

## Breast Cancer Detection Research

Sam Grant and Peter C. Oleson

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On 4 April 1995, the television networks' evening news programs carried an unusual item. The Acting Director of Central Intelligence, Adm. William O. Studeman, held a press conference at the National Photographic Interpretation Center (NPIC) to address the topic of breast cancer. Also participating were the chairman and vice chairman of the Senate Select Committee on Intelligence (SSCI), Senator Arlen Specter of Pennsylvania and Senator Robert Kerrey of Nebraska, and Dr. Susan Blumenthal, the deputy assistant secretary of Health and Human Services and head of the Women's Health Office of the Public Health Service.

Admiral Studeman announced that the Intelligence Community (IC) had been involved in an effort to identify and promote technologies developed within the IC that had promise in the national fight against breast cancer. He said this effort was to continue with the CIA, National Reconnaissance Office, and Community Management Staff (CMS) each contributing to the effort. A sum of \$375,000 had been identified for this research.

Admiral Studeman commented, however, that "breast cancer research is only one area in which our resources can make a difference. We are breaking down barriers that have kept the talents, expertise, and technical resources of the IC and our industry contractors from being applied to problems that lie beyond the scope of our traditional national security mission." Illustrative of the changed security outlook since the end of the Cold War, Admiral Studeman also

said, "This creative, cooperative work will open the achievements of the IC to the community at large." And he added, "Our work will also benefit from the exchange of ideas."

Senators Specter and Kerrey and Dr. Blumenthal all added their endorsements to the unusual dual use intelligence initiative announced by Admiral Studeman. This effort, however, had started somewhat quietly almost a year before.

### Breast Cancer National Action Plan

The National Cancer Institute (NCI) reported that in 1995 the estimated number of new cases of breast cancer in the United States for women and men would total 182,000. It also estimated that 46,000 Americans would die of breast cancer in 1995. After lung cancer, breast cancer is the second leading cause of death for American women. One in eight American women can expect to be diagnosed with breast cancer during her lifetime. An even higher percentage will have to undergo medical procedures—at considerable emotional and financial cost—because of the limitations in cancer detection technology available today.

In 1994, President Clinton announced the National Action Plan on Breast Cancer, a public/private partnership addressing breast cancer etiology, treatment, and prevention. One goal of the plan is to harness the resources needed to make a significant impact on breast cancer. Much of the government's work is concentrated in

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the NCI, the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) in the Department of Health and Human Services (HHS).

Without a reliable cure, early detection of microcalcifications within the breast is the most important factor in reducing deaths. This is mostly done through mammograms (a procedure using X-rays) and clinical breast examinations. According to the National Institutes of Health (NIH) all women age 50 and over should have an annual mammogram, as this is the population most at risk for breast cancer. In recent years, the percentage of women under 50 also obtaining periodic mammograms has increased significantly.

X-ray mammography, however, has several shortcomings. Its resolution is limited. With current technologies, the smallest microcalcifications that can be detected by this method are approximately 100 microns to 150 microns. Mammograms are typically printed on film and then reviewed by a radiologist on a light box, not dissimilar to an image interpreter's light table. A woman's latest mammogram is difficult for a radiologist to compare to earlier mammograms. Differences in angle, resolution, and a number of other factors complicate the process and make change detection in a woman's breast over time a tricky determination.

With current technology, 20 percent to 30 percent of cancers are not detected with mammograms. Approximately 11 percent of mammograms are classified as non-normal, requiring some type of followup action by the patient, such as a repeat mammogram, needle aspiration, biopsy, or other procedure.

Some of these non-normal determinations are false positives. The NCI estimates that there are five biopsies performed based on suspicious mammograms for every cancer actually found.

While the cost of a standard screening mammogram in the United States ranges from \$80 to \$120 with an average of \$90, experts at the NCI estimate that the "real" costs, including the costs of followup procedures occasioned by a suspicious mammogram, average about \$120. It is estimated that more than \$2 billion is spent each year on breast cancer screening in the United States. Improvements in the technology of mammography and its costs, therefore, have been identified as major goals under the National Action Plan.

#### **Request for Assistance**

In early 1994, Dr. Blumenthal wrote to other elements of the Federal Government inquiring whether they had technologies that might contribute to the initiative against breast cancer. As the head of women's health issues for the government, she had called attention to the need to devote more resources on breast cancer. Members of Congress from both parties had become increasingly focused on the problem. Senator Barbara Mikulski of Maryland, in introducing an initiative in 1991, stated, "If we can build Patriot missiles to intercept Scuds, we can do technology that will intercept

cancer cells." As a member of the Senate Science and Technology Committee, Senator Mikulski often addressed issues of technology and women's health. Dr. Blumenthal, when she joined the Clinton administration, took up the challenge.

In July 1994, the National Information Display Laboratory (NIDL) was invited by CIA's Office of Research and Development (ORD) to prepare a background paper for Dr. Blumenthal describing some of the advanced image-processing techniques that might be applied to the field of mammography. NIDL is a laboratory sponsored by the IC to help leverage advanced commercial and consumer technologies into the government.

DIA digitized some sample mammograms for NIDL experimentation. The experiments were sufficiently interesting that Dr. Blumenthal and an HHS committee of medical experts visited NIDL in September 1994. The image-processing techniques demonstrated to the group during that visit led her to invite NIDL to participate in a public symposium to be held on Capitol Hill the following month. For this symposium, NIDL—with the assistance of CMS and ORD—set up several demonstrations of advanced but unclassified image-processing technologies that were applicable to medical procedures. DCI R. James Woolsey attended the symposium and spoke of the need to apply national resources to such challenges.

#### **Technologies of Interest**

A number of advanced technologies and demonstrations were displayed

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at the October symposium, including searches of high-resolution digital images using various high-resolution displays. Specific technologies covered included experimental high-definition television and head-mounted displays; searching high-resolution digital mammograms; detection of changes in serial mammograms; pattern recognition tools; and 3-D alignments for detecting lesions in magnetic resonance (MR) breast scans.

**Search techniques.** An NPIC objective is to perform most image exploitation tasks in the future using digital soft-copy systems. Research has shown that image-exploitation tasks can be effectively performed on soft-copy workstations, *except* for search tasks. There are diverse opinions as to why image analysts do not like to search on soft-copy systems, including available field of view and human-computer interface issues. The National Exploitation Laboratory (NEL) in NPIC established a testbed project to determine how best to perform search exploitation using soft-copy systems. One goal of this testbed project, conducted at the NIDL, is to transfer the necessary technology and specifications to commercial off-the-shelf vendors to make search-capable soft-copy systems commercially available and therefore less expensive for the government.

A variety of technologies are being experimented with under the testbed program, including high-resolution displays (5 megapixels), high-definition television displays, head-mounted displays, speech-recognition systems, and tactile input devices. For the medical community, NIDL is investigating how the same technologies might be applied to digital mammography.

Analysis of mammograms is often the critical first step in the early detection of breast cancer. With today's technology, a radiologist visually scans a film image and prepares a report. This typically occurs within one or two minutes. The challenge is that a mammogram is a large, high-resolution image, and the small cues that indicate breast cancer are subtle and can be easily overlooked. These cues are most difficult to detect at the most crucial time—when the cancer is in its earliest stages. Innovative tools are needed to assist the radiologist in the early phases of the search process.

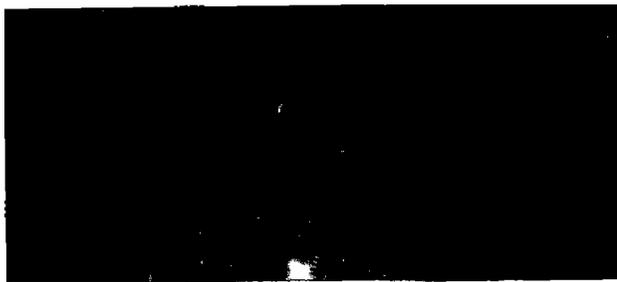
New medical imaging equipment that can produce high-resolution *digital* mammograms will enable radiologists to migrate from film-based mammography to a digital environment, allowing the application of powerful image-processing tools to assist in analysis. Because conventional monitors are low resolution, however, radiologists have to choose between viewing a large area of the X-ray at low resolution or a small area at high resolution. Neither choice is good. The use of current displays to search large images has been likened to viewing the world through a soda straw.

The same new technologies being developed in the NEL's testbed

effort, if applied to digital mammography, could revolutionize the radiologist's ability to analyze large mammogram images and improve the ability to locate cancers at early stages and to evaluate better the results of therapy. For example, with a head-mounted display, the radiologist would be able to view a mammogram from any point of view at high resolution. By turning his head in any direction, he would browse through the X-ray. By moving a "spaceball," he could zoom in and out and "fly" through the X-ray. By using instrumented "gloves," he would overlay one mammogram on another, register and differentiate between older and newer mammograms, and analyze small changes that might be indicative of a cancer. One objective of the NIDL effort is to improve and speed up the technology transfer from development laboratories to operational use by radiologists.

**Change detection in serial mammograms.** Comparison of mammograms taken over a period of time enables a physician to detect change that signals the early start of cancer. In current practice, a physician views two mammograms side by side, mentally matching key features to align and compare the mammograms. Change detection by this method is a challenging task because soft tissue takes on different shapes at different imaging sessions, resulting in misaligned mammograms. When cancer is first detectable by mammogram, important changes may be quite subtle and difficult to detect.

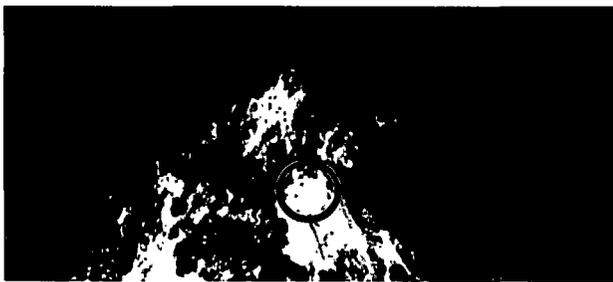
Computer-assisted change detection in mammograms is a dual-use application of change-detection techniques used for interpretation of reconnaissance imagery. At the



**Mammogram 1993**



**Mammogram 1994**



**Difference Image**



**Difference Image Using  
Intelligence Community Technology**

**Figure 1**

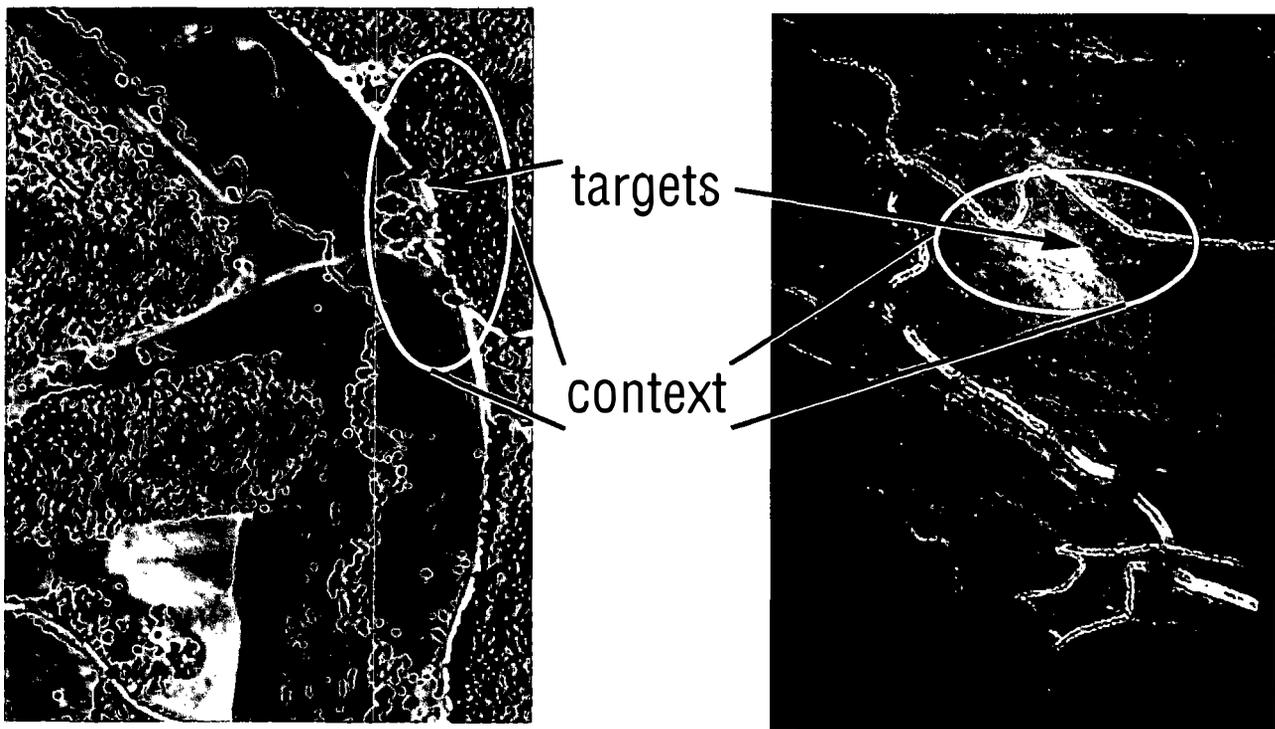
NIDL, techniques are being developed to align disparate aerial images for detection of changes such as new roads and military sites. For surveillance purposes, it can be imprecise, costly, and inefficient to have a human compare each image and search for change; the same holds true for mammogram evaluation. Computer-assisted change detection can provide an invaluable tool by supplementing and improving the physician's ability to detect change.

The first step in automating change detection is precise alignment of mammograms. Once aligned, two mammograms are digitally subtracted, and the physician can

examine the resulting "difference image."

Figure 1 shows two time-separate mammograms and the corresponding difference images before and after alignment. After alignment, regions that have changed appear bright in the difference image, while regions that have not changed appear dark. In the difference images, the suspicious areas have been marked with a red circle. The difference image before alignment is difficult to interpret because true change is obscured by differences due to misalignment. The difference image after alignment shows only those differences due to change, and the suspicious region is readily identified.

**Pattern recognition.** Besides change-detection approaches, pattern detection in imagery is potentially significant for both intelligence and medical purposes. Detecting small targets in reconnaissance imagery is a challenging problem for intelligence analysts because militarily significant targets may occupy only a very small region in a large image. A novel system being developed at the NIDL attacks this problem by using target context. The location of most targets is not random; rather, their position is linked to the surrounding area by some logic. For example, transportation requirements tend to place buildings near roads. (See figure 2.)



*Targets and associated context information for both a reconnaissance image and a mammogram*

Figure 2

Because roads stretch over large areas, they are more readily detectable in imagery and can be used to guide the search for associated small-scale targets, in this case buildings.

The automatic target detection tools being developed at the NIDL exploit this type of contextual information, making the detection scheme more accurate and efficient for the detection of targets of interest. The technique uses an advanced neural network—a computational processor inspired by biology—to learn context automatically through training on a large set of examples.

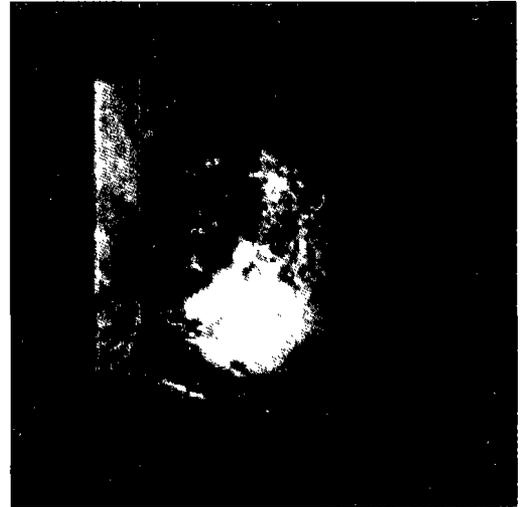
This detection approach can potentially be used for mammogram

screening. For example, microcalcification position often depends on mammalian duct and vasculature location. Integration of this context aids in detection of cancerous tumors. An advantage of the neural network approach is that, after the system has learned the task, the network can be analyzed to discover the specific nature of the underlying context that it recognized as being important. The system therefore can contribute in several ways to current state-of-the-art mammography, acting as both an automatic screening system and a tool physicians can use to uncover subtleties in the breast image that may not be easily detectable via traditional methods.

***Volumetric alignment for 3-D images.*** Besides mammogram X-rays, physicians are increasingly using MR imaging for breast cancer diagnosis. MR techniques use contrast agents that enhance the visibility of cancer in the MR scans. Cancerous areas appear as bright regions in the “post”-MR scans acquired after administration of the contrast agent. Tumors are detected by comparing the “post”-MR with the “pre”-MR scan to look for differences. This process can be facilitated and the accuracy increased if the two scans are subtracted to highlight change. Movement of the patient’s breasts, however, causes the “post”- and “pre”- MR scans to be misaligned. False bright areas that appear in the



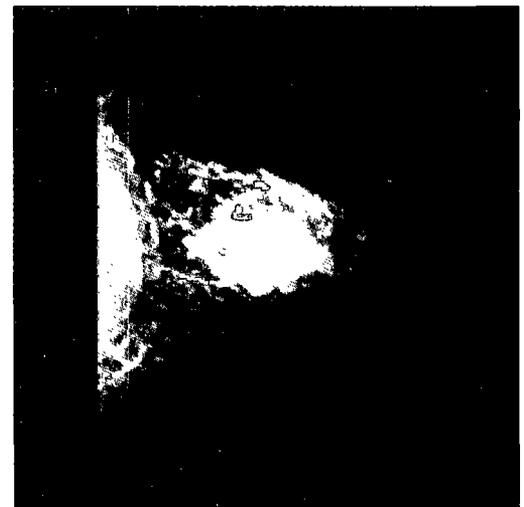
**View 1**



**View 2**



**View 3**



**View 4**

### **Volume Rendering of Difference Volume After Alignment of Pre and Post Breast MRI Data**

**Figure 3**

difference image may cause the physician to label improperly areas affected by the motion as cancerous. Therefore, for precise detection and

localization of a tumor by the doctor, it is necessary to align the “pre”- and “post”- MR data sets. Alignment of the scans is a challenging task for

computer-based techniques because of the nonrigid, flexible nature of breast tissue.

Techniques have been developed in the IC to align multisensor, two-dimensional images. They have been employed to detect change in a scene over time based on images taken from different viewpoints. These two-dimensional techniques are being extended to estimate the non-rigid three-dimensional deformation of the “pre”- MR breast scan to align with the “post”- MR scan. In figure 3, the top row shows a slice from a “pre”- and “post”- MR breast scan. The bottom row shows the difference slices before and after alignment.

Before alignment, the difference image (bottom left) falsely indicates the presence of a change in the upper left corner of the breast. This area is (correctly) not highlighted in the difference image after alignment (bottom right).

### Partnerships

Since the inception of the NIDL, partnering has been a key factor in many of its programs in support of government users. This is also the case with the support being provided to the Office of Women’s Health. Inasmuch as one of the purposes of the government’s effort is to promote the use of advanced technologies for improved cancer detection and treatment, NIDL has partnered with several leading medical centers, foundations, and experts, including Dr. Daniel B. Kopans of Harvard Medical School, a leading figure in radiology; the Murray Foundation; the University of Chicago; and the Robert Wood Johnson Medical School. Commercial partners interested in the technologies and

motivated by future commercial market opportunities also have joined in the effort, including Silicon Graphics, SRI, n-Vision, and NUMONICS Corporation. ORD and the NEL have overseen the effort on behalf of the government.

### NIDL Background

In establishing the NIDL in 1990, the government sought to leverage the resources of the world’s commercial and university leaders in crucial information technologies where developments and advances increasingly were outpacing the government’s efforts. Recognizing the dynamic developments in the commercial marketplace, the objective was to take advantage of commercial developments and replace the old acquisition paradigm that was slow, increasingly behind the state of the art, commercially incompatible, and comparatively expensive.

The NIDL brings together in partnership commercial and academic leaders in advanced display hardware, soft-copy information processing tools, computing, distributed collaboration and communications techniques, and other information technologies. The laboratory focuses on government users’ needs that often are several years in advance of commercial markets. One goal of the NIDL is to foster research in advanced capabilities in a manner that provides incentives for commercialization. When successful, this approach benefits government users in future years with commercially available technology and low-cost

products driven by the commercial marketplace.

The government provides limited core funding for the NIDL. Core funding provides for the essential infrastructure of the laboratory and allows “seed money” for exploration of solutions to users’ operational problems and the applicability of newly emerging technologies. Other commercial and government partners also provide funds and investment for specific projects applicable to their needs, for commercialization of developed technologies, and for research and development of commercially attractive technologies.

The NIDL is hosted by the David Sarnoff Research Center in Princeton, New Jersey, known for its world-leading developments in high-definition digital TV, advanced displays, and computing and soft-copy tools. NIDL is a distributed laboratory, encompassing many industrial and academic partners that are leaders in their respective fields. The goal is to obtain the best solution for government needs regardless of company or entity.

With today’s complex information-technology systems, no one company can satisfy government program offices’ range of requirements that tend to evolve rapidly with advances in information technologies. The NIDL with its partnership approach seeks the best solution for the specific users with specific needs. The laboratory also serves as an agent for advanced research within the academic community.

The NIDL has a sister lab, the National Media Laboratory (NML), which focuses on the critical technologies of mass storage and data archiving. NML is hosted by the 3M Company in St. Paul, Minnesota. NIDL and NML collaborate on a number of information technology-related programs.

The NIDL already had considerable dual-use experience with the medical community when Dr. Blumenthal's request to the IC was received. Working with the NEL, engineers at the NIDL had begun work on a high-brightness, high-resolution monochromatic display that would improve image analysts' abilities to work with digital reconnaissance imagery. One immediate challenge was how to make such an advanced display affordable. At a time when the intelligence budget was facing downsizing, the development of a \$100,000-plus imagery workstation was deemed too costly. At most, the IC might want to procure several thousand units of such a display.

NIDL personnel reasoned that the medical-imaging market, which was just at the onset of using digital technology, might be good leverage for the high-brightness, high-resolution display. Resolution and size requirements for monitors were discussed with radiologists. They were unhappy with the 14-inch-square monitor identified by the reconnaissance imagery analysts, preferring a 14-inch x 17-inch monitor that

equated to the size of a conventional chest X-ray film.

Imagery analysts reacted positively when presented with the option of a slightly larger display; their initial 14-inch-square requirement had been derived from their experience, and the larger format was deemed attractive. The medical-imaging market dwarfs the government image-interpretation market. NIDL analysts were able to converge the requirements of the two communities. This means that the potential market for the high-brightness, high-resolution monitor for the eventual manufacturer of the units will number in the hundreds of thousands. Estimates are that the monitors will cost between \$5,000 and \$10,000, an order-of-magnitude decrease.

### IC Interest

Women's health issues, including the fight against breast cancer, have strong constituencies on Capitol Hill in both parties. The intelligence oversight committees, however, have never really been involved in such topics. Interest in the potential application to breast cancer detection of technologies developed for intelligence purposes peaked in the spring of 1995, when Dr. Barry Horton, the principal deputy assistant secretary of defense (communications, command, control, and intelligence), invited Senator Kerrey to visit the NIDL and review the research plan.

Two weeks later, in a speech from the floor of the Senate, Senator Kerrey challenged the IC to complete rapidly its effort to transfer to the medical community useful tools that would enhance the latter's ability to fight cancer. Senator Kerrey said a deadline of 12 to 18 months would be appropriate. Consequently, the NIDL effort went into high gear. In late April 1995, an HHS working group was formed to oversee the NIDL-managed work and to help plan for clinical trials of the technologies transferred. FDA help has been requested to help guide the way through the FDA-managed medical device approval process. The FDA by law oversees mammography facilities in the United States.

### Conclusion

While work continues at the NIDL on the medical technologies, the IC is mining contractors for more relevant technologies. Given the more liberal security environment of the post-Cold War period, efforts are being made to capture clinicians' requirements, to communicate these to IC vendors, to form additional partnerships, and to obtain funding for promising technologies. From this initial case study in dual-use of intelligence technologies for medical purposes, government managers are planning to establish and institute a process to identify and transfer IC technologies relevant to other sectors of the government and the nation that can use them.