior clinical history form reviewed by the research coordinator several weeks in advance of a scheduled screening mammogram. The form will be reviewed by the research administrator or research technologist with the patient at the visit for the screening mammogram to determine, finally, whether the patient meets the study inclusion criteria and is not excluded by any of the exclusion criteria.

6f. Data collection procedures. Each patient enrolled in the study will be assigned a sequential study ID number to protect patient identity. The study ID number will not include any personal identifiers (name, social security number, hospital ID number, date of birth). Only the PI of the project and the research administrator at Emory will hold master keys that relate the assigned study ID number to patient identity (name and hospital ID number). No personal identifying information will ever be used in any reports or publication of this study. Five types of data will be collected on each patient enrolled in the study.

The first is the clinical history form that is part of the patient's medical record, and will be used to determine the patient's level of risk for development of breast cancer. A copy of the clinical history form will be stored in the project's research records, identified only by the subject's assigned study ID number.

The second data type is the set of digital mammographic images. The patient will receive a mammographic screening examination using the GE full-field digital mammography unit (GE Senographe 2000D) at the Emory Clinic's Breast Imaging Center. The screening exam will consist of two images (a stereoscopic pair) captured for each of the two standard views of each breast: cranio-caudal and medio-lateral-oblique views. The stereo pair of images will be separated by a 6-degree rotation of the x-ray tube between images while the breast remains compressed and unmoved. The first image will be acquired with the tube rotated clockwise 3-degrees from head-on alignment to the

compression table; the second image will be acquired with the tube rotated counter-clockwise 3-degrees from head-on. The images will be stored in the RADSTOR image archiving system used with the GE mammography unit, and become part of the patient's medical record. A copy of the digital images will also be burned onto a CD-ROM for reading on the stereo mammography workstation in the stereo reading condition. The CD-ROM will be labeled on its top surface only with the assigned study ID number. Image files are identified on the CD only with sequential serial numbers (IM1, IM2...). No personal identifying information exists in the filenames. After the reading of a case is complete at Emory, the CD-ROM will be sent to BBN for stereo image quality monitoring and for evaluation in making further improvements to the stereo workstation.

The third data type are the two mammography BI-RADS report forms, one filled out electronically by the radiologist reading the standard non-stereo digital mammograms and the other filled out by the second radiologist reading the stereo mammograms. These will become part of the patient's medical record. A copy of these forms will be printed out for the project's research records. These copies will be identified only by the assigned study ID number.

The fourth data type is a form filled out by the radiologist after completing the reading of a case in either the stereo or non-stereo reading condition. The radiologist will record on this form a quantitative judgment of the likelihood that a finding is a true focal abnormality, and a second judgment of the likelihood that a finding is cancer. This form will be identified only with the assigned study ID number.

The fifth data type is the form to be filled out by the research coordinator when talking to subjects at the 18-month follow-up phone call. The purpose of this phone call is to determine whether the subject has had any more recent breast examinations since the stereo imaging study and, if so, what the outcome was. Although the coordinator must necessarily know the patient's name and phone number to make the call, the form that will become part of the study records will be identified only by the assigned study ID number.

All research records for the subjects will be kept in the research coordinator's locked office at Emory. A copy of the several study forms collected for each subject and the CD-ROM containing the stereo images will be sent to BBN, each identified only with the assigned study ID number. These mailings will be addressed directly to David Getty, the PI, and labeled as "Confidential." At BBN, the data will be entered into a computer database for analysis. The only identification of subjects in the database will be by the assigned study ID number. The CD-ROMs and research records will be kept in a locked office under the control of the PI. The computer database will reside in a password-protected computer in the PI's locked office.

The master key list linking the subjects' personal identification information with the assigned study ID codes will be kept in the Emory research coordinator's locked office, separate from all other study records and accessible only by the research coordinator. A copy of this list will also be kept in Dr. Getty's locked office at BBN, again separate from all other study records and accessible only by Dr. Getty.

Agencies that have a right to examine patient records collected in this study include the Emory Institutional Review Board, BBN Technologies, and the U.S. Food and Drug Administration. In addition, representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects in research.

6g. Clinical assessments. The primary clinical assessment of the patient will come from the standard reading of the non-stereo digital mammograms and from the additional reading, by a different radiologist, of the stereo digital mammograms. Assignment of each participating radiologist to the two reading conditions will be counterbalanced across patients. The reading of the stereo mammograms, which will be done in the same time frame as the reading of the standard mammograms, will have the potential of contributing to the patient's current diagnosis if something is seen in the stereo mammogram that was not seen in the standard mammogram. Any finding, seen in either reading condition, will be acted upon as appropriate. Each patient will be called at about 18 months following stereo imaging to determine outcomes so as to score the contributions of stereo mammography to the accuracy and efficacy of diagnosis.

6h. Research interventions. The only thing that the patient may notice that is different from the experience of a standard mammography exam visit will be the experience of having, for each of the CC and medio-lateral views, a stereo pair of mammograms taken, rather than a single mammogram. There will be no additional compressions of the breast, only an adjustment of the x-ray source location by the x-ray technologist after the first image is acquired of the pair.

6i. Data analysis. Truth for each reported finding will be established from imaging workup, biopsy results or 18-month follow-up. Two types of truth will be determined. First, we will determine *lesion truth*: whether or not the reported finding is a true focal abnormality. Lesion truth will be determined either from imaging workup (film studies using spot compression, magnification or other views, and/or ultrasound examination), follow-up examinations, or from biopsy results. Second, for each confirmed focal abnormality, we will determine *cancer truth*: whether the finding is malignant or benign. Cancer truth will be established either from a biopsy or from follow-up phone call 18 months after imaging. All cases, where a confirmed focal abnormality was not deemed worrisome enough to be sent to biopsy, will be followed at 18 months to confirm whether that focal abnormality was truly negative for cancer.

We will conduct several analyses of the collected data. First, using standard ROC methods, we will compare the performance of stereoscopic digital mammography to non-stereo digital mammography for detection of breast lesions. The set of lesions to be used in this, and other, analyses will be the union of all findings reported in either the stereo reading condition or the non-stereo reading condition, or in both. A finding that is reported in one reading condition, but not the other, will be scored as a zero on the rating scales (likelihood of a true lesion and likelihood of cancer) for the reading condition in which the finding was not reported. ROC curves will be fitted to the judgments made independently in each of the two reading conditions. We will compute A_z, the area under the ROC curve, as a measure of accuracy for each fitted ROC. Statistical analysis will be conducted on the difference between the A_z computed for each reading condition, using

ROC methods that account for the correlation induced by the same case set being read in the two different conditions.

Similar ROC analyses will be applied to the judgments of the likelihood of cancer. Statistical analysis of the difference between the A_z's computed for stereo digital mammography and non-stereo digital mammography will be completed to determine if there is a difference in the cancer detection rate.

We will examine the frequency of recommended recall of patients for further workup or biopsy based on the BI-RADS classifications (classifications of 0, 4 or 5) obtained from each reading condition. Statistical analysis of the difference in this frequency for the two conditions will be conducted on the 2 x 2 table of frequencies using chi-square tests. In a related analysis, we will also construct an ROC curve for each condition using the BI-RADS classifications as a rating scale, ordered by increasing suspicion of malignancy as 1 (negative), 2 (benign), 3 (probably benign), 0 (need additional imaging evaluation), 4 (suspicious abnormality), 5 (highly suggestive of malignancy). By statistically comparing the two fitted ROC curves, we will determine whether there is a difference between the stereo and non-stereo readings in the predictive accuracy of recalling a patient for workup or biopsy.

7. Risks/Benefits Assessment

7a. Risks. There is no additional risk of physical injury in acquiring the stereo mammogram beyond that associated with a standard mammogram. There is the minimal risk of physical injury in the normal procedure of positioning and taking a mammogram. A compression paddle will be used to flatten the breast to a uniform thickness for the images. There is the risk that some bruising could occur due to the compression; this is the same risk as for the routine mammogram.

As a result of this study, participants will be subjected to a small additional amount of radiation. A typical technique will be: 28 kVp, 100 mA, and one-second exposure. A higher mAs will be used for more dense breasts, but the technique used will be about the same as with conventional film-screen imaging. The kVp utilized may vary by ±3 kVp depending on the thickness of the breast; this is standard practice in mammography. The beam will be collimated to an area no larger than the site of the image receptor plane. This measure contributes greatly to the reduction of the dose to the breast and to other parts of the body. The mean glandular dose received by the breast from each mammographic x-ray view will be 160 mrad. This is about the same dose given to patients in routine film mammography. This dose is approximately half the maximum dose of 300 mrad (mean glandular) recommended by the American College of Radiology (ACR) for a single-view mammogram. The Total Body Effective Dose Equivalent per view will be 8 mrem, or 16 mrem total for the two extra views specified by the experimental protocol.

As part of the routine mammographic examination, the patient will have been interviewed by the x-ray technologist with regard to pregnancy. In current routine practice, premenopausal patients are asked whether they are pregnant, or trying to

become pregnant. The majority of this group gives a negative response to this question, and mammography is performed in the usual manner. It should be noted that there is always a small theoretical probability that a woman in this group was pregnant and found out after the mammographic examination. As a precaution, strict measures are in place using proper x-ray beam collimation and equipment. Because of these measures and the very low energy of the x-ray beam, even in the case of the pregnancy, the dose to the fetus would be very close to background radiation. The same precautions will apply to the experimental procedure. Patients who are pregnant or trying to become pregnant will be excluded. As in routine mammography, we expect that most of the subjects will be beyond their childbearing years. Screening for pregnancy will be done only by asking questions and not by any blood or urine tests.

7b. Benefits. An individual participant may directly benefit from the stereo mammography examination if additional information is detected in the reading of the stereo mammogram that is not seen in the standard, non-stereo reading. In this case, further workup of the patient would occur using standard, approved procedures. In general, however, this research project is not intended to directly benefit the individual participants. But, the information collected in this study may lead to significant improvements in the earlier detection of breast cancer through the use of stereoscopic digital mammography. The results of this research could eventually benefit all women undergoing mammography.

7c. Compensation. Subjects consenting to take part in this study will not receive any compensation for their participation, nor will they experience any additional expense as a result of participation.

7d. Voluntary Participation/Withdrawal. A subject's participation in this study is entirely voluntary. A woman who is invited to participate may decline without prejudice. Likewise, a subject who has enrolled in the study may choose to drop out at any time. The decision to decline enrollment or to drop out will have no effect on the woman's current or future medical care or any benefits to which she is otherwise entitled. If a woman drops out of the study, her study records will be excluded from all further review and analysis.

Under unusual circumstances, the investigator may choose to terminate an enrolled subject's participation in the study. Such circumstances might include equipment failure, discovery of an exclusion condition not evident at the time of enrollment, or development of a medical condition that precludes participation.

8. Reporting of Serious or Unexpected Adverse Events

Every patient will be carefully monitored and closely followed during the imaging procedure. Carl J. D'Orsi, M.D., FACR, will be monitoring all phases of the study as they apply to Emory University. Dr. D'Orsi will be actively involved in all aspects of this study and will be available to assist if any medical emergency should arise. Dr. Andrew Karellas is the Director of Radiologic Physics and will monitor all equipment as it applies

to this study. Dr. Ernest Garcia, Ph.D. will serve as the medical monitor assigned to this study.

Adverse experiences that are both serious and unexpected will be immediately reported to the Emory University IRB and by telephone to the USAMRMC Deputy for Regulatory Compliance and Quality (301-619-2165) (non-duty hours call 301-619-2165 and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days, sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

9. Disposition of Data

The digital mammographic images will be stored in the RADSTOR image archiving system, as part of the patient's medical record. The copy of the stereo digital mammograms written on a CD-ROM, and identified only by the assigned study ID number, will be retained at BBN throughout the duration of the project and for 5 years following.

The data forms, identified only by study ID, will be retained through the period of the project at Emory University, and a copy at BBN, and kept for 5 years following. The database will be maintained at BBN for the duration of the project, and a copy sent to Emory at the termination of the project where it will be stored for 5 years. There will be no personal identifying information in the database. The master key list linking study ID numbers to subject personal identifiers will be kept at Emory University for 5 years beyond the termination of the project.

All study data forms, the database, and the mammographic image CDs will be destroyed 5 years after the termination of the project.

10. Modification of the Protocol

Proposed modifications or amendments to the protocol will be submitted to the Emory IRB and to the HSRRB for review and approval prior to implementation.

11. Departure from the Protocol

Should any departure from the approved protocol be deemed necessary due to unforeseen events, the Emory IRB and the HSRRB will be notified of the nature of the deviation, the reasons for its occurrence, and the proposed remedy, if appropriate, for review and approval prior to implementation.

12. Roles and Responsibilities of Study Personnel

BBN Technologies

David J. Getty, Ph.D., is Division Scientist at BBN Technologies and will serve as Principal Investigator for the project. As PI, he will provide oversight of the ongoing

activities of the project at BBN and at Emory University. He will have primary responsibility for the further development and refinement of the stereo display system that will take place at BBN. He will be responsible for overseeing the design of the electronic database, the design of data collection forms. He will have primary responsibility for carrying out planned analyses of the data comparing reading of the stereo mammograms with reading of the non-stereo mammograms. He will have primary responsibility for preparing the annual reports for the Army, and for presenting the results of the project at scientific meetings and in publications.

Prakash Manghwani, M.S. (Computer and Information Science), is a Staff Engineer at BBN. Mr. Manghwani is a highly experienced programmer who will be responsible for writing the software application that controls the stereoscopic display system. The goal of this effort is to develop an application that permits a radiologist to manipulate the appearance of a stereo mammogram in well human-factored ways that are powerful, convenient and efficient in a clinical setting. The application will be refined iteratively as we receive feedback from radiologists using the system over the course of the project.

BBN Consultant

Ronald M. Pickett, Ph.D., is a Professor of Psychology at the University of Massachusetts—Lowell. He has worked closely with Dr. Getty on related radiological imaging projects for the past 25 years. He is an expert on human visual perception experimental design, and ROC analysis methods. He will consult throughout the project in all of these areas: helping to improve the human factors of the stereo display system to maximize information provided to the radiologist, helping to design the reading study comparing the stereo and non-stereo reading conditions, and helping in the choice of the methods of data analysis and result interpretation.

Emory University

Carl J. D'Orsi, M.D., is Director of the Breast Imaging Clinic at Emory University. He will serve as primary investigator of the clinical portion of the project conducted at Emory University, with responsibility for overseeing the enrollment of patients into the project, acquisition of stereoscopic digital mammograms on those patients, reading of the non-stereo and stereo mammograms by participating radiologists, and entry of the collected data into the electronic database. Dr. D'Orsi is a renowned radiologist with an international reputation in mammography. He has worked with Dr. Getty on medical projects for more than 20 years. He will also work with Dr. Getty in designing the data collection forms and database to be used in the project.

Mary Newell, M.D., is a radiologist, specializing in mammography, in the Breast Imaging Clinic at Emory University. She will serve as a reader of both the stereoscopic digital mammograms and the standard, non-stereo digital mammograms acquired in the project.

Kathleen Gundry, M.D., is a radiologist, specializing in mammography, in the Breast Imaging Clinic at Emory University. She will serve as a reader of both the stereoscopic

digital mammograms and the standard, non-stereo digital mammograms acquired in the project.

Robin Tarpley, R.N., is a Research Coordinator in the Radiology Department at Emory University. She will be responsible for determining the eligibility of patients for inclusion in the study, for interviewing women meeting the requirements and conducting the informed consent process, and enrolling women who consent to participate. She will also have responsibility for entering clinical history and radiologic reading data on each patient into the database, including the assignment of study ID numbers. She will also have responsibility for sending copies of the data (digital mammographic images and the database) to BBN on a regular basis.

Andy Karellas, Ph.D., is the Director of Radiologic Physics at the Breast Imaging Clinic at Emory University. He will have primary responsibility in monitoring the x-ray equipment used in this project.

Ernest Garcia, Ph.D., is assigned the role of Medical Monitor for this project. He will be responsible for monitoring the care provided to enrolled patients, and providing medical care to any enrolled patient who experiences any serious and unexpected event that occurs as part of the study. He will review any such event and provide a written report within 3 calendar days of the initial report. This report will be forwarded to the USAMRMC.

Emory University School of Medicine
Department of Radiology
Consent to be a Research Subject

Title: An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall

Sponsor: Department of Defense Breast Cancer Research Program

Principal Investigator: Carl J. D'Orsi, MD

Co-Investigator: Mary Newell, MD
Kathleen Gundry, MD

Introduction/Purpose: You are being asked to take part in a research study. You have been asked because you are scheduled to have your annual screening mammogram and have a personal or family history of breast cancer. This study will compare two different ways of doing a mammogram, a standard digital mammogram vs. a stereoscopic digital mammogram. The stereo mammogram enables the radiologist to see the breast tissue in depth, as a 3D image. It does require a very small amount of extra x-rays. The digital mammogram is your standard screening method; it is not research. It is hoped that the stereo mammogram will reveal true, breast tumors at an earlier stage, and decrease the number of patients who have to come back for repeat mammograms when an abnormal area is seen at screening. You will not receive results from your standard mammogram today, as two different doctors are involved with reviewing of the images. Taking part in this study will require about 15 extra minutes of your time today. About 5 minutes of that time will be answering some questions about your medical history. Approximately 18 months from now, one of our research nurses will contact you by phone to see if you have had any problems or further tests (biopsies, ultrasounds, mammograms, surgeries) on your breasts. This phone call will take about 5 minutes of your time. If other tests have been done, we would like copies of those reports.

The total enrollment for this study is 2000 women, all to be done at Emory Clinic's Breast Imaging Center.

Procedures: If you agree to take part in this study, your mammogram will be done by both methods at the same time. Your breast will be compressed in the breast holder as is routinely done. The standard 2 x-ray images will be taken of each breast. In addition, 2 more images will be taken of each breast, from slightly different viewpoints. No additional compressions of your breast are required. A radiologist will read the stereoscopic images at a specially designed stereo-display workstation while wearing stereo-viewing glasses. The reading of those images will be compared to the reading of the standard digital images.

Although the stereoscopic mammogram is still experimental, your doctor will be told of any abnormal areas that may be noted on either the standard mammogram or the stereoscopic mammogram. You will receive a letter or phone call from the Breast Imaging Center within about 15 business days concerning your results. If any abnormalities are found, you will be called back for further work-up. Should you need to have further work-up or an area biopsied (needle inserted and tissue taken out), we are asking your permission to review your medical records and test results.

Risks: If you take part in this research, you will have a medical imaging study that uses radiation. The test you will have includes ordinary x-rays. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally occurring radioactive forms of water and minerals. This research gives your body the equivalent of about 3 extra months' worth of natural radiation. The radiation dose we have discussed is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests. Radiation exposure can potentially increase your chance of developing cancer, and of genetic malformation. This risk is very small, and may even be zero for the radiation exposure from this study. Pregnant women may not participate in this study due to the possible risks of radiation exposure to the fetus. Since any findings, either on the routine digital mammogram or on the experimental digital stereoscopic study will be evaluated, you could possibly have additional tests and/or breast biopsies that may not have happened if you did not participate in this study.

Benefits: Taking part in this research study may not benefit you personally, but we [doctors, researchers and scientists] may learn new things that will help others. It is also possible that a biopsy requested because of your participation in this study leads to detection of early breast cancer.

Alternatives: You may choose to not take part in this study and just have your standard screening mammogram.

Compensation and Cost: You will not be paid to take part in this study. Your standard digital mammogram will be billed to you or your insurance and there is no charge to you for the stereoscopic mammogram. We will arrange for emergency care if you are injured by this research. However, Emory University has not set aside funds to pay for this care or to compensate you if a mishap occurs. Your insurance may be billed for any medical care provided by Emory University, but Emory will not bill you for research-related medical expenses that are not covered by insurance (for example, deductibles or co-pays), or for these expenses if you are uninsured. You or your insurance companies are responsible for paying for any medical care provided by sources other than Emory University. You should also understand that this is not a waiver or release

of your legal rights. If you believe you have been injured by this research, you should contact Carl J. D'Orsi, MD at 404-778-4446.

Voluntary Participation/Withdrawal: Your participation is completely voluntary and you have the right to refuse to be in this study. You can stop at anytime after giving your consent. This decision will not affect in any way your current or future medical care or any other benefits to which you are otherwise entitled.

The study doctor/investigator and/or sponsor may stop you from taking part in this study at any time if they decide it is in your best interest, or if you do not follow study instructions.

Contact Persons: If you have any questions about this study or if you feel being in this study has harmed you, contact Carl J. D'Orsi, MD at 404-778-4446. If you have any questions or concerns about your rights as a participant in this research study, contact James W. Keller, MD, Chairman of the Emory Institutional Review Board at 404-727-5646.

New Findings: We may learn new things during the study that you may need to know. We can also learn about things that might make you want to stop participating in the study. If so, you will be notified about any new information.

Confidentiality (Protection) of Your Research Records: You will be assigned a study ID number that will be used on all study records. The study ID number will not include any personal identifiers, such as your name, social security number, medical record number, or date of birth. All study records at Emory will be kept in the Research Coordinator's locked office. All study records at BBN, including the digital mammographic images that will be stored on a CD-ROM, will be kept in a locked room controlled by the project's Principle Investigator.

The study's Research Coordinator at Emory will keep a master list that links your identity to your assigned study ID number. This master list will be kept in a separate file in the Research Coordinator's locked office. The project's Principle Investigator at BBN Technologies will also keep a copy of this master list in a separate file in his locked office. Only the Research Coordinator and the Principle Investigator at BBN Technologies will have access to the master lists. The master list will be kept for at least 5 years after the termination of the study.

The data forms generated in this study and the stereoscopic mammographic images that will be stored on a CD-ROM will be identified only by your assigned study ID number. No personal identifiers will be used. Copies of these forms and the mammographic images will be sent to BBN Technologies for analysis, identified only by your study ID number. At BBN, a computer database will be developed to analyze the data. Study participants will be identified in the database only by study ID numbers. The database will be kept in a password-protected computer.

People from the Emory University Institutional Review Board (IRB), Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), BBN Technologies and representatives of the U. S. Army Research and Materiel Command are eligible to review research records as part of their responsibility to protect human subjects.

We will not use or disclose your records in any ways other than those described in this form, and we will keep your records private to the extent allowed by law. We will do this even if outside review of your records occurs. Your name and other facts that might point to you will not appear when we present this study or publish its results.

Protected Health Information (PHI): Protected health information (PHI) is any health information provided to persons that identifies you or information that can reasonably be used to identify you. The people who are conducting this study (the "Researchers") may need to look at your medical records that contain this PHI. In addition, government agencies that make rules and policies about how research is done, including the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) and, have the right to review these records. Sponsors who pay for the study, the Emory University Institutional Review Board (IRB) and the U. S. Army Research and Materiel Command also have the right to review your medical records. In addition, these records may be disclosed pursuant to court order.

Under the Health Insurance Portability and Accountability Act (HIPAA), a federal law enacted to protect the privacy of your PHI, before we can use or disclose your PHI, we must provide you with information about what PHI will be used for this research study and how it will be used and disclosed. This section of this form provides you with this information regarding your PHI. Specifically, it will tell you what PHI the Researchers will look at; who will collect the PHI; who will use the PHI, with whom it will be shared and the purpose of each use or disclosure; the expiration date or event, if any, after which we won't use or disclose your PHI any more; and your rights under HIPAA to ask us not to use your PHI any more. If you decide to participate in this research, then you will be agreeing to let the Researchers and any other persons, companies or agencies described below to use and share your PHI for the study in the ways that are set forth in this section, so please review this section very carefully.

What PHI will the Research Team Use: As part of your clinical care, the Researchers will look at information that identifies you such as your name, patient identification number, medical records number, birth date and social security number. The Researchers will also look at your medical history and at any results from laboratory tests and physical examinations that you have had performed. In addition, if you have a bad outcome, or 'adverse event' then the Researchers may also need to look at your entire medical record.

Who will Collect the PHI: The Researchers will collect and copy the PHI described above. If any of the PHI is to be shared with other persons, as described later on in this section, then the Researchers also will be responsible for making these disclosures.

Who will Use the PHI; With Whom will it be Shared; and For What Purpose(s) Will it be Used or Shared: In order to conduct the study, the PHI that is collected regarding you will be used by or shared with the following persons, agencies or companies for the purposes listed in the chart below.

Person/Entity	Purpose
Researchers at Emory and BBN Technologies	To conduct the study entitled, " An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall."
Governmental Agencies with oversight over the research being conducted, including the FDA and OHRP	To monitor safety, efficacy and compliance with applicable laws and regulations.
University personnel, committees and departments charged with oversight of research, including the IRB.	To monitor safety and compliance with applicable laws, regulations and University policies and procedures.
Representatives of the US Army Medical Research and Material Command, the study sponsors.	To provide oversight for the study and as part of their responsibility to protect human subjects.

Expiration Date or Event: The Researchers will continue to use your PHI until the study is closed and the period for which any records relating to the study must be retained has ended.

Your Right Under HIPAA to Revoke Your Authorization and Ask Us Not to Use Your PHI Any More: Giving the Researchers your authorization to use and share your PHI is voluntary. At any time, you may choose to revoke your authorization for the Researchers to use and share your PHI. If you revoke your authorization, the Researchers may no longer be able to provide you with any research-related treatment, but your revocation will not otherwise affect your current or future health care. Further, if you revoke your authorization, there will be no penalty or loss of any benefits to which you are otherwise entitled.

If you decide that you want to revoke your authorization for us to use your PHI, you may do so by completing and signing the revocation letter that you receive with your copy of this Combined Informed Consent/HIPAA Authorization form and providing it to the researcher. If at any time you need another copy of this form, you may ask the Researchers to provide you with one. Once we receive your written revocation of your authorization to use your PHI, we will not make any other use of your PHI or share it with anyone else, except as follows: (a) we will let the study sponsor know that you have revoked your authorization; (b) we will not ask the study sponsor or any other parties to whom we said we would

disclose data to return any data that we provided to it/them before you revoked your authorization; (c) and, even after we receive your revocation, we will still provide the study sponsor and any other parties to whom we stated that we would disclose data with any data that is necessary to preserve the integrity of the research study, and we will provide any governmental or University personnel, departments or committees with any data that they may need in order to comply with/or investigate adverse events or non-compliance with any applicable laws, regulations or University policies.

PHI May be Re-disclosed: If we disclose your PHI to one of the other parties described above, that party might further disclose your PHI to another party. If your PHI is further disclosed, then the information is no longer covered by HIPAA.

Signature and Date: The Researchers will ask you to sign and date this form. A copy of your signed and dated consent/authorization will be placed in your medical record(s).

We will give you a copy of this signed consent form to keep.

If you're willing to volunteer for this research, please sign below.

Subject's Printed Name	Subject's Phone Number
Subject's Signature	Date Time
Person Obtaining Consent	Date Time

Dear Ms. _____

Thank you for agreeing to participate in our study evaluating stereoscopic digital mammography compared to standard digital mammography. Enclosed is a copy of the consent form. Please read it and if you wish to continue participation, sign the form and bring it with you to your screening appointment. If you have any questions, please do not hesitate to call Dr. Carl D'Orsi at 404-778-4446. All the mammograms will be done on a state-of-the-art digital mammography unit at the Breast Imaging Center at Emory located at 1365-B Clifton Road, N.E. If you have been scheduled for screening at our other screening center (1525 Clifton Road, N.E.), disregard that appointment.

Once again, many thanks.

Sincerely

Dr. Carl D'Orsi, Director
Breast Imaging Center
The Emory Clinic
1365-B Clifton Road, NE
Atlanta, GA 30322

Letter of Revocation for Research Study: An Evaluation of Stereoscopic Digital Mammography for Earlier Detection of Breast Cancer and Reduced Rate of Recall.

Dear Dr. D'Orsi:

I want to end my participation in the research study that is named above. In addition to ending my participation I would like to [choose one of the following options]:

Option 1: REVOKE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not participate in the research study, and I revoke my authorization to permit the researchers to collect and use any more information about me. I understand and agree that in certain circumstances the researchers may need to use my information even though I have revoked my authorization, for example, to let me know about any safety concerns, or to make any required reports to governmental regulatory agencies.

Option 2: CONTINUE MY AUTHORIZATION FOR THE RESEARCHERS TO COLLECT AND USE MY INFORMATION:

_____ I will not actively participate in the research study any more, but the researchers may continue to collect and use information from my medical record as needed for the research study, but only for the reasons discussed in the consent form that I signed.

I understand that the researchers will respond to this letter by letting me know that they have received it.

Sincerely,

_____ _____

Signature of Study Participant Date

SDM DATA FORM A1 - STANDARD READING

PATIENT STUDY NUMBER: _____

DATE OF EXAM: _____

DATE OF READING: _____

READER'S INITIALS: _____

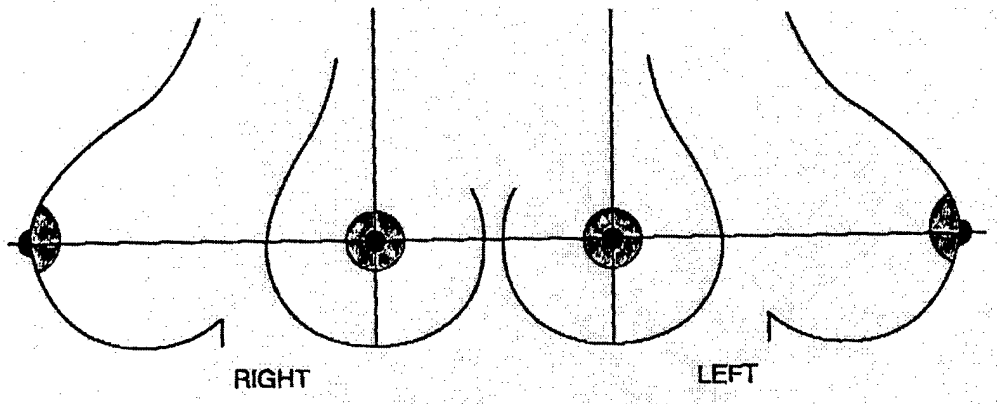
1. Is there a finding(s) which you feel requires recall of the patient?

☐ Yes ☐ No

2. State the number of findings in:

Left Breast	
Right Breast	

3. Mark findings on the picture below using the following codes: M-Mass, F-Focal asymmetry, A-Architectural distortion and C-Calcifications. (Numbers starting from 1 can be appended to the code for more than one finding of the same type).



4. Rate the findings:

Finding code	Rate, on a scale of 0 to 100, that the finding is real.	Rate, on a scale of 0 to 100, that the finding is malignant.

SDM DATA FORM A2 - STEREO – MLO VIEW ALONE

PATIENT STUDY NUMBER: _____

DATE OF EXAM: _____

DATE OF READING: _____

READER'S INITIALS: _____

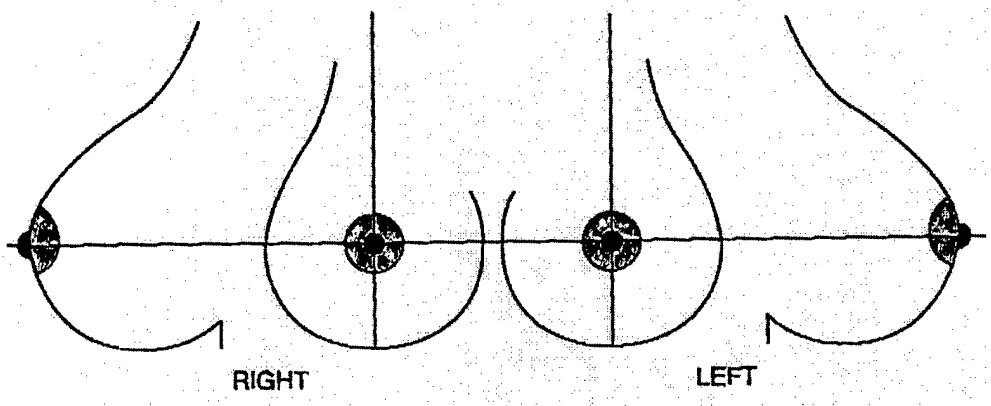
1. Is there a finding(s) which you feel requires recall of the patient?

☐ Yes ☐ No

2. State the number of findings in:

Left Breast	
Right Breast	

3. Mark findings on the picture below using the following codes: M-Mass, F-Focal asymmetry, A-Architectural distortion and C-Calcifications. (Numbers starting from 1 can be appended to the code for more than one finding of the same type).



4. Rate the findings:

Finding code	Rate, on a scale of 0 to 100, that the finding is real.	Rate, on a scale of 0 to 100, that the finding is malignant.

SDM DATA FORM A3 - STEREO – MLO & CC VIEWS

PATIENT STUDY NUMBER: _____

DATE OF EXAM: _____

DATE OF READING: _____

READER'S INITIALS: _____

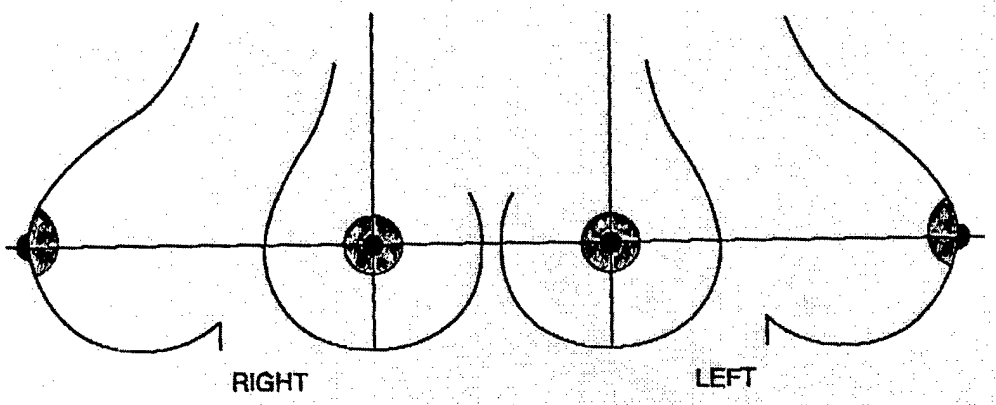
1. Is there a finding(s) which you feel requires recall of the patient?

☐ Yes ☐ No

2. State the number of findings in:

Left Breast	
Right Breast	

3. Mark findings on the picture below using the following codes: M-Mass, F-Focal asymmetry, A-Architectural distortion and C-Calcifications. (Numbers starting from 1 can be appended to the code for more than one finding of the same type).



4. Rate the findings:

Finding code	Rate, on a scale of 0 to 100, that the finding is real.	Rate, on a scale of 0 to 100, that the finding is malignant.

SDM Script
18-months Follow-Up Call

Hello Ms. _____

My name is _____ and I am working on the grant you so graciously agreed to participate in about a year and one-half ago when you had a stereoscopic digital mammography exam. We need some information to complete our data for the grant. This should only take about 5 minutes of your time.

Have you had any additional imaging examinations of your breasts, such as ultrasound, MRI or additional mammograms since the stereo digital mammogram?

What recommendations were given to you regarding those exams?

Have you had a breast biopsy or surgery since the stereo digital mammogram?

What were the results?

Thank you for your time. If you have any questions, please call me or Dr. D'Orsi at 404-778-4446.

SDM DATA FORM B
18 MONTHS – FOLLOW-UP CALL

PATIENT STUDY NUMBER: _____

DATE OF CALL: _____

DATE STUDY DONE: _____

1. Other imaging studies since digital mammogram? ☐ Yes (R L) ☐ No
   (circle one or both breasts)

Ultrasound	☐ Yes (R L)	☐ No
Mammogram	☐ Yes (R L)	☐ No
MRI	☐ Yes (R L)	☐ No
Other	☐ Yes (R L)	☐ No

2. If Yes, recommendation resulting from the exam(s):
   - ☐ Normal screening
   - ☐ Accelerated follow-up
   - ☐ Biopsy

3. Breast biopsy since digital mammogram? ☐ Yes (date) _____ ☐ No

If Yes, continue

4. Type of Biopsy: ☐ Excision ☐ Percutaneous
5. Side of Biopsy: ☐ Right ☐ Left ☐ Bilateral
6. Results of Biopsy: ☐ Benign ☐ Malignant
7. If malignant, treatment:
   - ☐ Lumpectomy/Radiation Therapy
   - ☐ Mastectomy
   - ☐ Lumpectomy only
   - ☐ Chemotherapy

Stereoscopic digital mammography: perceptual and display factors leading to improved early detection of breast cancer

David J. Getty

BBN Technologies, 10 Moulton Street, Cambridge, Massachusetts, 02138, U.S.A.
getty@bbn.com

Abstract. Stereoscopic digital mammography holds the promise of improving the early detection and diagnosis of breast cancer compared to standard planar views. A stereo mammogram provides the radiologist with an in depth view of the breast, in which a subtle lesion is directly seen volumetrically. The increased detection sensitivity from stereo seems to arise from the separation of overlying and underlying normal tissue from the lesion, and also from capabilities provided to the reader to manipulate characteristics of the displayed stereo image. In a recently completed project, stereo mammography was shown to significantly improve diagnostic accuracy and led to detection of a significant number of new lesions in the stereo mammograms *that were not detected in the films.*

1. Stereoscopic versus Planar Digital Mammography

Standard planar mammography is widely regarded as one of the most difficult radiographic exams to interpret. It is often difficult to detect a very subtle lesion because of superimposed overlying and underlying normal tissue that masks its presence. To confirm a lesion as real, a radiologist has to find it in each of two orthogonal views. And constructing a mental image of the three-dimensional structure of a lesion from two orthogonal projections is a difficult task, at best.

Stereoscopic digital mammography holds the promise of significantly reducing these problems. In a stereo mammogram, a radiologist is able to directly view tissue and the internal structure within the breast in depth. With stereo, detection of subtle lesions is improved because overlying and underlying normal tissue, superimposed on the lesion in 2D projections, is separated away from the lesion in depth. With stereo, false alarms are reduced because normal tissue lying at different depths, aligned by chance in a 2D projection, does not superimpose to resemble a focal abnormality.

With stereo, classification accuracy is improved because the stereo mammogram enables a direct perception of a lesion's volumetric shape. Also, by separating the lesion from superimposed tissue, the stereo mammogram can present the critical diagnostic features in a clearer and sharper form. For a cluster of microcalcifications, the volumetric distribution of the elements can be directly appreciated. This is novel information since finding a one-to-one correspondence of many elements in orthogonal 2D projections is essentially impossible.

2. Stereoscopic Image Acquisition and Display

We have been acquiring stereoscopic digital mammograms, illustrated in Fig. 1, on a GE Senographe 2000D with the x-ray source rotated by 6 degrees between exposures while the position of the breast and the digital detector remains fixed, as shown in Fig. 2. The stereo pair of mammographic images is viewed by the radiologist on a stereo display workstation, shown in Fig. 3, while wearing special stereo-viewing glasses made by StereoGraphics,. The two images are presented alternately in rapid succession (at a 120 Hz. refresh rate) on a high-resolution (2300 x 1900 pixel) MegaScan monochrome monitor. The stereo-viewing glasses contain LCD lenses that function as optical shutters. They are synchronized to the display and alternately block each eye's view of the display—effectively routing each image to the appropriate eye. The radiologist's visual system fuses the two images into a single in-depth perceived image of the internal structure of the breast.

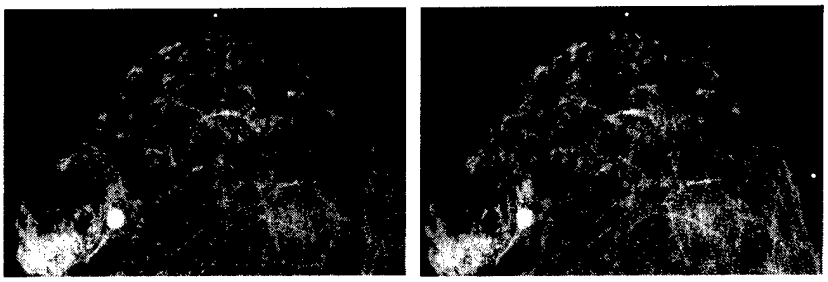


Fig. 1. Stereoscopic pair of digital mammograms, with a benign mass at 8 o'clock. It is possible to fuse these two images into a single image seen in depth by crossing one's eyes.

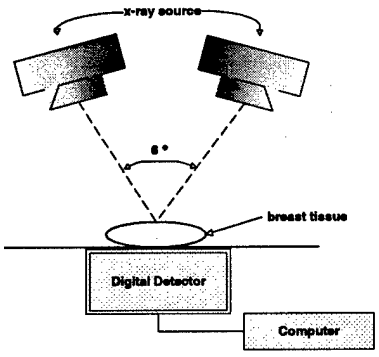


Fig. 2. Stereo mammogram acquisition.

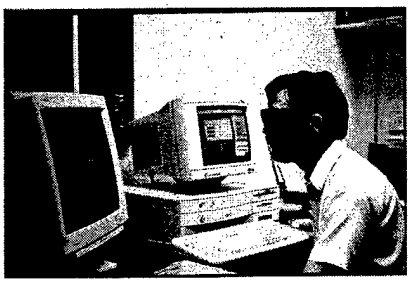


Fig. 3. Stereo display workstation.

Because of their separation, our two eyes have slightly different views of the world. There is sufficient information in these two differing views for the visual system to determine the relative depth of different objects in the visual scene. The perceptual result is a single fused image with objects seen as distributed in depth.

This visual process is called "stereopsis." The basis of stereopsis is the angular horizontal disparity between corresponding points of an object in the two retinal images. When you fixate an object, your eyes rotate, or "converge," to bring the point of fixation onto the fovea of each retina. There is zero retinal disparity in the depth "plane" defined by the point of fixation. A point on an object that lies farther away from you than the fixation point creates images on the two retinas that have "positive" retinal disparity, determined by the angular difference of the corresponding points from the fovea on the two retinas. Similarly, a point that lies closer to you than the fixation point creates retinal images that have "negative" retinal disparity. The magnitude and sign of the retinal disparity are sufficient to determine an object's depth relative to the point of fixation.

In a stereo display, retinal disparity is created by horizontal parallax—the separation of corresponding points in the left- and right-eye images on the display screen. There are three types of parallax, illustrated below in Fig. 4. If a point belonging to an object is displayed at exactly the same position in the left- and right-eye images, then it is said to have "zero parallax." The perceptual effect is that the object is seen to lie at the surface of the display screen.

In the other two cases, a point belonging to an object is displayed at different locations in the left- and right-eye image. If the right-eye point is displaced to the right of the left-eye point, then the object will be perceived to lie behind the screen surface. The larger the separation, the farther the object will be from the screen surface. This case is called "uncrossed" or "positive" parallax.

In the third case, if the right-eye point is displaced to the left of the left-eye point, called "crossed" or "negative" parallax, then the object will be perceived to lie in front of the display surface. Again, the larger the separation, the farther the object will be from the screen surface.

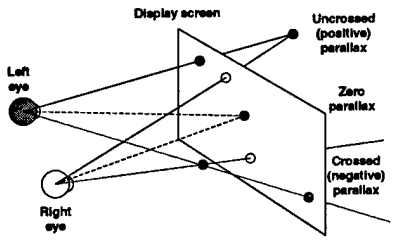


Fig. 4. Three cases of horizontal parallax. Images for the left eye (filled dots) and right eye (open dots) are shown superimposed on the display screen.

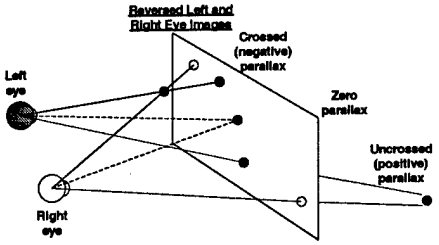


Fig. 5. Inversion of depth resulting from swapping left- and right-eye images. Compare to Fig. 4.

While the stereo point-of-view of the displayed breast tissue is determined by the point-of-view at image acquisition, there are two other aspects of the viewed volume that the user can manipulate. First, one can invert depth by swapping the two images—presenting the left-eye image to the right eye and the right-eye image to the left eye. Consider the two points corresponding to uncrossed parallax in Fig. 4. When we swap the images, as shown in Fig. 5, the filled dot becomes the open dot and vice versa. So now we have crossed parallax and the object will be seen not

behind the screen, but in front of it. Similarly, dots originally displaying crossed parallax will now have uncrossed parallax. Thus, objects originally seen in front of the screen will now be seen behind it, and vice versa. Dots with zero parallax will still have zero parallax, and remain seen at the screen surface. Thus, the effect of swapping images is to invert depth—much like reaching into a glove in a pressurized bio-isolation chamber and pulling it inside out. If, in addition to swapping the two images, one also spins each image 180 degrees about a vertical axis, then the inverted depth image is seen as if one had walked around the object to view it from the backside.

Inverting depth can be important in stereo viewing, especially of stereo mammograms. The visual system is set up to attend much more strongly to objects seen in the foreground, as opposed to the background. By allowing a radiologist to invert depth, tissue originally at the back of the displayed breast volume can be moved to the front of the volume, making it easier to perceive structure there.

A second aspect of the viewed volume that can be manipulated is the location of the displayed volume in depth with respect to the screen surface. If one shifts the right-eye image slightly to the left while holding the left-eye image fixed, as shown in Fig. 6, then the horizontal parallax of all points will be changed in the direction of uncrossed parallax. Points originally with uncrossed parallax will have larger uncrossed parallax, and points with crossed parallax will have decreased crossed parallax. The perceived effect is to shift the entire viewed volume forward in depth, with the amount of shift in depth proportional to the amount of left lateral shift of the right-eye image. Shifting the right-eye image in the other direction, to the right, will shift the viewed volume away from the viewer relative to the screen surface. It is only the amount of relative shift of the two images that matters, so one could just as well make shifts to the left-eye image, or to both.

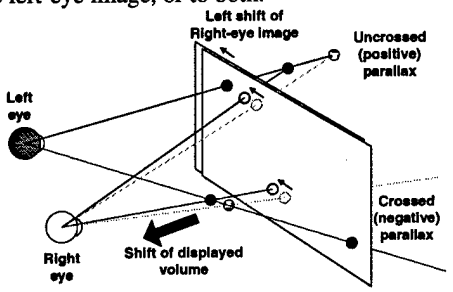


Fig. 6. Shift of the displayed volume towards the viewer with a left shift of the right-eye image.

Control of volume location is useful in that many people initially find it difficult to perceive a displayed volume that begins at the screen surface and comes towards one in space. Usually, they are more comfortable with a displayed volume that starts at the screen surface and goes back into the monitor. It's always possible to achieve this condition by using relative shifts of the two images. On the other hand, with increasing experience, people often come to prefer a displayed volume that comes out into space. As an interesting note, when the stereo image is occupying accessible physical space in front of the screen, one can actually use a pencil to point to an object of interest within the volume that other viewers can see.

3. Evaluation of Stereoscopic Digital Mammography

A project has recently been completed to evaluate the improvement in diagnosis of breast cancer achieved by stereo mammography. Over several years we acquired both standard film and stereo digital mammographic images on a number of women scheduled for biopsy of a suspicious focal breast lesion. We conducted a reading study to determine the diagnostic accuracy achieved by standard film alone compared to standard film read together with the stereo mammogram. A second goal, added as the project progressed, was to obtain preliminary data on the capability of stereo mammography to detect subtle lesions that are not visible in the corresponding film studies.

The reading study was conducted with 5 experienced mammographers individually reading 129 path-proven cases with 137 malignant and benign lesions. The reading of each case was conducted in two successive stages. The reader first examined the full set of film mammograms from the diagnostic study that led to biopsy, rating the probability that the lesion was malignant on a scale of 0 to 100. The reader was then shown the stereo view of the lesion and asked to again rate the probability of malignancy. The stereo image was always a CC view acquired just prior to biopsy. For each case, the reader was also asked to report on any additional lesions seen in either the films or the stereo mammogram, in addition to the known, biopsied lesion.

We conducted an ROC-based analysis of the accuracy of the readers' predictions of malignancy for the two viewing conditions. Diagnostic accuracy, measured by Az (the area under the ROC curve), was .83 when the readers viewed the film study alone, rising to .86 when readers also viewed the stereo mammogram. This is a statistically significant improvement.

Perhaps a more important finding was that readers detected a very significant number of likely new lesions in the stereo mammogram—ones that were not detected in the films. In all, 39 new lesions were reported in the 129 cases, corresponding to 30% of the cases. Of these 39 lesions, 30 were reported as masses, 6 as new calcification clusters, and 3 as architectural distortions. We are still awaiting confirmation of some of these lesions from later mammograms. However, we do have truth now on one subset: masses detected only in the stereo mammogram in association with prior film-detected calcifications. Of 12 such cases, the path report for 11 of the 12 cases reported that the calcifications were located *within a mass*.

4. Conclusions

Stereo mammography, as an adjunct to film, significantly improves classification accuracy of detected lesions. Perhaps of more importance is the finding that stereo mammography appears to be more sensitive than standard film mammography in detecting subtle masses and architectural distortion, enabling mammographers to detect possible lesions that are not visible on standard films. The increased detection sensitivity from stereo seems to arise from the separation of overlying and underlying normal tissue from the lesion, and also from the reader's ability to manipulate characteristics of the displayed image, including inversion of depth and grayscale windowing. Significantly, stereo mammography would be relatively easy to implement on the new digital mammography systems now being developed.