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14. ABSTRACT Breast Cancer remains a leading cause of death for women in the US despite the popularity of mammography as a preventive tool. At diagnosis, many breast cancers are at an advanced stage of disease, even for women undergoing annual screening, resulting in costly and painful follow-up procedures. It has been shown that molecular markers can increase our ability to diagnose early stages tumors. This has been demonstrated by current clinical practices using the CA-125 marker and PSA for the detection of ovarian and prostate cancer, respectively. The purpose of this study is to search for breast cancer biomarkers and evaluate their effectiveness in detecting early stage carcinoma. By combining molecular diagnosis with current imaging analysis of breast tissue, we may further reduce the number of deaths as well as the number of women undergoing surgery due to breast cancer. To date, we have created the infrastructure necessary for our interdisciplinary team of investigators to obtain study samples from a well-characterized population, analyze candidate biomarkers, and efficiently communicate research findings. We are also exploring more efficient and sensitive biotechnology that may better assist our study investigators.					
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Introduction

Although mammography significantly reduces its toll, breast cancer remains a leading cause of cancer mortality in the U.S. Many breast cancers are advanced at the time of diagnosis, even among women participating in screening. The discovery of molecular markers associated with breast cancer potentially increases our ability to diagnose early stage tumors. We are proposing that molecular diagnosis be combined with imaging to enhance our ability to identify breast cancer when it is most treatable, i.e. still localized to the breast. This study will test the hypothesis that use of a breast cancer serum biomarker panel can improve the performance of mammography in early detection of breast cancer. The primary aims of the study are: 1) to validate and refine the ability of candidate biomarkers measurable in blood products to predict disease status; 2) to evaluate panels of serum markers for use as an adjunct to mammography, to detect all breast cancer at a highly curable stage; and 3) to identify the molecular signatures of benign, pre-invasive and invasive breast tissue and explore their associations with serum markers in the panel.

We are focusing on markers that can be measured in serum, as they are generally inexpensive and not subjective in their interpretation. To avoid over-diagnosis, we will perform molecular profiling to identify aggressive subsets of breast cancer that are most likely to be missed by mammography and in need of early detection. Our current list of candidate markers includes circulating antibodies to oncogenic proteins known to be associated with aggressive disease such as Her2/neu, p53, and IGFBP-2; and circulating tumor markers including growth factors associated with angiogenesis such as VEGF, DNA methylation markers, lipid markers, Kallikreins, CD 24, Psoriasin (S100 A7), Prolactin, Mammaglobin, and a panel of 10+ cytokines.

Although some of the markers listed above will be measured in participating laboratories using standard ELISAs, we are also planning to use bead based ELISA style assays on a BioPlex Suspension Array System at the FHCRC (Luminex based technology) to measure all candidate markers using the sample sets included in our approved Statement of Work. Over the last year, Dr. Nathalie Scholler, FHCRC Senior Staff Scientist, and her laboratory technicians have been developing bead based ELISA style assays for breast and ovarian cancer early detection markers. To date, they have been able to develop, optimize, and validate bead based assays for several markers including CA-125, HE4, Mesothelin, CD 24, Prolactin, and Mammaglobin. Dr. Scholler will develop additional bead based assays for known breast markers as part of the COE. In addition to studying the markers listed above, we have been conducting extensive literature searches and seeking new collaborations with investigators who have discovered new targets that have shown to be associated with breast cancer. For example, after hearing Dr. Sarah Sukumar's talk at the Breast Cancer Research Program's Center of Excellence meeting, Dr. Urban approached Dr. Sukumar about investigating the feasibility of developing a bead based ELISA style assay for a targets that was identified through her studies.

Our statistical analysis will use screening history as suggested by McIntosh & Urban¹ to generate what is called a PEB algorithm, for Parametric Empirical Bayes. The PEB approach can be combined with methods developed by McIntosh & Pepe² to permit use of multiple marker panels in longitudinal algorithms. Decisions on screening are made by observing the deviation of a marker from its expected normal behavior, but where PEB methods are used to determine this normal behavior.

At the end of this Center of Excellence study, the expected result is a panel of markers and decision rules for its use clinically to improve the performance of mammography.

Body

As previously reported, our time and effort during the first year of funding was largely spent working with Peter Marshal, DoD Human Subjects Protection Specialist, toward receiving DoD Human Subjects approval on protocols and materials associated with this study. The first protocol was approved on February 2004 and covers activities associated with the Mammography Tumor Registry (MTR). The approved methods within this protocol allow us to receive regular downloads of electronic mammography data from participating radiology facilities. We have developed methods and a linking algorithm to link aggregate mammography data to the Washington State Cancer Registry. This linkage work is done in collaboration with the Fred Hutchinson Center's Cancer Surveillance System (CSS). In aggregate, this data can be used to report cancer outcomes to participating radiologists through a feedback report that summarizes false positive and false negative rates within a given time frame. In addition, passive follow-up for cancer can be achieved at minimal cost by these routine linkages with a high quality cancer registry. Also, for women who have consented to participate in the study, mammography data (assessment codes, follow up recommendations, and breast density) are used in coordination with family history to determine risk of breast cancer (that is, high versus average risk).

Early efforts also included implementation of a "consent to contact about future research studies" process at the Swedish Breast Care Center (SBCC). Funded through another IRB-approved resource, we are building a network of women who are receiving screening mammograms at the Swedish Breast Care Center (SBCC) and who indicate an interest in participating in future research studies. This network is titled the *Women's Cancer Prevention and Detection Network*. All women who undergo mammograms at SBCC are invited to read a brochure describing the Network, and to complete a "Join the Network" form. The "Join the Network" form gives permission for researchers to maintain a woman's name indefinitely in a confidential "registry" and invite her to participate in future research studies. This process assures compliance with HIPAA for all of our studies.

The second protocol, approved in May 2004, is the Fred Hutchinson Center's Clinical Recruitment protocol (DoD file number A 11711.2). This covers clinical/recruitment activities in Seattle where women receiving annual mammograms, a pre-scheduled stereotactic biopsy, or breast related surgery may be approached for an annual blood donation. The Seattle surgical population can also be approached for a blood *and* tissue donation. We have made significant progress in recruitment over the last funding period, which we consider our first "full year" of recruitment. Indeed, we have exceeded our year one accrual goals in several categories. In addition, we continue to make progress in other areas such as enhancements to the Seattle Informatics Management system (SIM) and development of a new interactive project management website that fully supports real-time communication and collaboration across participating COE sites. All of these activities are described in detail below.

The third protocol, recently approved in July 2005, addresses specific recruitment and enrollment activities at Cedars Sinai Medical Center (DoD file number A-11711.2b). This protocol addresses the recruitment of women undergoing a biopsy or surgery for a one time only blood donation *and* tissue donation when feasible. It is important to note that the two clinical protocols have been standardized between recruitment sites as much as possible including use of common data collection instruments with data being entered into a web enabled data entry system. Drs. Beth and Scott Karlan lead study efforts at Cedars-Sinai. In September 2005, the group enrolled and collected specimens on its first study participant and has two additional women who have signed their informed consents with their surgeries to take place within the next few weeks.

Our patient advocate coordinator, Shannon Marsh, continues to play an important role in our COE. Over the last year, Ms. Marsh has worked closely with Dr. Urban and COE staff members to develop and refine study materials. In addition, she has helped with human subject issues such as representing the study at Institutional Review Board (IRB) meetings and explaining why a certain protocol modification will benefit the study participant. Ms. Marsh has also been working on community outreach materials. In July 2005, Ms. Marsh completed the first *Women's Cancer Prevention and Detection* newsletter (Appendix A). This newsletter will be developed and distributed on a quarterly basis and will be sent to all women in the Women's Cancer Prevention and Detection Network, as well as all women participating in our COE. Ms. Marsh attends COE investigator and staff meetings and participates in all conference calls ensuring that the patient perspective is always represented and heard. In October 2005, Ms. Marsh attended the Breast Cancer Research Program's Center of Excellence meeting in Baltimore where she had an opportunity to network with other patient advocates and learn about activities happening at other COE sites. In the future, Ms. Marsh's goal is to form a small core of dedicated patient advocates who can work with COE investigators on our most challenging issues. For example, the patient advocates will help determine how best to use markers clinically and will work to identify and overcome barriers to minority recruitment, particularly recruitment of Asians and African Americans, in the greater Puget Sound area.

Investigators continue to refine a previously developed micro simulation model to explore the impact of DCIS diagnosis on breast cancer mortality and associated over diagnosis. Clinical use of a marker panel is a complex area of study that requires integration of all of the information from marker analyses and molecular profiling as well as economic and health systems considerations. It is critical to understand what we want our biomarker panel to detect. The latter considerations are being studied through a micro simulation model⁴ that was developed through a previously funded DoD grant (DAMD17-94-J-4237). We are currently using the model to investigate the impact of DCIS detection and treatment on breast cancer mortality and associated over diagnosis. Specifically, the model is being used to generate disease histories, including disease onset, progression to diagnosis, and mortality, for a cohort of women in the United States. Mammography screening schedules are superimposed on these disease histories, allowing investigation of the efficacy of early detection of breast cancer, including the in situ stage. Cancer incidence data are combined with data from autopsy studies to estimate the prevalence of breast cancer, including DCIS, in the population. Model parameters are selected to replicate diagnosis patterns reported in published studies.

Using available data for breast cancer growth rates, mammography performance, and stage-specific survival, our analyses suggest that mammography use, including detection of DCIS at current rates, yields a 25% reduction in breast cancer mortality. We estimate that detection of DCIS accounts for over 20% of this reduction (5.6%), that 64% of screen-detected DCIS would remain latent until death due to other causes (over-diagnosis), and that mammography detects only one fifth of the prevalent DCIS. These results are reported in a manuscript titled *Quantifying Risks of Breast Cancer Mortality and Overdiagnosis due to Mammography-diagnosed DCIS* that will be submitted during the next funding period.

Because it took almost 2 years to obtain human subjects approval, the enrollment portion of the study is nearly 2 years behind schedule. As suggested in the review of our year two annual report, we have revised our Statement of Work to reflect our current timeline (see Appendix B). We fully anticipate being able to meet our study goals; however, we will be requesting several no-cost extensions to extend the length of the study. In addition, as suggested in the review of last

year's report, this year's report is organized according to the specific tasks in the approved Statement of Work and contains detailed information on our progress to date.

TASK 1: Recruit women undergoing mammography to donate serial blood samples (Mammography Cohort)

Task 1a: Obtain Consent to Contact and Screening Questionnaire from women undergoing mammography at participating facilities (months 22-60). This task is currently underway. We began approaching women to sign the consent to contact form (that is, a Join the Network Form as described above) in October, 2002. We initiated distribution of the screening questionnaire in September, 2003. Both of these activities were initially conducted through another IRB-approved study. To date, we have collected 1,858 consent to contact forms and sent each participant a screening questionnaire. About 60% of the questionnaires have been returned. Information from these forms is entered into the Seattle Informatics Management system (SIM), and has been used to invite eligible women into the COE study since May 2004 when DoD human subjects approval was obtained.

Task 1b: Obtain mammography data from participating facilities (month 22 and quarterly thereafter). This task is currently underway. We obtained our first electronic data download in December of 2004 from Swedish Medical Center's Mammography Reporting System (MRS). This system is used by all Swedish Medical Center radiology facilities. The first download contained 288,000 electronic mammography exam records. We have also completed a Mammography Data Collection Form (Appendix C) and a data entry screen on SIM that is used to capture specific mammography data on our study participants. We are currently working on identifying the fields in the MRS data structure that correspond to the fields in the SIM mammography data structure. Once this is complete, we will be able to run a linking algorithm to match study participants to their mammography results. This, in turn, will allow us to characterize a woman's risk of breast cancer based on mammography assessment codes and breast density. If a woman does not receive her annual mammograms from a facility that uses MRS, then we have procedures in place to request hard copies of mammography reports directly from her radiology facility. Study staff are trained to abstract data from the reports and enter a woman's information directly into SIM.

We have arranged to receive updated electronic mammography data every 3 months from participating facilities. Collected data is stored on a password-protected network drive, accessible only to authorized personnel who have signed a confidentiality agreement.

Task 1c: Using on-going sampling technique, stratify population by risk, and select a risk-enriched subset of the population for blood donation approach (month 37 and quarterly thereafter). As reported above, we have collected 1,858 Consent to Contact ("join the network") forms and have received completed screening questionnaires from about 60% of these women. If determined eligible, women were sent a COE study invitation packet. To date, we have invited 1,019 women to participate in the study as part of the mammography cohort with 443 or 43% enrolling into the study.

During the next several months, we plan on sending a follow up mailing to the 764 women who have not returned a screening questionnaire. The mailing will include another copy of the screening questionnaire as well as a HIPAA approved mammography release form. A signed mammography release form, will give us permission to access a woman's mammography results even though she has not been invited to participate in the study yet. If a woman returns both then we will be able to use the information on the screener as well as her mammography results to

determine her risk status. A woman will be determined to be at high risk for breast cancer based on several "or" criteria: family history, GAIL Model, breast density, mammography assessment codes, or any prior history of receiving biopsy. As this resource builds, we will begin stratifying women by risk, selecting a high risk enriched subset to join the study and provide an annual blood donation. In addition, all new women who "Join the Network" are sent an initial mailer with the screening questionnaire and mammography results release form. These women will also be included in this sampling technique.

Task 1d: Approach selected women for blood donation (months 25-66). This task is currently underway. We approached our first group of potential study participants who had signed a consent to contact and completed a screening questionnaire in October, 2004. Of the 443 women enrolled in the COE mammography cohort, 55% or 243 women have completed their first blood donation. Specimen Collection Specialists work directly with study participants to schedule their blood donation appointments on or around the day of their annual mammogram.

Task 1e: Send blood donation appointment letters and epidemiologic risk factor questionnaires to consenting women (months 27-72). This task has been underway since December, 2004. As mentioned above, we have sent initial blood donation appointment letters for the first appointment to 443 women, and of these 55% have completed a study blood draw and received the epidemiologic risk factor questionnaire (baseline questionnaire). Some participants have already completed the same baseline questionnaire for a different study (that is, baseline data is already entered into SIM) and are not asked to complete it again for the COE. Study participants also receive a shorter health status questionnaire which provides an update on medical history and asks about factors that might affect their biomarker levels at the time of the draw. We request that study participants complete the health status questionnaire during their study appointment and take the longer baseline questionnaire home to complete and mail back to the study office at a later date.

As of October, 2005 we began sending second appointment blood donation letters to study participants who are due for their annual mammogram this fall. We anticipate second study blood draw appointments to begin in November or December of this year. At each follow-up appointment study participants are asked to complete another health status questionnaire to update information that might change (ex. Personal and family history of cancer).

Task 1f: Receive and data enter questionnaires (months 26-76). To date, 358 baseline questionnaires have been received and 325 have been entered into the SIM database. 291 health status questionnaires have also been received and entered into the SIM database. Quality control data entry is performed on all baseline questionnaires and approximately 10% of the shorter health status questionnaires.

TASK 2: Recruit women undergoing stereotactic biopsy to donate pre-biopsy and serial follow-up blood samples (Biopsy Cohort)

Task 2a: Finalize approach procedures to be used by Swedish Breast Care Center (completed). In September 2001, Dr. Urban received funds from an NCI-Avon "Progress for Patients" award that allowed us to develop and test procedures to recruit and enroll women who were undergoing stereotactic biopsy at the Swedish Breast Care Center (SBCC). Referred to as the "Avon study" women were asked to provide a one-time only pre-biopsy blood donation and complete study questionnaires. To date, we have successfully enrolled 128 women at the Swedish Breast Care Center. We will use the same procedures to recruit and enroll women into the COE Biopsy cohort starting in December 2005. Women enrolled into the COE will be asked to give a blood sample

prior to their biopsy procedure *in addition* to an annual sample at the time of subsequent mammograms.

In order to provide women with continuing opportunities to participate in research, we revised our protocol to be able to recruit women into the COE who had completed "other study participation." Of the 128 Avon biopsy women who have completed their Avon participation, 36% have agreed to participate in the COE study. These women were consented into the mammography cohort and have agreed to give serial (annual) blood donations at the time of their annual screening mammograms and complete a health status update questionnaire at the time of each draw.

Task 2b: Research Nurse or Specimen Collection Specialist attends biopsy appointments to obtain informed consent, collect pre-biopsy blood sample, and provide epidemiologic risk factor questionnaire (months 38-72). As stated above, we are well-positioned to begin our COE biopsy recruitment efforts in December 2005. Learning from our initial recruitment efforts at the SBCC, we realized that less than half of all women who receive stereotactic biopsies actually have a *pre-scheduled* appointment with at least 2 to 3 days lead time. Following the approved COE protocol, this lead time is needed for study staff to contact the woman about study participation giving her at least 24 hours to consider participation prior to signing an informed consent form. In order to reach our accrual goals in a timely manner, we felt we needed to recruit women with pre-scheduled stereotactic biopsies at multiple sites. Therefore, we have revised the protocol to include more than one radiology facility (that is, facilities in addition to the Swedish Breast Care Center) where women who are pre-scheduled for a stereotactic biopsy may be approached about study participation. We will implement the same approach method that is currently being used at the Swedish Breast Care Center at the other sites.

Even though we have not initiated this activity yet as part of the COE, we anticipate that we will be able to realize our accrual goal of 100 women/year, since we will be collaborating with multiple radiology facilities. From previous experience, we have been able to enroll about 40-50 biopsy women/year at a single site.

TASK 3: Recruit women undergoing surgery to donate pre-surgery and follow-up blood samples, and collect tissue on selected breast cancer cases (Surgical cohort).

Task 3a: Work with surgeons' offices to integrate patient approach procedures into the patient care flow. (completed). We have worked closely with participating breast surgeons and clinic staff to design and implement patient approach procedures for recruitment that have proven to be successfully integrated with normal clinic flow. Currently, we have 7 physicians who are referring patients to our study. Our study staff are able to maintain an open dialogue with participating physicians about study progress and procedures by checking in with them and their staff on a daily basis. This creates an environment where physicians and study staff are able to work together to continuously refine and improve our approach procedures.

Participating clinicians are also invited to participate in COE investigator meetings and the annual All-Investigator Workshop where they are able to ask questions and raise any issues or concerns they may have about the study. This year, Dr. David Beatty, Director of the Breast Cancer Program at Swedish Medical Center, will be a featured speaker at the All-Investigator Workshop and at least 3 other surgeons plan to attend.

Task 3b: Pilot patient approach and specimen collection procedures (completed).

Patient approach began in July, 2004. To date we have enrolled 123 participants into the surgical cohort. Of the total number of women who are enrolled in the study, we have successfully collected blood and matched tissue on 35% and blood only on 65%.

Task 3c: Routinely approach selected women undergoing surgery for blood and tissue collection or blood only collection (Months 24-72). This task is currently underway. Following our approved protocol, Swedish Medical Center surgeons help to identify patients that are likely candidates for surgical specimen collection. At the time of the pre-surgical visit, surgeons may introduce study participation to their patients. A Study Flyer is posted in clinic offices to advertise the study. The flyer instructs interested patients to discuss participation with their physician. If the patient is interested, the physician will then obtain verbal consent for study staff to contact the patient either in person or by phone. At this time, the physician distributes a study packet containing a study brochure and a cover letter. If a study staff member is present at the clinic, the physician invites the woman to speak to a study representative directly who can help answer immediate questions or concerns. If the patient chooses, she may also be enrolled at this time (if she meets the eligibility requirements). Otherwise, study staff contact her later by phone to discuss the study in further detail and set up an enrollment appointment. An overview of this complete process is provided in the Surgical Flowchart attached as Appendix D.

Task 4. Recruit women undergoing biopsy or surgery to donate a one-time only pre-surgical blood *and* tissue samples, as feasible, at Cedars Sinai Medical Center.

Task 4a: Finalize approach procedures to be used by Dr. Scott Karlan at Cedars-Sinai Medical Center (completed). This task has been completed and the Cedars-Sinai Clinical and Recruitment protocol received DoD Human Subjects approval in July 2005.

Drs. Scott and Beth Karlan have approached physicians who attend Breast Center conferences, to educate them about available research protocols for interested patients. Recruitment flyers have been posted around the Cedars Sinai campus (specifically, the Saul and Joyce Brandman Breast Center and the Cedars-Sinai Outpatient Surgery Center) and made available to raise patient awareness. This study will also be listed on the Cedars-Sinai web site.

Eligible women will be recruited from patients previously scheduled for breast surgical procedures that involve the removal of some or all of their breast tissue. The patient's surgery will have previously been scheduled as a result of either a benign or malignant condition. Patients will not be scheduled for surgical procedures for the purpose of this study alone. The Principal Investigator, co-investigators, or treating physicians (usually a breast surgeon, occasionally a radiologist or a medical oncologist) will identify potential subjects. The treating physician will make initial contact with potential subjects.

Task 4b: Routinely approach selected women undergoing biopsy for blood and tissue collection (starting in month 37). In October 2005, Drs. Beth and Scott Karlan and their study staff began recruiting and enrolling eligible women into the COE study at Cedars Sinai Medical Center. Following their approved protocol, Cedars will enroll 50 surgical women per year for the next four years, including women with benign lesions and premalignant breast diseases, as well as women with in-situ and invasive carcinoma. Both fresh-frozen tissue and blood samples will be donated by women in the Cedars Sinai cohort (CSC). Blood and tissue donors are recruited from patients previously scheduled for breast surgeries that involve the removal of some or all of their breast tissue. The patient's surgery will have been scheduled previously as a result of either a benign or malignant condition. To date, they have successfully enrolled 1 woman and collected

specimens and questionnaire data. Additionally, two women have signed their informed consents and are awaiting their breast surgeries.

Task 4c: Surgeon to collect benign lesions, atypia, in situ disease, and invasive carcinoma tissue samples. (starting in month 37). As stated above, the Cedars Sinai team has implemented the tissue collection protocol and has collected a tissue sample from 1 study participant to date.

Task 4d: Tissue collected at both FHCRC and Cedars Sinai to be used for molecular profiling work (starting in month 49). Immediately after the surgeon has removed the necessary tissue and the pathologist has taken what is required for pathologic diagnosis, a study Specimen Collection Specialist is permitted to collect specimens from the removed tissue for the purposes of the COE.

All or part of the un-needed tissue is collected, labeled and processed for storage. The tissue is embedded in OCT and/or snap frozen. Tissue collected includes malignant tissue and, if possible, adjacent normal tissue.

We have developed a "Patient Level Clinical Diagnosis" form which uses information that has been abstracted from pathology and other medical reports to characterize a woman based on TNM staging and grade of disease at the time of her diagnosis. A study staff member completes this form with the research nurse conducting quality assurance.

Working closely with Dr. Allen Gown, breast pathologist, we are developing a histopathology (tissue review) form that will allow us to characterize all tissue samples. Once it is implemented, Drs. Gown and Barry at Phenopath Laboratory will complete this form. We are also working on a clinical follow-up form that will capture specific information on treatment. All of this information will be used to determine which tissue samples are most appropriate for future molecular profiling and gene expression work.

Task 5. Blood samples from Mammography and Surgical Cohorts are collected, processed into serum and plasma cryovials, and logged into specimen tracking system (months 26-74). In all blood collections, the Specimen Collection Specialist collects up to 50 ml of whole blood, which is distributed between 3 red top (serum) tubes, 1 purple top (EDTA plasma) tube, and one yellow top (ACD-plasma and lymphocytes) tube.

Tubes are stored at room temperature and processed within 4 hours of receipt. In the event of a late afternoon draw, the ACD tube may not be processed until the following day due to the more involved buffy coat processing procedure. Standard protocols are followed to process specimens into sera and plasma and aliquoted into cryovials uniquely labeled with study specimen ids. Specimens are then logged into the specimen tracking system (STS). Typically, the tubes are processed to obtain:

- up to fifteen 1mL aliquots of serum
- up to five 1mL aliquots of EDTA-Plasma
- two 1.8mL aliquots of ACD-Buffy Coat Cells and
- one ~4mL aliquot of ACD-Plasma

The blood specimens are stored in 1 ml quantities to avoid damaging freeze-thaw cycles. Aliquoted specimens are entered into the specimen tracking system then transported to the study repository for long-term storage and will eventually be delivered to laboratory investigators for future analysis. Blood draw date and time, and time of processing and freezing are recorded in the specimen tracking system, as well.

The table below provides a summary of the number of specimens in the COE repository as of October 12, 2005:

Population	Sub-Population by Histology	Number of Collections	Serum (1mL aliquots)	Plasma (1mL aliquots)	ACD-Plasma (4 mL aliquots)	ACD-Buffy Coat (1.8 mL aliquots)	Frozen Tissue (Viats)	OCT Tissue (Molds)
Mammography		227	3245	1167	224	444		
Surgery	Normal	3	33	13	2	4		
	Benign	4	38	18	4	8		
	In-situ	15	207	71	15	30	5	6
	Invasive	97	1259	439	89	178	177	184
	Carcinoma Unknown	1	14	5	1	2		
	Report Pending	43	482	185	39	78	96	66

Task 6. Revise existing ovarian cancer database to accommodate breast tissue specimens and questionnaire

Task 6a: Analyze current system and prepare preliminary assessment of revised software design specifications (completed). As reported last year, FHCRC programmers have enhanced an existing specimen tracking system (STS) to accommodate specimens and specimen data being collected as part of the COE. Currently tracked for COE specimens are date of blood and/or tissue donation, specimen processing, amount of specimen collected, types of specimen storage, and storage location of specimen aliquot or tissue block. Figure 1 illustrates the tracking of patient specimen donation and figure 2 illustrates the tracking of specimen location.

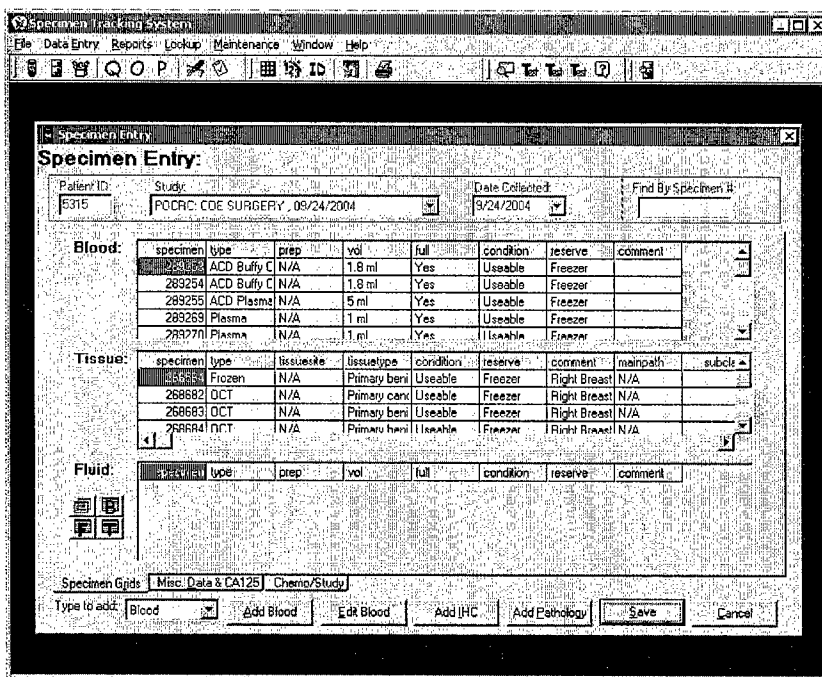


Figure 1 Specimen Tracking System: patient specimen donation

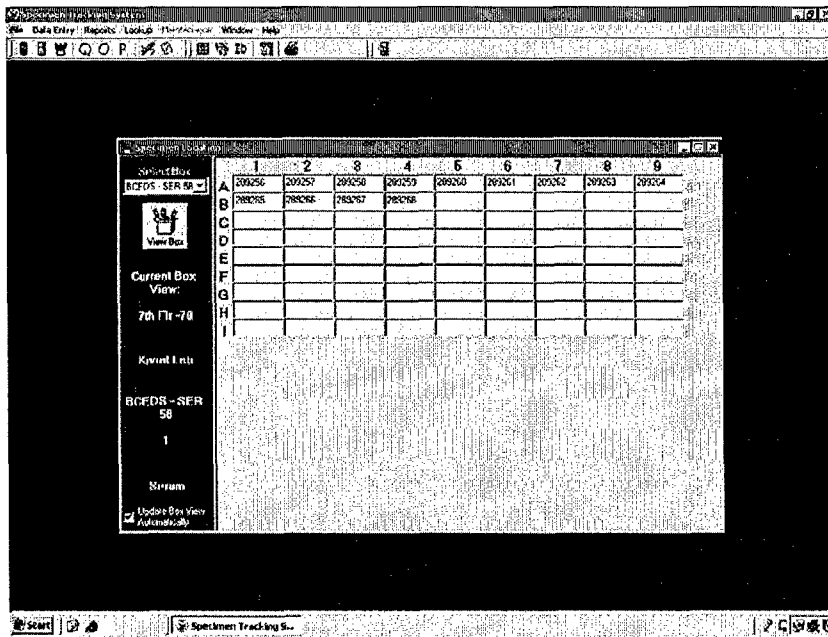


Figure 2 Specimen Tracking System: specimen location

Task 7. Develop an implementation test utilizing proposed software with a middle tier and internet interface for the **Clinical Data Module** (completed).

As previously reported, we have prepared much of the informatics infrastructure required to support the COE study. Infrastructure in place include: web server hardware, web service software, access security, data entry form templates, and referential integrity between database objects. In addition, template reports, data dictionary documentation, and a high-risk algorithm have been developed. Figure 3 shows the current structure of the design in place.

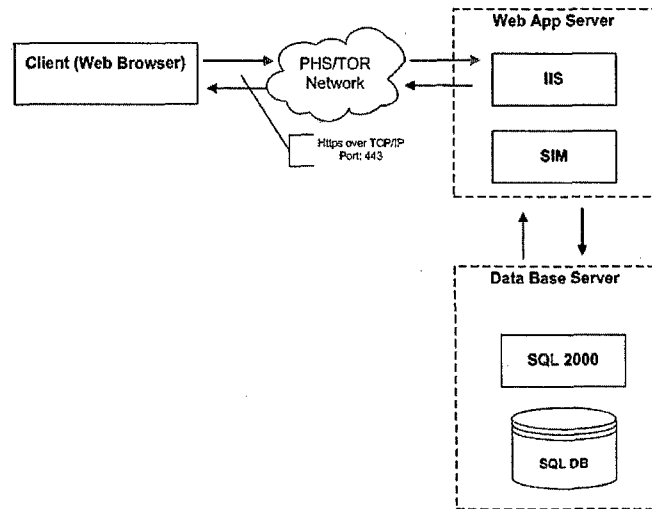


Figure 3. Infrastructure of the Seattle Informatics Management (SIM) System

Security has been implemented in a layered approach. Only persons authenticating to the server that hosts the web service can access the web service. However, the server is set up to accept authentication from a limited set of IP addresses, and from a limited set of client machine operating systems. Once users have authenticated to the host server, they must login to the application. Additionally, users do not have access to the directories where data are stored. Access is limited to the web service, which acts as the proxy to communicate with the database retrieving data for web based requests. Authentication and application login screens are illustrated below in Figure 4.

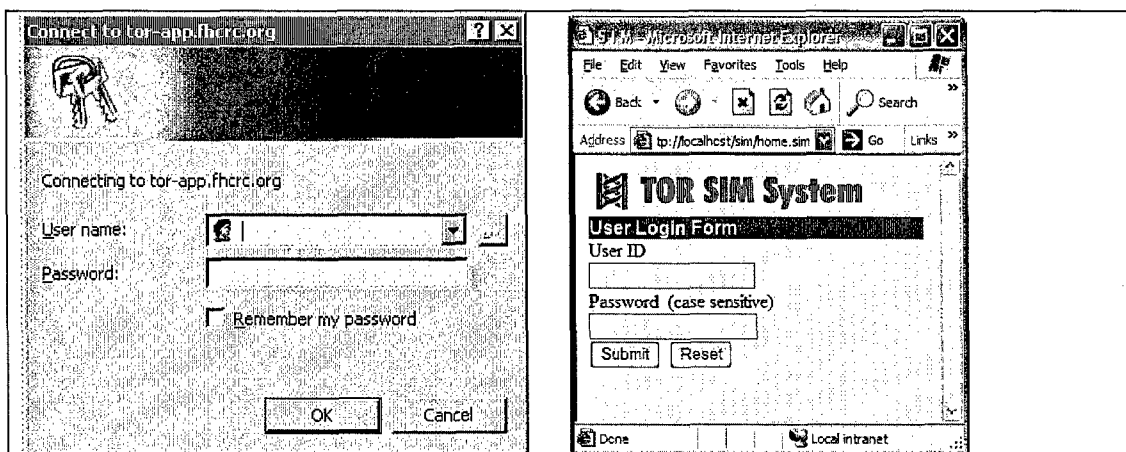


Figure 4. Server Authentication and Application Login

Web based screens for questionnaire data entry have been developed and are currently in use by the two COE recruitment sites: FHCRC and Cedars Sinai. Routines for data validation with each submission of data to the server have been implemented. Every value entered is checked for validity. Any outliers are returned to the data entry specialist for verification before the data are committed to the database. In addition, attempts to re-enter data that have previously been collected, are preempted via referential integrity. Figure 5 minimally illustrates the kinds of validation that data entry specialists see prior to the acceptance of data by the database.

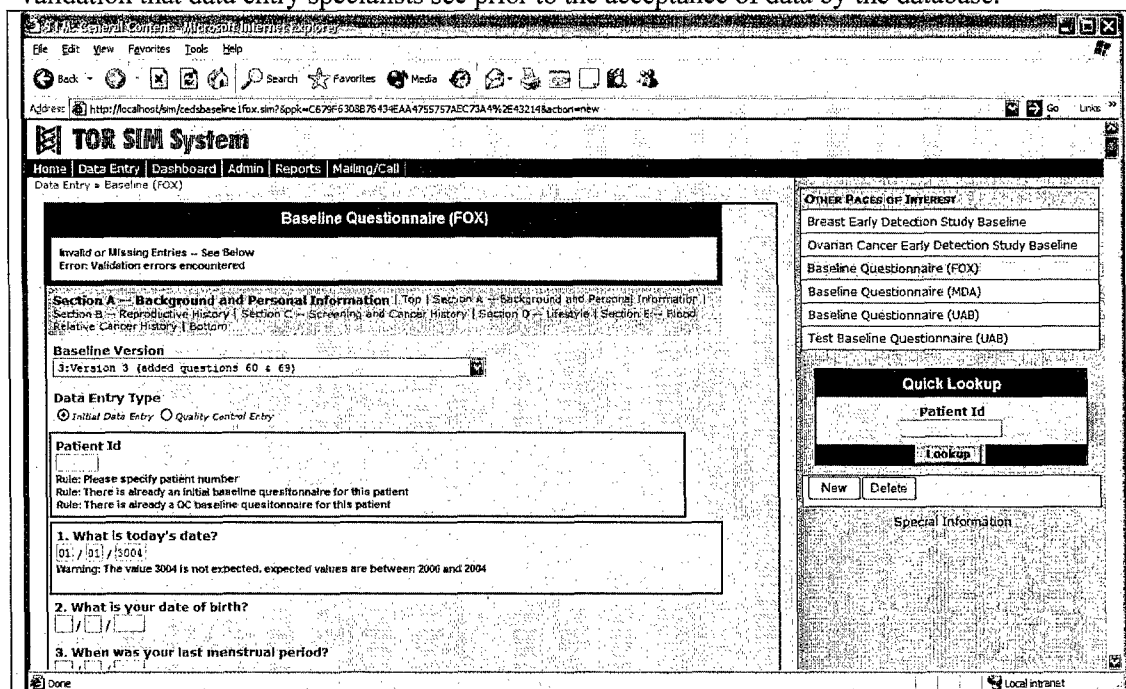


Figure 5. Data Entry Validation

We have also developed a patient tracking module that follows study participants through the various steps of the COE protocol. Figure 6 illustrates patient tracking for a participant in the COE mammography cohort.

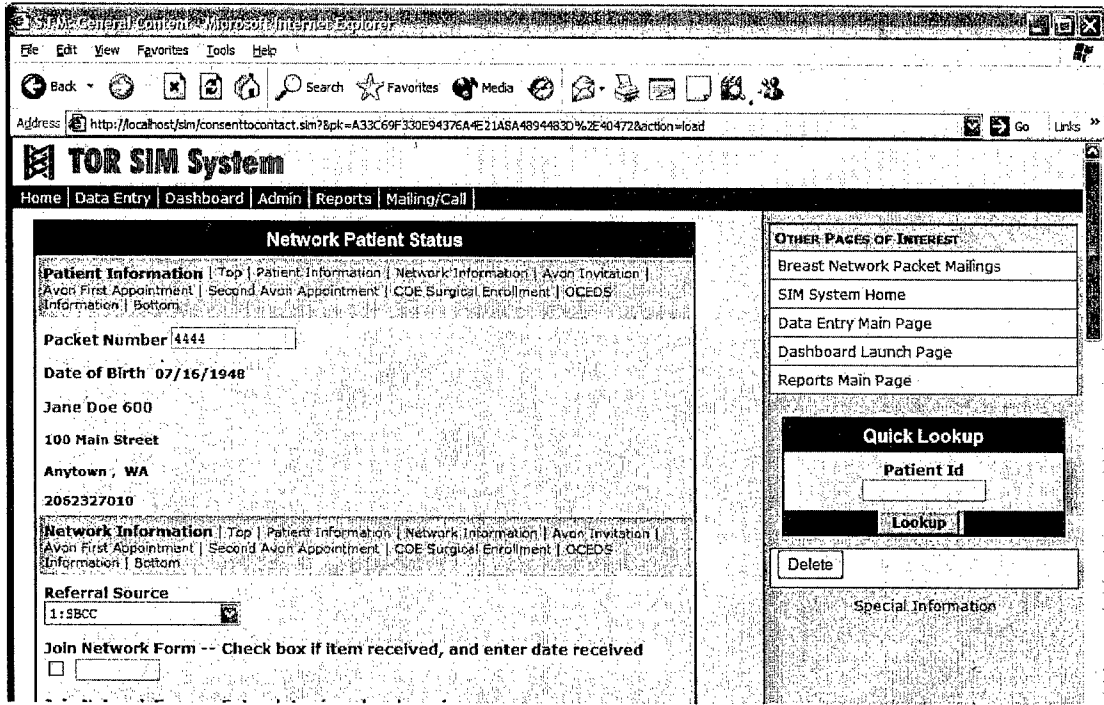


Figure 6 Patient Protocol Status

We have developed an Access database to track information that is collected on our Patient Level Clinical Diagnosis Form. This form provides appropriate information to characterize a woman based on TNM staging and grade of disease at the time of her diagnosis. The Access database acts as our “clinical module” and is linked to SIM, our primary data management system, which in turn is linked to the Specimen Tracking System. (STS). Figure 7 below is an example screen shot of the Access database.

BCEDS Patient Level Clinical Diagnosis

Date Entered: Study Site: Study:
 Packet ID: UPN: Patient DDB: Patient ID Number:
 Form Completed by: Form QC'd by:

Histologic Summary

Check all histologic cell types found

Normal Assessment
 Benign Assessment
 Atypia Assessment
 In-situ Assessment
 Invasive Assessment
 Carcinoma Unknown

Indicate the most severe diagnosis found per report collected

Report 1 Diagnosis:
 Report 2 Diagnosis:
 Report 3 Diagnosis:
 Report 4 Diagnosis:
 Report 5 Diagnosis:

Figure 7 Patient Level Clinical Diagnosis data screen

Finally online reports have been implemented. For example, in place are reports summarizing participants' race, risk status, family history, the data entry completed to date, data entered, and double entry inconsistencies. These are set up to run on a nightly basis and are downloadable by persons authenticating to the server and logging into the SIM system itself.

Task 8. Develop breast specimen tracking database to replicate and enhance the current system's functionality adjusting per information gained in the implementation test (months 40-52).

In order to complete this task, we will focus on replicating the existing specimen tracking database functionality with contemporary database software. Though the existing system will be functional for the foreseeable future, the current software is in danger of becoming obsolete as a data warehouse. Therefore, we will gradually move the specimen tracking functionality to a database platform with more support such as SQL Server or Oracle. During the transition, functionality currently in the existing system will be replicated. Additional functionality and performance enhancements will be added during the transition using the information gained in the first implementation. Currently, additional staff are being recruited to support this work. Once personnel are in place, feasibility and functionality assessments to determine the most efficient way of replicating and then moving functionality to a new database platform will be undertaken. Functionality will move one module at a time with testing to assure that existing functionality is not lost during the transition.

Task 9. Develop collaborative web site

Task 9a: Develop site to support real-time discussion and information sharing among investigators (Months 1-12; new site developed during months 30-32). During the first two years

of the study, we were using a Flex KB knowledge base to support study communication among investigators and staff. A number of resources were posted on the site including the approved study protocol, meeting minutes, presentations, literature reviews, a study organizational chart and contact and background information on each collaborator and study staff member.

This site was recently replaced, however, with a much more user-friendly application built by Dr. Martin McIntosh and his informatics group at the Fred Hutchinson Center named the Comparative Proteomics Laboratory (CPL). Working closely with former Microsoft developers and software engineers, the group is developing proteomics analysis tools that are open source and available for use on a website they have titled Computational Proteomics Analysis System (CPAS). This work is being done as part of a project funded by an NCI subcontract (23XS144A).

One of the features available on CPAS is a wiki based project management tool. COE investigators and staff and have been trained to use this project management and communication tool. Over the last 6 months, staff have developed a study website that is now able to support real-time communication and information sharing among COE investigators and their staff. A username and password are required to access information on this site; however, there are several pages that are open to "guests" that do not contain study sensitive information. The content on CPAS is organized hierarchically into projects and subfolders, much like the file directories on your computer; therefore, users find it easy to navigate through and use. The left side of each CPAS web page displays this tree-like structure as shown below.

The screenshot shows the CPAS website interface. At the top left is the Fred Hutchinson Cancer Research Center logo. The main header includes 'CPAS Computational Proteomics Analysis System' and user options like 'My Account' and 'Logout'. A navigation menu on the left lists various site sections such as 'Home', 'BCEDS', 'Action Item List', 'Advocacy Activities', 'Cedars Sinai', 'COE Manager Call', 'FHRCRC', 'Avon Enrollment', 'Biopsy', 'Mammography', 'COE Enrollment', 'Biopsy', 'Mammography', 'Surgery', 'Leadership Meetings', 'Reports', 'Monthly Clinical Core Staff Meetings', 'MTR', 'Network', 'Specimen Repository', 'Sample Distribution', 'Informatics (SIH)', 'BCEDS Reports', 'Specimen Tracking and Reporting', 'Investigator Meetings', 'COE Investigator Call', and 'Investigator Workshop 2005'. The main content area is divided into several sections: 'Project BCEDS' with a 'Home > BCEDS' link; 'Breast Cancer Early Discovery Study' with a description and a feedback link; 'Enrollment Goals' with a report description; 'Avon proposal goal for study in bold' with a list of patient counts; 'COE at FHRC' with 'Year 1 goals for study in bold' and another list of patient counts; and 'COE at Cedars' with 'Year 1 goals for study in bold' and a list of patient counts. At the bottom right, there are buttons for '<Select Part>' and 'Add Web Part'.

There are several useful features, which support real-time interactive communication among users. First, one is able to post messages on a message board. Once the message is posted, an automatic alert is sent out to other users letting them know a message has posted. Second, one is able to post documents with ease, using simple attachment buttons. These documents can be downloaded by others and re-posted once modified. By the same token, documents can be deleted as needed by using a delete button. The system also serves as an archive with all messages and documents stored in system data files.

Task 9b: Develop extensions that will give investigators ability to query specimen tracking system and download summary reports (Month 32-42). The COE CPAS site is linked to the study's data management system; therefore, investigators are able to access and view data reports as if they were in the SIM system as illustrated by the screen below. We are currently working on developing extensions that will allow investigators to query the COE specimen tracking system and specimen availability via CPAS.

CPAS
Computational Proteomics Analysis System

Project BCEDS
Home > BCEDS > Informatics (SIM) > BCEDS Reports

BCED and COE Reports ... Δ ▽ X

Avon and COE Race Reports [edit content] [edit attachments] [delete] [print]

COE Surgical Reports ... Δ ▽ X

This page has not been created yet.
[create page]

Avon Enrollment Reports ... Δ ▽ X

Click here to access Avon monthly enrollment reports. [edit content] [edit attachments] [delete] [print]

Various BCEDS Reports ... Δ ▽ X

Health Status Error Rates

Health Status: Questionnaires Selected for QC Entry

Health Status Questionnaires Missing Survey Date

Potential Matches between CCRreceived Women and existing TOR Patients

Patient vs ccreceived.xls Discrepancies

Breast Study Enrollments

Avon and COE Race Reports [edit content] [edit attachments] [delete] [print]

Task 9c: Develop web pages for each investigator that are linked to collaborative site (Month 34). We have developed folders on CPAS for each laboratory based investigator. Each investigator will be able to design their own folder and create subfolders suiting their specific needs; however, we will request that investigators use their folders to upload all laboratory results and to view marker results.

Specimen Repository

Sample Distribution

Informatics (SIM)

BCEDS Reports

Specimen Tracking and Reporting

Investigator Meetings

COE Investigator Call

Investigator Workshop 2005

IRB

Kiviat Lab

Mills Lab

TOR Lab

Virtual COE Repository

Reports

Review Committee

Messages Δ ▽ X

[Post New Message] [Email Preferences] [Admin]

COE Investigator Workshop 2005 (1 response) lisozaki@fhcrc.org Sep 14, 2005

SAVE-THE-DATE!
This year's Breast Cancer Center of Excellence Investigator Workshop has been scheduled for **Friday, October 21, 2005 from 9am to 4pm**. The meeting will take place in the Arnold Building (Public Health Sciences building) on the Fred Hutchinson campus. Stay tuned for more information....
[View Thread]

<Select Part> Add Web Part

We have also developed folders to support investigator specific meetings and collaborative activities, such as the quarterly investigator calls and the developing Specimen Review Committee. In addition, we have created a folder that is open to the public to support the upcoming COE investigator workshop on October 21, 2005. All workshop materials are currently posted on this site and are easily accessible by clicking on the following link: <http://proteomics.fhcrc.org/CPAS/Project/BCEDS/Investigator%20Workshop%202005/begin.vie>
w?

Tasks 10-13: Biomarker Development and Evaluation

We anticipate that the first specimen set, called the Assay Refinement/Triage Set (ARTS), will be prepared around month 46, near the end of our fourth year of funding, with biomarker analysis starting around month 47-48. This set will be comprised of 40 cases, 40 controls, and 20 benigns.

Although tasks 10-13 have not been initiated yet, we have completed pre-validation work to test candidate biomarkers using samples provided by Dr. Andrew Godwin at Fox Chase Cancer Center. This work is being conducted as part of the Avon study in collaboration with other funded ovarian SPORE sites. The pre-validation set included 30 controls (13 pre-menopausal and 17 post-menopausal), 30 benigns (13 pre-menopausal and 17 post-menopausal), and 29 cases (12 pre-menopausal and 17 post-menopausal). Nine markers were measured in this sample set with the laboratory investigators blinded to case status. The marker results were analyzed by Drs. Urban and Martin McIntosh and ROC curves for the best single marker and the best marker combination, based on sensitivity at 90% and 95% specificity were developed and are shown below:

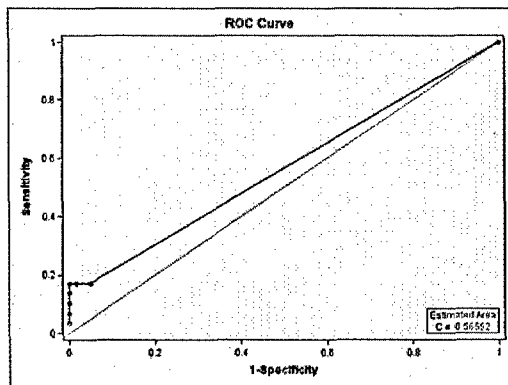


Figure 8a: Best single marker

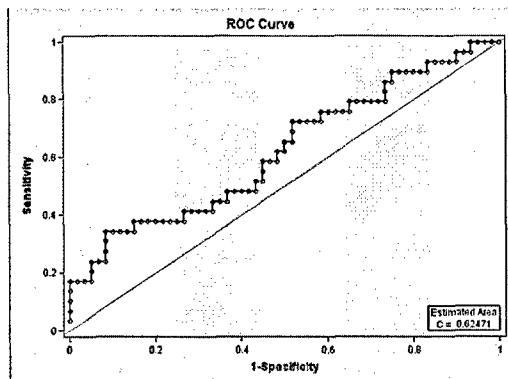


Figure 8b: Best marker combination

The best marker combination, figure 8b, has an area under the curve (AUC) of .625 with sensitivity of 24% at 95% specificity, and 35% at 90% specificity. The best single marker, figure 8a, has 17% sensitivity at both 90% and 95% specificity, and two other markers have sensitivity of 21% at 90% specificity. Our work continues as we try to develop a composite marker that is able to perform better (that is, able to detect cancer better) than any single marker alone. As we face a challenge in identifying a marker panel with high sensitivity and specificity, we are seeking additional collaborators. Several new laboratory investigators may work with us including Dr. Saraswati (Sarah) Sukumar at Johns Hopkins University who received COE funding in 2003 to identify molecular targets involved in breast cancer metastasis. Dr. Sukumar and colleagues have identified several markers that may be applicable to early detection including HOXB-7, HEYL, and SPARC.

Key Research Accomplishments

Year three of this study focused on on-going recruitment and enrollment efforts and continued development and maintenance of the Data Management System and the interactive website on CPAS. The table below summarizes targeted enrollment versus our actual accrual to date. Clearly, we have made significant progress in recruiting women into the mammography and surgical cohorts, exceeding our targeted enrollment in several areas.

	Yr 03 25-36 Target	Yr 03 25-36 Accrual
Mammography Cohort – High Risk	375	71
Mammography Cohort – Average Risk	125	342
Risk Status pending		30
Mammography Cohort – Biopsy	100	0
<i>Subtotal: Mammography Cohort</i>	<i>600</i>	<i>443</i>
SMC Surgical Cohort: Blood and Tissue	25	38
SMC Surgical Cohort: Blood Only+		71
<i>Subtotal: Surgical Cohort</i>	<i>25</i>	<i>109</i>
Cedars Biopsy Cohort: Blood and Tissue	50	1
Total	675	553

The systematic evaluation of biomarkers for early detection requires access to large numbers of high-quality blood samples. Cases and disease-free women are needed to evaluate the markers' ability to distinguish malignant from healthy individuals. In cases, it is critical that blood samples are obtained prior to treatment of any kind, including surgery, because treatment is likely to affect marker levels. Serial specimens obtained from healthy women are needed to evaluate the variance in marker levels within individual women over time to establish criteria for marker positivity. Specimens from women representing the range of diagnoses (histology, grade, stage) are needed to assure the marker panel is sensitive to all disease types. Blood samples must be collected, processed and stored identically, as some assays are sensitive to these parameters.

We are addressing all of these challenges as we build a specimen resource from a well-characterized population with associated demographic and risk factor information, mammography findings and follow-up data on clinical treatment and cancer outcomes. Both COE recruitment sites are following a standardized specimen collection, processing, and storage protocol to

minimize variability among specimens. This resource will support the work of our COE investigators as we begin to evaluate our candidate markers. In addition, it will be made available to outside investigators conducting promising early detection breast cancer research. Following the model that was established by Dr. Urban's ovarian SPORE grant, investigators will be able to request use of specimens in the COE repository through a well-tested and thorough specimen request and review process. All specimen requests will be evaluated by a COE Specimen Review Committee led by Drs. Urban and Garnet Anderson. This committee will review "initially promising" data by outside investigators to determine whether or not their study merits access to the COE samples. If an investigator is given permission to access samples, then he/she must agree to several conditions including providing data back to COE statisticians for analysis and acknowledgement of the study in all manuscripts and presentations that use data obtained from use of specimens. A summary of the COE repository can be referenced on page 11 of this report.

Reportable Outcomes

A web-based Seattle Informatics Management System (SIM) has been developed that is used to collect and organize all study data.

As mentioned above, CPAS is open source and is free to download at:
<http://cpas.fhrc.org>

Conclusions

No research conclusions are available at this time.

References

1. Generating Longitudinal Screening Algorithms Using Novel Biomarkers for Disease; McIntosh M, Urban N, Karlan B. *Cancer Epidemiology, Biomarkers, and Prevention*. 2002;11:159-166.
2. Combining several screening tests: optimality of the risk score; McIntosh MW and Pepe MS; *Biometrics*; 58(3): 657-64; September 2002.

Appendices

- | | |
|-------------------|---|
| Appendix A | <i>Women's Cancer Prevention and Detection</i> newsletter |
| Appendix B | Statement of Work with revised timeline |
| Appendix C | Mammography Data Collection Form |
| Appendix D | Surgical Flowchart |

NEWS BULLETIN

Summer 2005

Thank You to Our Participants!

Welcome to the first publication of the Women's Cancer Prevention and Detection Network newsletter. We thank you for your willingness to participate in research studies focused on finding better ways to prevent, detect, and treat cancers affecting women. It is only with your assistance that our research team can help reduce the pain and suffering caused by cancer.

We are excited that several studies involving our network participants are now underway. The Breast Cancer Early Discovery Study (BCEDS) is an exploration of biomarkers that may be associated with early breast cancer. Biomarkers are proteins and other substances found in the tissue, blood, or other body fluids of individuals with cancer or other diseases. An increase or a change in levels of certain biomarkers may suggest the presence of some types of cancer. Biomarkers you may have heard of include CA 125 (ovarian cancer) and PSA (prostate cancer). The goal of the Breast Cancer Early Discovery Study is to identify a panel of biomarkers that can be used by clinicians to detect breast cancer early in the disease process. If successful, we will develop a simple blood test that can be used with mammography to find breast cancer early while it is still confined to the breast and is curable.

In addition, biomarkers can provide beneficial information for patients already diagnosed with cancer. Biomarkers indicating that a cancer is aggressive allow doctors to more accurately predict a patient's outcome and to select the best course of therapy. For example, women with HER-2/neu positive breast cancer can usually be treated successfully with Herceptin. By measuring a patient's level of certain biomarkers before and during treatment, doctors can determine if a treatment is working and modify a patient's therapy quickly if necessary. Biomarkers can also be used to detect the very earliest signs of recurrence, allowing doctors to provide additional treatment well before the cancer becomes advanced.

The Ovarian Cancer Early Detection Study (OCEDS) is another ongoing study that will help determine if CA125 and other blood tests and ovarian ultrasounds can improve our ability to detect ovarian cancer early, when it is most curable. Women whose family history indicates they may be at increased risk for developing ovarian cancer are eligible for this study. If you have not yet been contacted to participate in either of these studies, your contact information remains in our network database so that you can be told about these as well as future research opportunities.



Nicole Urban, Sc.D.,
Principal Investigator

It is our hope that this newsletter will provide you valuable information on issues relating to the prevention and detection of women's cancers. If you have any suggestions about future topics, please contact Shannon Marsh at 206-667-4587 or email smarsh@fhcrc.org with any suggestions.

Thank you!

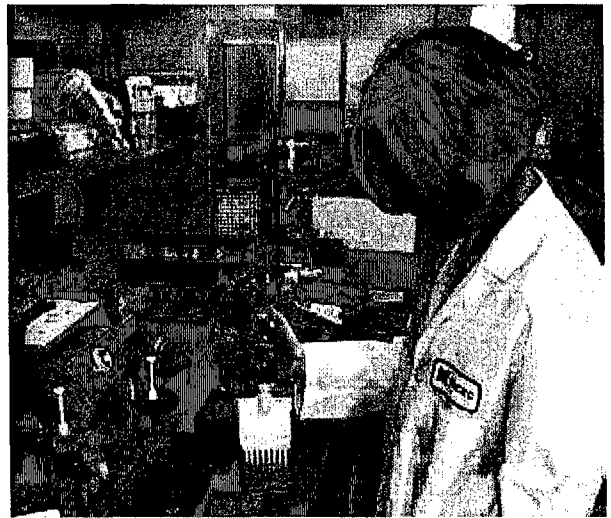
Nicole Urban, ScD
Principal Investigator

The Patient's Voice Shapes the Direction of Our Research Studies

Investigators with the Women's Cancer Prevention and Detection Network pay close attention to the patient's voice when implementing their research projects. Dr. Urban has integrated the patient's perspective into her research studies for many years. Volunteer breast and ovarian cancer patient advocates are often asked to review study protocols, informed consent forms, and educational materials. Patient advocate participation helps to ensure that study procedures are sensitive to the needs of the potential participant and study materials are understandable to the community. In 2001, Sheryl Eisenbarth was hired to bring the patient's perspective to Dr. Urban's ovarian cancer research studies. Sheryl participated in the development and implementation of recruitment and study materials, ensured that patient's needs were addressed in designing study protocols, and helped identify and address barriers to communication among scientists, clinicians, and consumers. Sheryl's involvement and significant contributions to the research program paved the way for Shannon Marsh to be hired in the spring of 2004. Every aspect of Shannon's life has been touched by cancer – as survivor, caregiver, family member, and advocate. As Shannon explained: "It is so encouraging to participate in research discussions and strategic planning meetings and realize that the patient's perspective is valued. There really is a team approach here with the goal of bridging the gap between research and the community."



Shannon Marsh (sitting) planning a patient advocacy meeting with (standing from left to right) Kristi Schurman, Lisa Isozaki, and Susan Dearborn



Pictured above is Meghan Crawford, FHCRC Research Technician, who is conducting an experiment to measure CA125 and HE4 levels in serum samples that are donated by study participants.

Improving the Diagnosis of Ovarian Cancer

A team of Seattle researchers, including the Fred Hutchinson Cancer Research Center scientists, has identified a protein that could improve diagnosis of ovarian cancer, a disease that often goes undetected until it is advanced and difficult to cure. Researchers found that a protein known as HE4 was more effective at distinguishing true cancers from benign ovarian disease than the only other commercially available test, which detects the presence of a protein called CA125.

HE4 is a protein that is secreted by ovarian-cancer cells into the bloodstream. Center researchers Drs. Nicole Urban and Martin McIntosh and colleagues at the Pacific Northwest Research Institute found that the HE4 test successfully identified cancer in 30 of 37 blood-serum samples from women known to have the disease. The CA125 test identified 29 cases. When used together, both biomarkers detected 33 of the 37 cancer cases. However, the number of women with benign ovarian disease who have elevated levels of HE4 is far smaller than with CA125. This indicates that the HE4 test yields fewer false-positive diagnoses.

"If the HE4 biomarker performs well in larger studies, HE4 could become a cancer-screening test that reduces the number of needless surgeries performed as a result of false-positive diagnoses," said Urban, who directs the Pacific Ovarian Cancer Research Consortium.

Recipe for Summer Cooking

Candice Bergen's Salmon Burgers

Makes 4 servings

- 1 1/2 pounds boneless, skinless salmon fillet
- 1/4 cup chopped shallots
- 2 teaspoons chopped fresh dill
- 1 tablespoon fresh lemon juice
- 2 tablespoons nonfat cottage cheese
- 2 egg yolks
- 3/4 teaspoon salt
- 1/4 teaspoon black pepper
- Olive oil



Yogurt Dill Sauce

Makes 3/4 cup

- 1/2 cup nonfat yogurt
- 1 tablespoon lemon juice
- 2 teaspoons minced garlic
- 1/2 teaspoon salt
- 1/4 teaspoon black pepper
- 1 tablespoon chopped fresh dill
- 1/4 cup grated, and squeezed dry, English cucumber

1. Finely chop the salmon, or cut into chunks, then pulse in food processor until finely chopped (do not purée).
2. Combine salmon with remaining ingredients except oil. Mix well, then shape into 4 patties, 1/2 to 3/4 inch thick.
3. Brush a nonstick frying pan with olive oil. Fry the salmon cakes over medium-high heat, turning so that they are crisp and golden on the outside but medium-rare on the inside, about 2 1/2 to 3 minutes per side.
4. Serve with Yogurt Dill Sauce. To make the Yogurt Dill Sauce, mix the yogurt, lemon juice, garlic, salt, and pepper. Stir in dill and cucumber.
5. Refrigerate, covered, until ready to serve.

Recipe taken from *Star Palate*, co-authored by Tami Agassi and Cathy Casey, published by Documentary Media. *Star Palate* is available at major booksellers and at Amazon.com. All proceeds will benefit the Marsha Rivkin Center for Ovarian Cancer Research and The Breast Cancer Research Foundation.

Toolbox

To find out more information about women's cancers, contact:

- **1-800-4CANCER**
- www.cancer.gov—National Cancer Institute
- www.fhcr.org—Fred Hutchinson Cancer Research Center
- www.pocrc.org—Pacific Ovarian Cancer Research Consortium
- www.cancer.org—American Cancer Society
- www.cancer.org—CancerCare, Inc.
- www.facingourrisk.org—FORCE

Contact Us

Are you moving? Do you have any questions about our research studies or suggestions for articles or features to improve our newsletter? Please call Shannon at 206-667-4587 or email at smarsh@fhcr.org to keep us updated or to request information at any time. We welcome your feedback!

Upcoming Events

Danskin Triathlon. August 21, 2005, 7 am at Genesee Park. This triathlon supports the Breast Cancer Research Foundation. For more information, contact **800-304-1555** or go to www.seattledanskintri.info.

POCRC Advocates Science Seminar. August 29, 2005, 11:00 am at Fred Hutchinson Cancer Research Center. These bi-monthly seminars address issues relating to ovarian cancer research. For more information, contact Shannon Marsh at **206-667-4587**.

Reebok Women's Triathlon. September 10 and 11 in Federal Way. This event benefits the Ovarian Cancer Research Fund. Find out more at www.reebokwomenstriathlon.com.

8th Annual Take a Hike, Bike or Roll. September 18, 2005, 8:30 am at Redhook Brewery in Woodinville. Join the Expedition Inspiration team of breast cancer survivors, who not only climb mountains, but who move them! The mission is to raise money to fight breast cancer by supporting cutting-edge research at the UW Medical Center Breast Care and Cancer Research Center. For more information or to register, please go to www.eitakeahike.org or call **208-726-6456**.

International Cancer Cup Dragon Boat Festival. September 4, 2005. This festival is sponsored by Team Survivor Northwest and will be held at Newcastle Beach Park in Bellevue. Register at www.teamsurvivornw.org or call **206-732-8350**.

Walk for Hope. October 2, 2005. Help raise money to fight against breast cancer by participating in either a 5k run or walk. There is also a 1k Kid's Stroll in the Park and post event activities for the whole family. The event will take place on the shores of Lake Washington at Magnuson Park in Seattle beginning at 9:00 am. You can register as an individual or as a team at www.walk4hope.org/seattle.

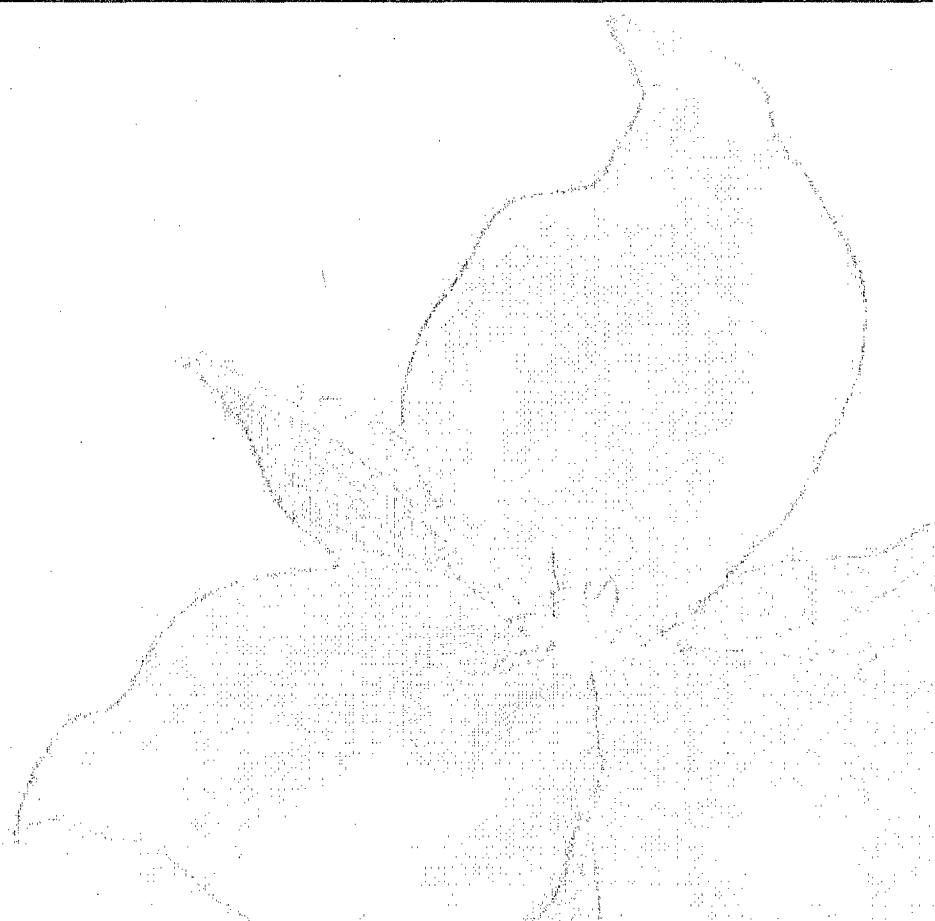
Macy's Fashion Show. October 15, 2005. Breast Cancer Survivor Fashion Show featuring and honoring breast cancer survivors to benefit breast cancer causes, at the downtown Macy's store. For more information, contact Ann McKenzie at **206-506-7556**.

September is Ovarian Cancer Awareness Month.

October is Breast Cancer Awareness Month.

Women's Cancer Prevention and Detection Network

1100 Fairview Avenue N., M2-B230
Seattle, Washington 98109



Statement of Work
Center for Evaluating Biomarkers for Early Detection of Breast Cancer

Clinical

- Task 1. Recruit women undergoing mammography to donate serial blood samples. (n=500)
- a. Obtain Consent to Contact and Screening Questionnaire from women undergoing mammography at Swedish Breast Care Center. (Months 22-60)
 - b. Obtain mammography data from Swedish Breast Care Center (Month 22 and quarterly thereafter)
 - c. Using on-going sampling technique, stratify population by risk, and select a risk-enriched subset of the population for blood donation approach. (Month 37 and monthly thereafter).
 - d. Approach selected women for blood donation. (Months 25-66)
 - e. Send mammogram reminder letters, blood collection packets, and epidemiologic risk factor questionnaires to consenting women. (Months 26-72)
 - f. Receive and data enter epidemiologic risk factor questionnaires. (Months 26-76)
- Task 2. Recruit women undergoing stereotactic biopsy to donate pre-biopsy and serial follow-up blood samples. (n=400)
- a. Finalize approach procedures to be used by participating radiology facilities. (Months 10-20)
 - b. Research Nurse or Specimen Collection Specialist attends biopsy appointments to obtain informed consent, collect pre-biopsy blood sample, and administer epidemiologic risk factor questionnaire. (Months 38-72)
- Task 3. Recruit women undergoing surgery to donate pre-surgery and follow-up blood samples, and collect tissue on selected breast cancer cases. (n=600; 200/yr in Years 2-4; 50/yr to donate tissue)
- a. Work with surgeons' offices to integrate patient approach procedures into the patient care flow. (Months 1-20)
 - b. Pilot patient approach and specimen collection procedures (Months 20-24)
 - c. Routinely approach selected women (Surgical Cohort) undergoing surgery for blood and tissue collection (Months 24-72)
- Task 4. Recruit women undergoing biopsy to donate a pre-surgery sample, and collect tissue from core biopsy (n=200)
- a. Finalize human subjects and approach procedures to be used by Dr. Scott Karlan at Cedars-Sinai Medical Center (Months 12-35)
 - b. Routinely approach selected women undergoing biopsy for blood and tissue collection (Months 36-72)
 - c. Surgeon to collect benign lesions, hyperplasia, in situ disease, and invasive carcinoma tissue samples. (Months 36-72)
 - d. Tissue to be used for molecular profiling work (Months 49-72)
- Task 5. Blood samples from Mammography and Surgical Cohorts are collected, processed into serum and plasma cryovials, and logged into specimen tracking system. (Months 24-72)

Informatics and Database Management

- Task 6. Revise existing ovarian cancer database to accommodate breast tissue specimens and questionnaire
- a. Analyze current system and prepare preliminary assessment of revised software design specifications (Months 1-24)

- Task 7. Develop an implementation test utilizing proposed software with a middle tier and internet interface for the Clinical Data Module.
- List module features via meetings with persons who will use the module. (Months 1-16)
 - Develop interfaces, get feedback from users and revise to better meet project needs. (Month 13-40)
- Task 8. Develop breast specimen tracking database to replicate and enhance the current system's functionality adjusting per information gained in the implementation test.
- Create and review with key project personnel list of information to be captured by the system. (ongoing)
 - Roll existing data into the new structure. (Month 46-48)
 - Develop interface and port legacy data to a web based interface. (Month 48-54)
- Task 9. Collaborative web site (new site has been developed and has replaced original Flex KB site)
- Re-design study website to better support real-time discussion and information sharing among investigators and staff (Months 26- 34 with ongoing maintenance and updates throughout project period)
 - Develop extensions (links) that will give investigators ability to query patient and specimen tracking systems and download summary reports (Months 26-34 with ongoing updates and maintenance)
 - Develop new web pages for each investigator that are linked to collaborative site. (Month 36 with ongoing updates and maintenance)

Biomarker Development and Evaluation

- Task 10. Prepare and analyze the Assay Refinement/Triage Set (ARTS)
- Provide 100 blinded samples from a set of 100 women (40 cases, 40 controls, and 20 benigns) to Drs. Kiviat, Mills, Mann, King, and Scholler (Month 46-47)
 - Preliminary assay measurement data to Dr. McIntosh for statistical evaluation (Month 47-48)
 - Unblind samples; laboratory scientists continue assay refinement (on-going process starting around month 48)
- Task 11. Prepare and analyze Panel Development Set (PDS)
- Provide blinded samples from a set of 500 women (200 cases, 200 controls, and 100 benigns) to Drs. Kiviat, Mills, Mann, King and Scholler. (Month 55-56)
 - Laboratory scientists to send data to biomarker validation team (Months 57-60)
 - Laboratory scientists to receive unblinded information (Month 60)
- Task 12. Conduct statistical work to evaluate candidate biomarkers.
- Establish cut offs for normals (Month 61-63)
 - Assess single marker sensitivity and specificity for candidate biomarkers. (Months 61-63)
 - Examine stability of markers over time within and between subjects (Months 61-72)
 - Using augmented logistic regression, estimate optimal combinations of markers in a longitudinal setting. (Months 61-72)
 - Use ROC curves to evaluate the contribution of markers to mammography. (Months 61-72)
 - Provide feedback to laboratory scientists via website each step of the way (starting around month 47)

Task 13. Prepare and analyze Panel Validation Set (PVS)

- a. FHCRC Laboratory Technician to conduct biomarker assays on blinded samples from 500 women in the validation set. (Months 73-78)
- b. Blinded samples given to laboratory scientists to continue refinement of new assays. (Months 73-78)
- c. Data to Dr. McIntosh to validate the ability of the marker panel to discriminate breast cancer from non-cancerous conditions (Month 78-80)
- d. Biomarker validation team to evaluate the improvement in performance attributable to marker panel (Months 78-81)
- e. Prepare reports and manuscripts describing performance of marker panel. (Months 78-84)

BCEDS Mammography Data Collection Form: Version 1

REQUIRED EXAM INFORMATION (To be abstracted by study personnel at each site) Patient ID _____

1. Date of examination
 ____ / ____ / ____ (mm/dd/yyyy)
2. Indication for examination
 (Check one)
- ₀ Screening (asymptomatic)
₁ Diagnostic (additional evaluation of recent abnormal screening mammogram)
₂ Diagnostic (short interval follow-up)
₃ Diagnostic (evaluation of a breast problem)
₈ Other: _____ (core biopsy or other non-imaging)
3. Assessment based on:
 (check all that apply)
- | | Left | Right |
|--------------------------|---------------------------------------|---------------------------------------|
| Standard views (MLO, CC) | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Additional views | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Other: _____ | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |

4. Breast density
 (Check denser breast if left and right differ)
- ₀ Almost entirely fat (<25% fibroglandular)
₁ Scattered fibroglandular densities (approximately 25%-50% fibroglandular)
₂ Heterogeneously dense (approximately 51%-75% fibroglandular)
₃ Extremely dense (>75% fibroglandular)

5. BI-RADS® assessment category
 (Check all that apply)
- Category
- | | Left | Right |
|---------------------------------------|---------------------------------------|---------------------------------------|
| 0 Needs additional imaging evaluation | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 1 Negative | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 2 Benign | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 3 Probably benign | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 4 Suspicious | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 5 Highly suggestive of malignancy | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 6 Known malignancy | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |

6. Management recommendations
 (Check all that apply)
- | | Left | Right |
|---|---------------------------------------|---------------------------------------|
| 1,2 Routine interval follow-up, next mammogram: | | |
| 1 year | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Return at age 40 | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Other: _____ | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 3 Short-interval follow-up: | | |
| 6 months | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Other: _____ | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 0 Additional imaging evaluation | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 4 Consider biopsy | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 5 Appropriate action should be taken | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 6 Appropriate action should be taken | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
- Specify immediate management:
- | | | |
|---------------------------------|---------------------------------------|---------------------------------------|
| Compare with previous mammogram | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Additional mammographic views | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Ultrasound | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| MRI | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Nuclear medicine | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Cyst aspiration | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| FNA biopsy | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Core biopsy | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Needle localization | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Clinical examination | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Surgical consult | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| Other: _____ | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |

OPTIONAL EXAM INFORMATION (Optional, complete if available)

7. Symptoms (Check all that apply)
- | | Left | Right |
|---------------------------|---------------------------------------|---------------------------------------|
| 1 None | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 2 Lump | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 3 Bloody nipple discharge | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 4 Pain | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |
| 5 Other: _____ | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ |

8. Physical exam results
- ₀ Negative
₁ Positive (suspicious for malignancy)
₂ Not performed
9. Comparison with previous mammogram?
- ₀ No (first examination)
₁ No (previous films not available)
₂ Yes ____ / ____ / ____ (mm/dd/yyyy)
₃ Pending, waiting for outside films

Questions 1-2, 4-6, and 9 reprinted with permission of the American College of Radiology (ACR). ACR BI-RADS®--Mammography, 4th Edition. In: ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas. Reston, VA. American College of Radiology; 2003.

Breast Cancer Early Detection Study Surgical Approach and Recruitment Overview

