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13. ABSTRACT (Maximum 200 Words) Breast Cancer remains a leading cause of death for women in the U.S. 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 yearly screening, resulting in costly and painful follow-up procedures. Based on the ongoing studies in many research institutions, 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 and chemotherapy due to breast cancer. To date, we have created the infrastructure necessary for our interdisciplinary team of investigators to obtain study samples, characterize candidate biomarkers, and efficiently communicate research findings. We have also increased the number of potential biomarkers and looked into 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 biomarker panel can improve the performance of mammography in early detection of breast cancer. The primary aims of this study are: 1) to validate and refine the ability of candidate biomarkers to predict disease status; 2) to evaluate panels of biomarkers 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 cancers and explore their associations with biomarkers 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 antigens³, growth factors associated with angiogenesis, DNA methylation, and antibodies to oncogenic proteins known to be associated with aggressive disease such as Her2/neu, p53, IGFBP-2, Cyclin D1, Cathepsin, and Topoisomerase IIA.

We 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 multiple marker algorithms over time. 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

Throughout the second year of this study, investigators continued to focus efforts on developing a robust infrastructure to support the scientific objectives of the study and to meet study goals as outlined in the statement of work. By the end of our first year, the Mammography Tumor Registry (MTR) portion of this study had received approval by the Office of Research Protections; however, investigators and staff continued to work closely with Peter Marshall, DoD Human Protections Specialist, throughout the second year to receive human subjects approval on the study's clinical/recruitment protocols. This study has two clinical and recruitment protocols. The first one covers clinical/recruitment activities in Seattle where women receiving annual mammograms, a pre-scheduled stereotactic biopsy, or breast related surgery may be approached for a blood only donation. The Seattle surgical population can also be approached for a blood *and* tissue donation. The second protocol covers specific recruitment activities at Cedars Sinai Medical Center in Los Angeles where women undergoing a biopsy or surgery may be approached for blood *and* tissue donation. These protocols have been standardized between recruitment sites as much as possible. In May 2004, the DoD's Office of Research Protections approved the clinical/recruitment protocol that will be followed in Seattle. Investigators continue to await DoD human subjects approval on the Cedars Sinai protocol.

In addition to working with Peter Marshall and the Office of Research Protections toward receiving human subjects approval on the clinical/recruitment protocols, investigators and study staff have concentrated their efforts in the following areas over the last year: 1) refinement and use of a breast cancer micro simulation model to investigate the impact of DCIS diagnosis on breast cancer mortality and associated over treatment of this disease; 2) integration of patient advocates into the overall research program; 3) implementation of the Mammography Tumor Registry components of the study; 4) organization of investigator meetings/conference calls to refine the study protocol, to develop standardized specimen collection and processing procedures, and to discuss progress on breast cancer biomarker assays that are being developed or refined in collaborating laboratories; 5) continued development of relationships with clinicians who will provide access to patients for the study; 6) collaboration among investigators to complete development of data collections instruments; 7) continued development of a web-based informatics system and adaptation of an existing specimen inventory and tracking system to accommodate breast specimens; and 8) development of a web-based knowledge management system to support communication among investigators.

Investigators have refined a previously developed micro simulation model to explore the impact of DCIS diagnosis on breast cancer mortality and associated overdiagnosis. 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 to JNCI.

COE patient advocates continue to influence the direction of the research study. We are developing a well-integrated patient advocacy program that is focused on addressing the most critical issues in the Center of Excellence study. Ms. Joan McAree was hired to support this effort last year, but has left the study to devote time to an organization that she co-founded with her sister named the Ovarian and Breast Cancer Alliance of Washington State. Ms. Shannon Marsh, who is an attorney by trade and has personal experience with participating in research studies, has replaced Ms. McAree. Since joining the study, Ms. Marsh has had many training opportunities to learn more about patient advocacy in support of research. For example, she attended the NCI sponsored SPORE Investigator Workshop last July where she participated in patient advocacy

training sessions led by Ms. Deborah Collyar. In addition, she has been working closely with Ms. Sheryl Eisenbarth who leads the Pacific Ovarian Cancer Research Consortium (POCRC) Patient Advocacy group at the Fred Hutchinson Center. Under Ms. Eisenbarth's leadership, the POCRC advocacy group has become nationally recognized and is used as a model for many developing patient advocacy groups.

Recent experiences with our ovarian work have shown that there are many intellectual property rights issues that must be addressed before multiple markers that are "owned" by different entities can be combined in a marker panel. In addition, it is imperative that agreements are established with commercial partners to expedite the development and movement of the panel through clinical testing. With the support of Center lawyers and technology transfer specialists, Dr. Urban has been working through these issues. Recently, she has asked Ms. Marsh to assist her with this work knowing that her legal expertise would be valuable. In addition, learning from this experience will help Ms. Marsh work with COE investigators to address intellectual property rights with the breast cancer marker panel and future identification of appropriate clinical applications.

In addition to working with Dr. Urban on intellectual property rights, Ms. Marsh is also focusing efforts on facilitating communication between scientists and consumers, and increasing minority participation. Specifically, Ms. Marsh has attended many community events including the Susan G. Koman *Race for the Cure* in June. At this event, she spoke to over 100 women and discussed in detail the goals and requirements for becoming involved in the COE study. In addition, she distributed a variety of educational materials on detection and prevention of breast cancer. Generally, women are very excited and interested in learning more about participation in research studies, particularly early detection biomarker studies in breast cancer.

Another effort that will support greater communication between scientists and the community is development of a quarterly newsletter. This newsletter will be sent to all women participating in the Women's Cancer Prevention and Detection Network and those specifically participating in the Center of Excellence study and will feature articles that focus on women's cancers and cancer research. We will encourage women to write or telephone in any questions they may have so that a dialogue develops between the research community and its study participants; thus, the newsletter will provide a mechanism to reach out to the community facilitating communication among scientists and patients.

Ms. Marsh has also taken the lead on developing study materials including approach letters, consent forms, and the Women's Cancer Prevention and Detection Network brochure. A draft copy of the brochure is included as Appendix A. While developing this brochure, Ms. Marsh paid particular attention to issues important to the patient, such as privacy issues and access to medical records. The brochure was also designed to encompass many different minority groups.

As recruitment efforts ramp up this year, Ms. Marsh will focus attention on minority recruitment working closely with collaborating physicians toward increasing minority enrollment in all populations. We will concentrate efforts on specific minority groups (ex. Asian and Hispanic) that are most prevalent at participating facilities, and will explore the feasibility of translating our study materials into appropriate languages in order to reach a wider minority base.

Mammography Tumor Registry protocol has been implemented. The first step toward implementing this protocol was hiring a systems analyst programmer/data coordinator dedicated to this work. At the start of the second year, the MTR programmer developed methods to receive regular downloads of electronic mammography data from the Swedish Breast Care Center's

Mammography Reporting System (MRS). 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. Using "old" data, the MTR programmer piloted methods and a linking algorithm to link the MRS aggregate data to the Washington State Cancer Registry. This linkage work is done in collaboration with the Fred Hutchinson Center's Cancer Surveillance System (CSS). Because CSS recently changed its data structures, it was necessary to update existing CSS import algorithms and study data structures (particularly cancer staging structures) to accommodate to this change. To test for quality control, the MTR programmer is currently in the process of comparing current linkage results using the new algorithm with previous linkage results. Once this step is complete, investigators will work on developing a feedback report with new outcomes data that will be provided to participating radiologists at the Swedish Breast Care Center.

In accordance with the approved protocol, *individual* mammography data will be used only after a woman has signed a HIPAA authorization form giving us permission to review her mammography records. This mammography results release form will be mailed to potential study participants with a one-page screening questionnaire. If a mammography results release form is on file, mammogram findings (assessment codes, follow up recommendation, breast density) will be used in addition to the information from the screening questionnaire to determine risk status for an individual woman^{5,6}. If a release form is not on file, then we will use information obtained through the screening questionnaire only to determine initial risk status. These instruments allow us to determine study eligibility and help us to prioritize women for invitation into the study.

COE investigators have been meeting regularly to standardize procedures between recruitment sites and to discuss marker assays. We have organized quarterly investigator conference calls to refine protocols and data collection instruments that will be used in this study. Specific efforts were made to work with Dr. Scott Karlan, lead surgeon/investigator at Cedars Sinai Medical Center, and his staff toward the development of similar clinical recruitment protocols using standardized consent forms and data collection instruments. The data collection instruments include a baseline questionnaire, health status questionnaire, and a health status update. Both the FHRC and Cedars Sinai clinical/recruitment protocols are included as Appendices B and C. In addition, investigators are working closely to implement standardized tissue collection and processing protocols, as well as a centralized tissue review and characterization process that will be completed by Dr. Nancy Kiviat (pathologist) in Seattle. Investigators have also used this opportunity to discuss candidate biomarkers and the progress the laboratory investigators are making toward refining their specific marker assays.

COE annual investigator meeting was held in January 2004 to discuss candidate and novel early detection markers. COE investigators presented recent work on their markers at the first COE annual investigator meeting. Dr. Gordon Mills was scheduled to present his lysophospholipid markers; however, due to a scheduling conflict he could not attend. In his place, Dr. Nicole Urban presented his work suggesting that certain lysophospholipids represent a novel class of bioactive factors for breast and ovarian cancer that can potentially be measured through SELDI-TOF mass spectrometry⁷. Dr. Nathalie Scholler, senior staff scientist at the Fred Hutchinson Center, presented the concepts behind the use of a yeast display library of single chain Fragment variable (scFv) antibodies for rapid ELISA development. Dr. Scholler also presented the possibilities of using a multiplexing system that would enable simultaneous measurement of several markers on the same sample set. This technique can be done in Seattle, using a BioRad Protein Array machine that was purchased by the Fred Hutchinson Center and the Pacific Ovarian Cancer Research Consortium/SPORE in ovarian cancer. The machine is currently located in Dr. George McDonald's cytokine shared resource laboratory. With the support of Center leadership,

Drs. McDonald and Urban are working to obtain CLIA approval for this lab, which will eventually allow investigators to act clinically on marker results as appropriate.

To close the workshop, Dr. Nancy Kiviat from the Univ. of Washington presented her work with Mammaglobin and discussed its potential for assessing clinical stage, nodal status, and recurrence of breast cancer⁸. In addition, Dr. Kiviat discussed her work in DNA methylation and its ability to detect early stage cancer. We have started to plan the next workshop, which will be held in Seattle in February 2005.

Investigators will begin testing markers using samples from collaborators. We have received pre-validation samples from various collaborators and will begin testing our candidate markers for inclusion in the marker panel. In addition, we are using some of these pre-validation samples to analyze markers that are currently not on our list of candidates. For example, Dr. Scholler at the Fred Hutchinson Cancer Center is exploring use of a cytokine panel and an assay for CD24. If one of the candidate markers is ineffective, we will be poised to add a new marker to the panel that could increase its ability to detect specific forms of breast cancer.

Recruitment of women without breast cancer. While awaiting DoD human subjects approval, we have been working to identify potentially eligible women to invite to participate in the study. 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. Women are also sent a one-page screening questionnaire that asks about family history of breast or ovarian cancer, and a mammography results release form. Currently, the network contains about 1,800 women. We anticipate that this network will grow substantially over the next couple of years with the immediate possibility of adding a few more radiology facilities.

Some of these women, approximately 740, have already been invited to participate in a breast cancer research study funded by a NCI/Avon *Progress for Patients* award (PI: Nicole Urban). We refer to this study of high-risk women as the "Avon study." Of the women invited, 341 have enrolled in the Avon study and most are approaching study completion. These women have proven to be a motivated group with many indicating that they would like to continue some type of participation in research. Towards that end, we have developed an approach letter and have revised the study protocol to enable us to invite these women to participate in the Center of Excellence study. This modification is currently under review by Peter Marshall, Human Protections Specialist. Once approved, study invitation letters will be mailed to all women in the Avon study. We anticipate that the enrollment rate for this population will be over 90%.

Since obtaining human subjects approval to begin patient recruitment, we have worked on refining our procedures to classify the remaining network population by risk status based on family history information. Women at high-risk will be over-sampled to increase the expected number of women with serial blood samples obtained prior to a breast cancer diagnosis. Study invitation packets are being mailed each week in batches of 25. Based on our recent experiences with the Avon study, we expect an enrollment rate of 60% or more in this population.

Recruitment of women with breast cancer. Under the leadership and guidance of Dr. David Beatty, Director of the Breast Cancer Program at Swedish Medical Center, we have organized several meetings with the Swedish breast surgeons and pathologists to develop detailed surgical recruitment and specimen collection plans that are feasible within their specific clinical environments. The Swedish group remains enthusiastic and committed to making this collaboration and the study a success. Meeting minutes are included as Appendix D. With the surgeons' guidance it was determined that the ideal surgical candidate who could potentially donate both tissue and blood would be a woman who presents with disease that is T2 or greater, DCIS or invasive carcinoma where the patient is undergoing total mastectomy, or suspected lesions >2 cm. With the pathologists' guidance, we have been able to develop a detailed blood and tissue collection and processing protocol that is included as Appendix E.

In August 2004, we implemented specific recruitment procedures in the surgeons' offices on the First Hill and Providence campuses of Swedish Medical Center. We anticipate a learning curve as physicians and clinic staff familiarize themselves with specific study guidelines, but once procedures become routine then enrollment and collection rates should increase dramatically. To date, we have enrolled 12 women into the surgical cohort with 11 providing a pre-surgical blood donation and 1 declining this option. Five women have provided a blood donation at the time of surgery. In addition, we have successfully obtained a pre-surgical blood donation, as well as a blood *and* tissue donation from 1 of these 12 women at the time of her surgery. A detailed enrollment report based on specimen donation and clinical diagnosis is currently being developed.

Taking things in a stepwise fashion, we will begin to work with the clinicians and their staff to implement biopsy enrollment procedures, once the surgical enrollment procedures are running smoothly. Towards that end, in order to increase study efficiency in the surgeons' offices, we have organized in-services with the clinic staff, as past experiences have shown that clinic staff play a key role in successful recruitment efforts. Shirley Gough, Research Nurse, and other study staff met with clinic nurses, assistants, and schedulers to present the study and to discuss recruitment procedures that could fit into normal clinic flow. These meetings have been very informative and have resulted in several ideas that can be easily implemented toward increasing effective communication among the surgeons, their staff, and the research staff.

In addition to study specific meetings with the physicians, we are planning monthly Interdisciplinary Working Group meetings to facilitate regular scientific exchange between scientists and community physicians. Although these meetings have not been scheduled yet, we have identified meeting chairs, Drs. David Beatty and Kristine Rinn. Supported by study staff, Drs. Beatty and Rinn are working together to find a convenient meeting time, and are developing overall meeting objectives, list of attendees, and an initial list of presenters.

Pathology data collection instruments have been developed. A "Patient Level Clinical Diagnosis" form has been developed and will provide appropriate information to characterize a woman based on TNM staging and grade of disease at the time of her diagnosis. A study staff member will complete this form with the research nurse conducting quality assurance. Working closely with Dr. Kiviat, lead pathologist, we have also developed a histopathology (tissue review) form that will allow us to characterize all tissue samples. Once it is implemented, Dr. Kiviat will complete this form. We are now working on a clinical follow-up form that will capture specific information on treatment. The pathology data collection instruments are included as Appendix F.

Programmers have developed a web-based interface to manage study data. We have prepared much of the informatics infrastructure required to support COE study. Infrastructure now 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 1 shows the current structure of the design in place.

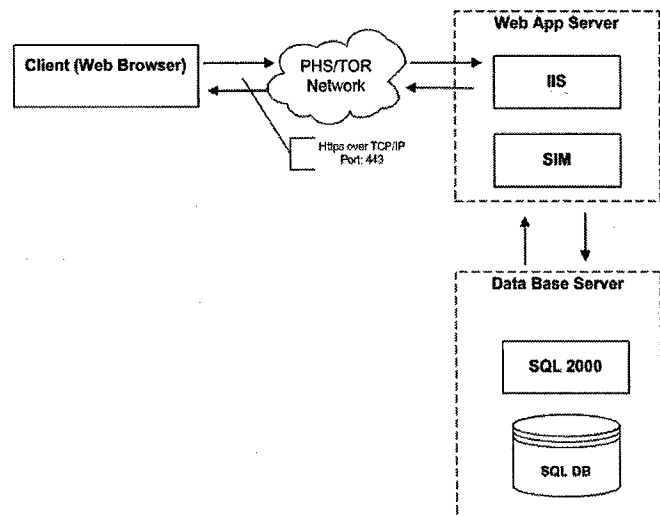


Figure 1. Infrastructure of the Seattle Informatics Management (SIM) System

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 2.

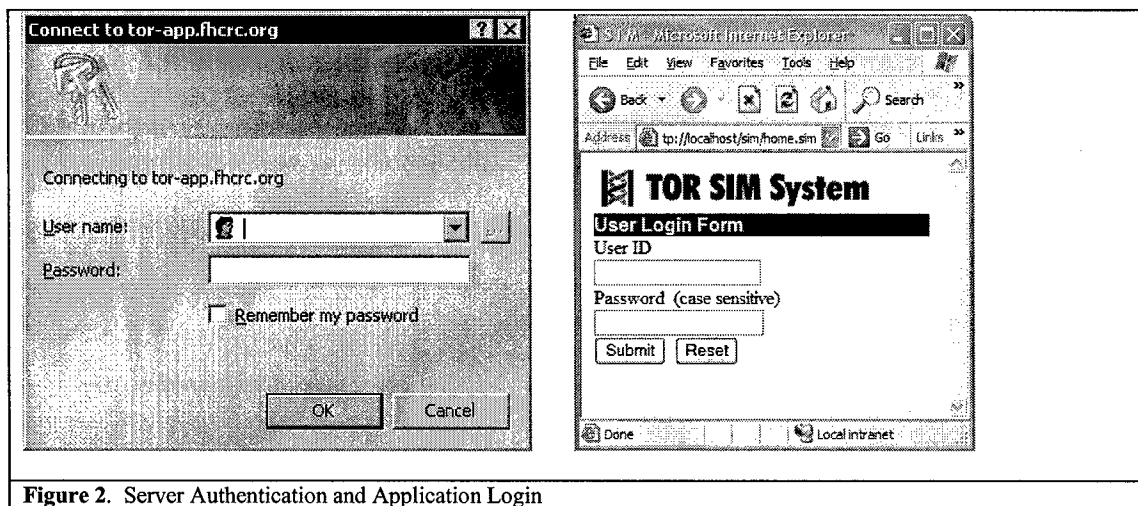


Figure 2. Server Authentication and Application Login

Web based screens for questionnaire data entry, similar to those needed by the COE project, have been developed and are currently in use for the Avon study by FHCRC staff and collaborators at MD Anderson Cancer Center, the University of Alabama Cancer Center and Fox Chase Cancer Center. During the development of these questionnaires stumbling blocks related to, remote site access, security, and data validation issues have been removed. 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 3 minimally illustrates the kinds of validation that data entry specialists see prior to the acceptance of data by the database.

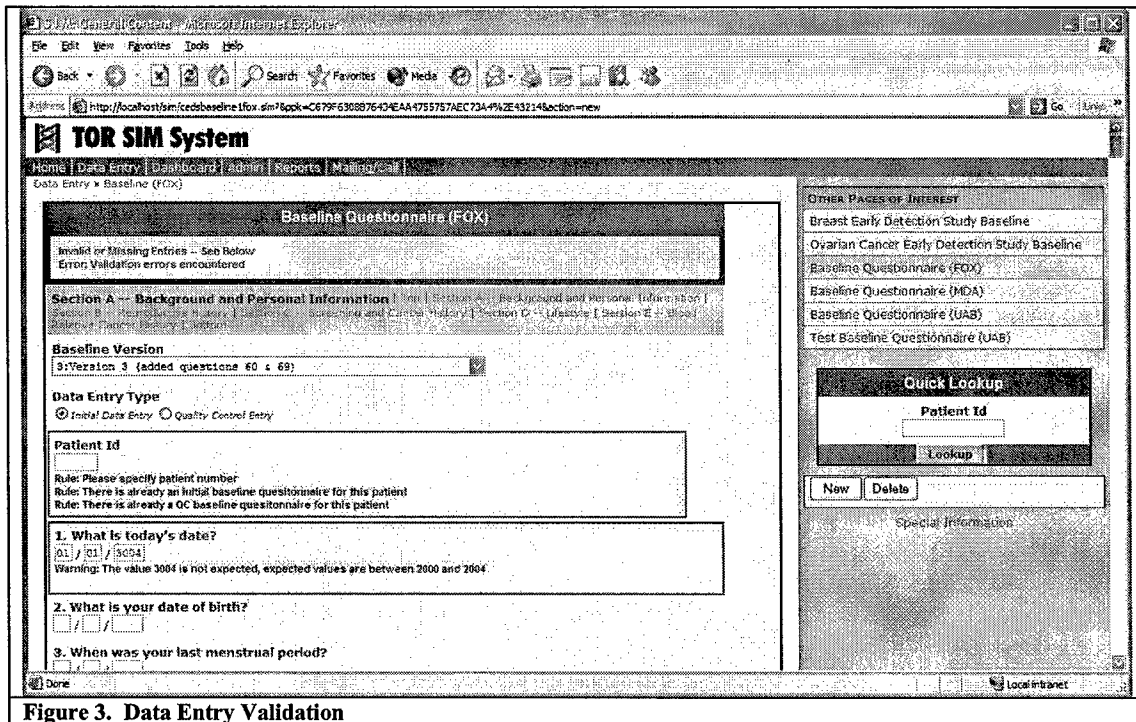


Figure 3. Data Entry Validation

Analyses of the patient tracking needs for COE participant protocol are outlined in spreadsheet software, prior to their import and implementation in web based tracking. Systems for similar use have been developed during the last year for use by other projects as a model for the COE work. Figure 4 shows tracking for screens developed for another project. A COE patient tracking system will be implemented within the next couple months.

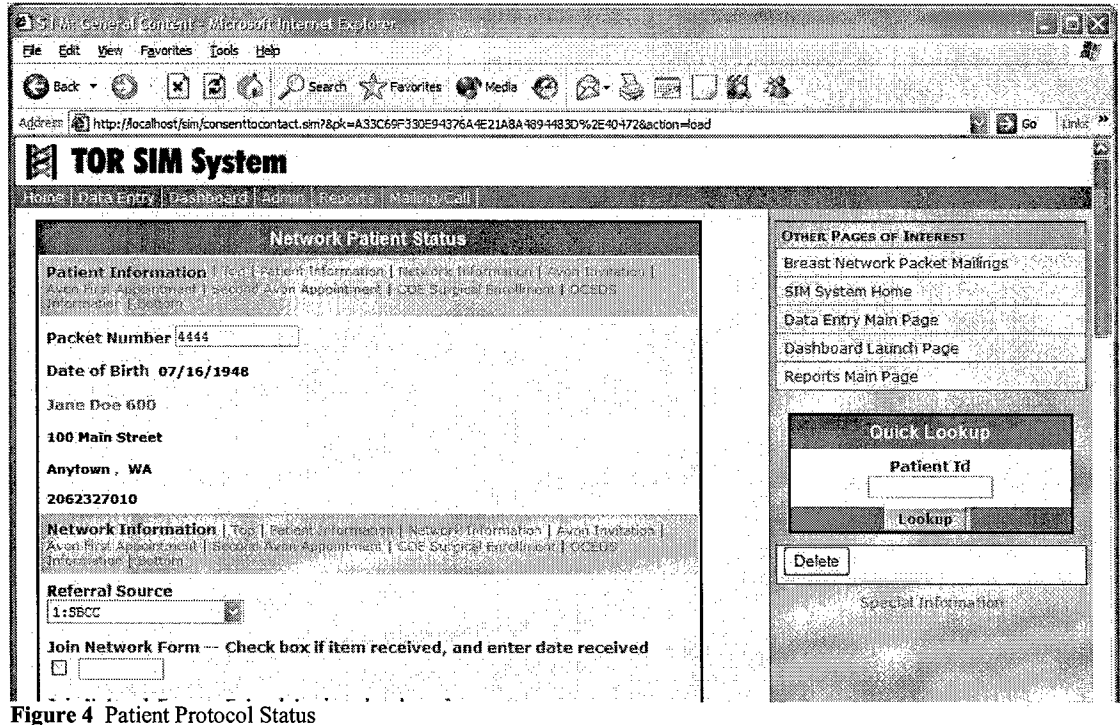


Figure 4 Patient Protocol Status

Specimens are tracked utilizing existing specimen tracking software developed for work with ovarian specimens. 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. Current POCRC specimen tracking systems include modules for characterization of patient and tissues with respect to ovarian disease. Additional modules for tracking with respect to breast disease are currently under development. Figure 5 illustrates the tracking of Patient specimen donation, while Figure 6 illustrates the tracking of Specimen location.

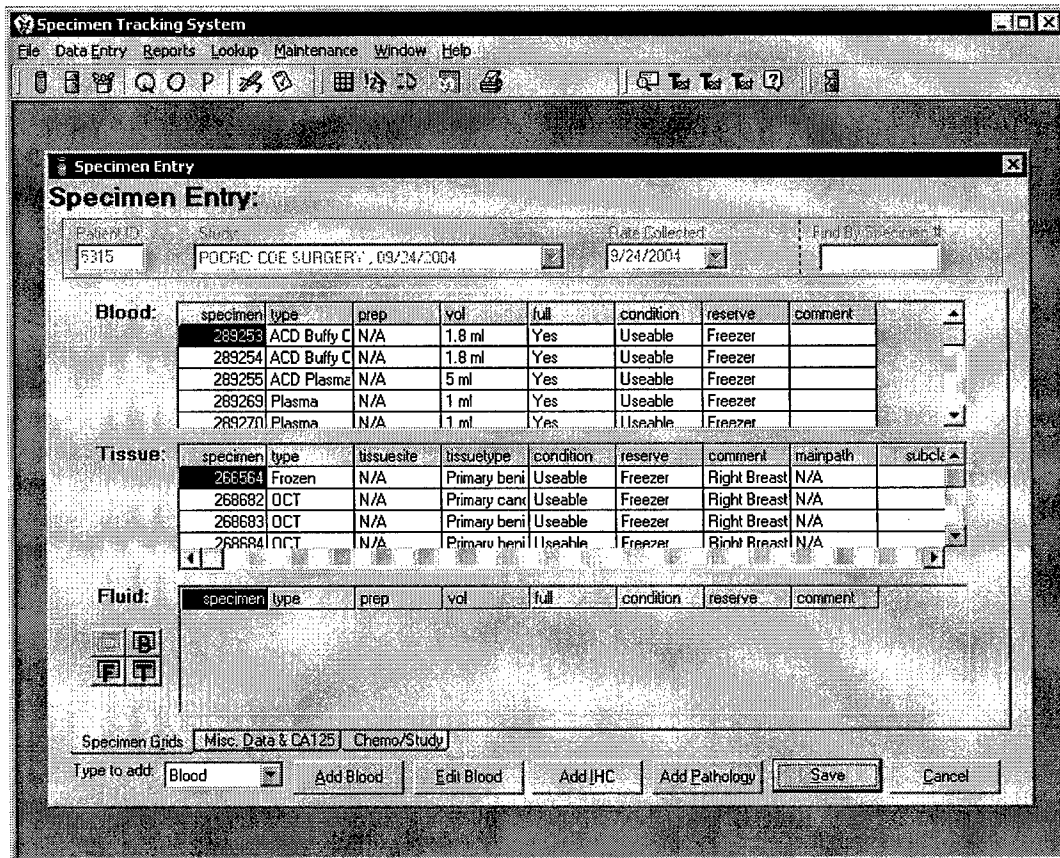


Figure 5 Specimen Tracking System: patient specimen donation

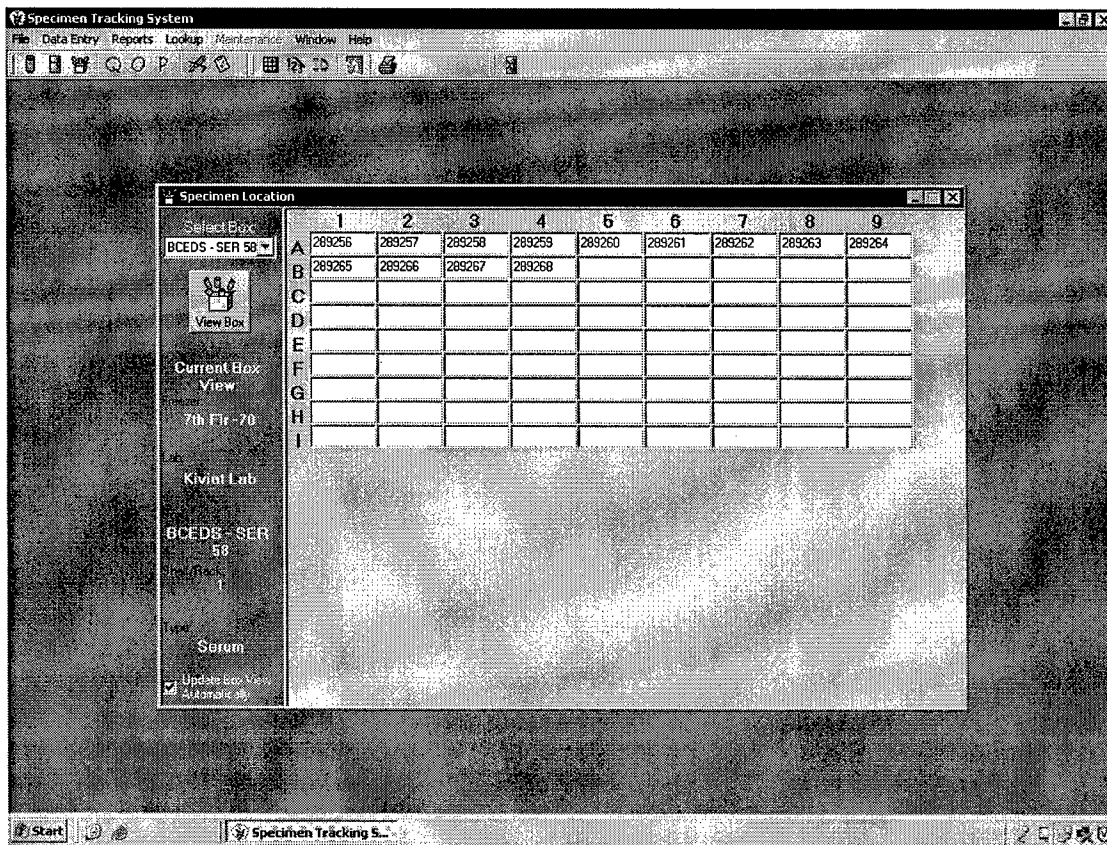


Figure 6 Specimen Tracking System: specimen location

Finally online reports have been implemented. Again, reporting is in place for other work we are currently doing and will serve as a template for COE project reporting. For example, in place are reports summarizing the data entry to date, data collected, double entry inconsistencies, participants race, and a risk status report. These are set up to run on a nightly basis and are downloadable by persons authenticating to the serve and logging into the SIM system itself.

A web-based knowledge management system supports communication among investigators. A private web-based Flex KB knowledge base has been built for collaborators on the study. A number of resources have been added to the site including the currently approved study protocol, meeting minutes, presentations, literature reviews, important dates, a study organization chart and contact and background information on each collaborator and study staff member. Future features will include study timelines, repository reports, and an area for manuscript development.

One critical design goal for this system is to provide each collaborating site with secure, private access to their entire data set (as entered in SIM) while at the same time providing aggregate reporting to the whole group. In addition, we envision that collaborators will be able to submit ad hoc specimen availability queries through the Flex KB and receive real-time summary statistics back. Eventually, we envision that the Flex KB will serve as an interface that provides links to aggregate reports. A security plan is now in place and the final details are being discussed with the collaborating groups as certain aspects of the security measures depend on the computer equipment and software at each site.

Key Research Accomplishments

Year two of this study has continued to focus on infrastructure development and start-up efforts. No research results are available at this time.

Reportable Outcomes

No manuscripts, presentations or publications have yet resulted from this study. A web-based database to support informatics is being developed. Screen shots are shown above.

Conclusions

No research conclusions are available at this time.

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Appendices

- Appendix A** Women's Cancer Prevention and Detection draft brochure
- Appendix B** FHCRC clinical/recruitment protocol
- Appendix C** Cedars-Sinai clinical/recruitment protocol
- Appendix D** Surgeon and Pathologist meeting minutes
- Appendix E** Blood and tissue collection and processing procedures
- Appendix F** Pathology data collection instruments

Appendix A

Women's Cancer Prevention and Detection Draft Brochure



FRED
HUTCHINSON
CANCER
RESEARCH
CENTER

**WOMEN'S CANCER
PREVENTION *and* DETECTION
NETWORK**



*Approximately 240,000 women will get
breast or ovarian cancer this year.*

*Join our research team to help
reduce the pain and suffering
from these diseases.*





Why are research studies important?


Scientists and doctors rely on volunteer research participants from the community to help them find ways to improve health and cancer care. Research studies are the best way to answer scientific questions and increase knowledge about cancer. Because participation by women is essential to successful research, we need your help.

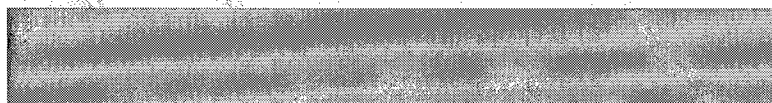
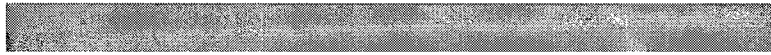





What will happen if I mail in the "Join the Network" form?

You will be sent a one-page questionnaire, which asks about your personal and family medical history, and a medical records release form that will give researchers permission to look at your mammography results. Later, if you are eligible for one of the studies, you will be sent a description of the study along with a telephone number so that you can ask questions. Participation in a study is optional. If you choose not to participate in a study, your contact information remains in the network so that you can be told about future research opportunities. Joining the network does not require that you participate in a research study, or guarantee that you will be invited to participate in a research study. All network members will receive a quarterly newsletter that provides updates on our research studies and other news about cancers that affect women.









**Is the information I provide
kept private?**

Yes, we take extreme care and follow strict procedures to keep all network and study records private. Only authorized members of the research team will see the information you provide. Your information will be entered into a database that is accessible only to study staff. All paper files are stored in our research office, located in a secured area of the Fred Hutchinson Cancer Research Center. Network information is used only to inform women about research opportunities; it will not be sold or distributed.

Every research activity conducted at the Hutchinson Center is carefully reviewed and approved by the Institutional Review Board, which protects the rights of people who participate in research studies.







If I join, how long will I be in the network?

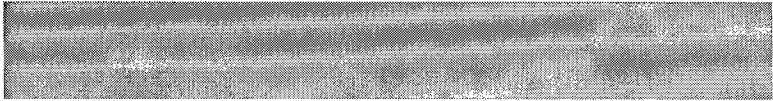
Your name will remain in the network indefinitely, even if you decide not to participate in certain studies, unless you ask that it be removed.


Can I change my mind about participating in the network?

Yes, you can change your mind. If you decide that you prefer no further contact about research opportunities, please call the study office and request that your name be removed from the network.

Are there risks or benefits associated with being in the network?

Joining the network does not involve any risk or direct benefit to you. Participation in research studies, however, may benefit women in the future who are at risk for cancer or who are living with cancer.





What kinds of studies will I learn about?

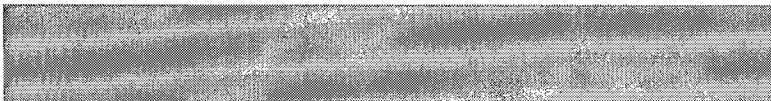
Researchers conduct many different kinds of studies on cancers affecting women. Currently, women from the network are being recruited for the following studies:

- **The Breast Cancer Early Discovery Study.**

The purpose of this study is to identify substances in blood that can be used to detect breast cancer early in the disease process. The goal is to develop a simple blood test that can be used along with mammography to improve the early detection of breast cancer. Eligibility for this study depends on your risk for breast cancer.

- **Ovarian Cancer Early Detection Study.**

The aim of this study is to determine if CA125 blood tests and ovarian ultrasounds are useful for the early detection of ovarian cancer. Women whose family history indicates they may be at increased risk for developing ovarian cancer are eligible for this study.





Questions?

Please contact the Network's study office at (206) 667-5624 or (800) 732-4589 to learn more about the Women's Cancer Prevention and Detection Network.



**WOMEN'S CANCER
PREVENTION *and* DETECTION
NETWORK**



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**WOMEN'S CANCER
PREVENTION *and* DETECTION
NETWORK**

"Join the Network" Form

First Name _____

Middle Name _____

Last Name _____

Street Address _____

City _____

State _____ Zip _____

Date of Birth _____

Telephone _____

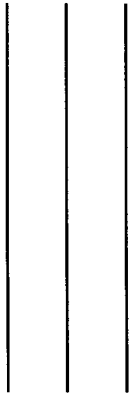
Home Work Cell

Signature _____

Date _____

Please
place
first-class
stamp
here

Women's Cancer Prevention and Detection Network
1100 Fairview Ave N., M2-B230
P.O. Box 19024
Seattle, WA 98109-1024



Appendix B
FHCRC Clinical/Recruitment Protocol

Center for the Evaluation of Biomarkers for Early Detection of Breast Cancer

Funded by the Department of Defense as a Breast Cancer Center of Excellence

Award Number: DAMD 17-02-1-0691

proposal Number: BC013002

Recruitment and Specimen Collection Protocol (IR#5317)

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1. **Protocol Title:** Breast Cancer Early Discovery Study
2. **Phase.** Not applicable
3. **Principal Investigator:** Nicole Urban, ScD
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P.O. Box 19024
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Medical Monitor: This study has been determined to be minimal risk by the Department of Defense Human Subject Reviewer, so identification of a medical monitor is not necessary.

4. Locations of Study:

Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North, M2-B230 P. O. Box 19024 Seattle, WA 98109	University of Washington (Kiviat Laboratory) Harborview Medical Center Dept. of Pathology Box 359791 325 Ninth Ave. Seattle, WA 98104
Group Health Cooperative Center for Health Studies 1730 Minor Avenue Suite 1600 Seattle, WA 98101	PhenoPath Laboratories 3000 First Avenue #1 Seattle, WA 98121
Virginia Mason Research Center 1201 Ninth Ave. Seattle, WA 98101	MacroGenics 1441 N 34th St Seattle, WA 98103
Pacific Northwest Research Institute 720 Broadway Seattle, WA 98122	University of Texas MD Anderson Cancer Center 1515 Holcombe Blvd. Houston, TX 77030-4095
University of Washington Medical Center 1959 N.E. Pacific Seattle, Washington 98195	University of California Los Angeles Cedars-Sinai Medical Center, #160-W Los Angeles, CA 90048-0750
Swedish Medical Center	Swedish Medical Center

Breast Care Center (Radiologist) Dr. Stracener (Radiologist) 1101 Madison St., Suite 310 Seattle, WA 98104	Drs. Beatty, Hart, Florence and Horton (Breast Surgeons) Arnold Pavilion 1221 Madison, Suite 1411 Seattle, WA 98104-1360
PacMed Clinics Dr. Needle (Breast Surgeon) 1200 12 th Avenue South Seattle, WA 98144	

5. **Expected Start and Completion Dates:** 10/1/2002-9/30/2006

6. **Purpose and Objectives:**

Purpose. The purpose of the Center is to assemble the team and the infrastructure needed to accelerate progress in breast cancer early detection biomarker research. We will develop a unique resource for inter-institutional collaborative breast biomarker research, and evaluate the potential of biomarkers detectable in serum or plasma to improve existing breast cancer early detection strategies. We will use the resource to evaluate the performance of candidate breast cancer biomarkers in a cohort of women participating in mammography.

Our vision is that a simple blood test could be used in conjunction with mammography to detect all breast cancer early in the disease process. For example, one clinical scenario might work as follows: at the time of her annual physician visit, a woman could have her blood drawn and tested for a panel of breast cancer markers. If the mammogram were clearly positive, she would be referred for biopsy. If the mammogram were equivocal, she would be referred to biopsy only if the marker panel suggested a malignancy. If the mammogram was negative, but the marker panel suggested malignancy, she would be referred for additional imaging such as MRI. Other scenarios may be preferable, and indeed one of the purposes of our study is to explore other possibilities. For example, use of the marker panel between annual mammograms might identify women with fast-growing tumors.

The expected result of the proposed Center is a panel of markers and decision rules for its use. The panel will be useful clinically, to improve the performance of mammography. Our comprehensive approach and access to an appropriate specimen repository increases the probability of our success. 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 (i.e. intraclass correlation), 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. Because high-quality specimens are frequently not available, investigators often rely on samples that were obtained from different sources for cases and healthy women. They may have been obtained during remission or even during treatment, or processed and stored differently in ways that affect marker levels. As a result, many markers that appear initially to be very promising prove later not to be useful, and the development process is characterized by false starts and missed opportunities. The scientific

community is often skeptical about the claims made for new markers, in part because many initially promising results cannot be replicated in different laboratories.

Another barrier is the clinical challenge we will face if we are successful. Markers could be ordered before, at the same time as, or after a mammogram, by the primary care physician, a radiologist, or the specialist who evaluates suspicious findings. Each strategy will affect the sensitivity and specificity of the combination of tests. If markers identify cancers that cannot be seen on a mammogram, clinical work up to identify the location of the tumor will be required. Cost-effective strategies will be needed. As we will obtain serum for women in several stages of evaluation—prior to screening, just prior to biopsy, and just prior to surgery—we will be in a unique position to evaluate the clinical utility of markers at all these potential stages of screening.

Objectives. Our goal is to evaluate breast cancer biomarkers for their contribution to early detection of breast cancer. Subsets of breast cancer that are missed by mammography, or that grow too quickly to be detected in early stage by annual mammography, are of particular interest. Our aims are:

1. To validate and refine the ability of candidate biomarkers to predict disease status;
2. To evaluate panels of biomarkers 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 subsets of in situ and invasive breast cancers and explore their associations with biomarkers in the panel.

To support the research goals we will build a unique resource for multidisciplinary, inter-institutional research on breast cancer biomarkers including

1. Blood samples obtained annually and processed identically in women with and without breast cancer,
2. Fresh tissue matched to blood samples on a subset of the women with breast cancer,
3. Epidemiological, clinical and follow-up information for women who donate specimens, and
4. A system to facilitate use of the specimens, including state-of-the-art information systems.

We will develop a specimen resource from a well-characterized population, with associated risk factor information, mammography findings and follow-up data on cancer outcomes. It will include blood samples obtained from selected women who have mammograms, biopsy or breast cancer surgery over the 4-year period of the grant. We will evaluate candidate biomarkers for their ability to distinguish among women with healthy breasts and women with various breast conditions, including invasive ductal and lobular carcinoma, lobular carcinoma in situ, comedo- and noncomedo-type DCIS, hyperplasia and other potentially premalignant conditions, and benign conditions. We will evaluate the role of biomarkers detectable in serum or plasma in improving our current breast cancer early detection strategies.

For selected women, we will explore the feasibility of collection and analysis of fresh-frozen tissue in order to characterize malignant conditions at the molecular level. This will allow us to correlate biomarkers included in the panel with subsets of breast tumors identified through molecular profiling.

Our hypotheses are:

- (a) Used alone, biomarkers detectable in blood products can detect subsets of, but not all, breast cancer;

- (b) Use of a breast cancer biomarker panel can improve the performance of mammography in early detection of breast cancer.

7. Study Population.

The study population includes three cohorts defined by recruitment source. The first is the approximately 8,600 women who obtain mammograms and undergo biopsies at the Swedish Medical Center Breast Care Center each year. All women seen for mammography at Swedish Breast Care Center (SBCC) will be asked to join the Women's Cancer Prevention and Detection Network by signing a **Consent to be Contacted for Future Research Studies** (Join the Network Form) for potential participation in women's cancer research. The Consent to be Contacted form provides permission for the research study to maintain the woman's name and contact information indefinitely so that she may be invited to future studies. Women who sign and return the consent to contact at the SBCC or other participating facilities will be mailed the **Women's Cancer Prevention and Detection Network Questionnaire**, the **Women's Cancer Prevention and Detection Network Release Form**, and a **Women's Cancer Prevention and Detection Network Cover Letter** asking them to complete the questionnaire and/or release form and return them to the study office in the stamped, self-addressed envelope provided. Women who return the completed questionnaire and/or the Release Form will be sent a **Thank You Letter**. Women who are recruited at the SBCC or any other Swedish facilities will not be approached for future participation in other research studies unless those studies have first been approved by the Swedish Cancer Institute Research Steering Committee.

Every 3 months, data describing mammogram findings will be submitted to FHCRC in accordance with Mammography Tumor Registry procedures (FHCRC IR#3636). For women undergoing mammograms, data from the Network Questionnaire will be used to classify women with respect to risk status. If a Release Form is on file, mammogram findings (assessment codes, follow up recommendation, breast density) will also be used to determine risk status for an individual woman.

A stratified random sample of women who participate in the Network will be identified and asked to provide blood samples annually at the time of subsequent mammograms. Women at high risk will be over-sampled to increase the expected number of women with sequential blood samples obtained prior to a breast cancer diagnosis. As shown in Table 1, 500 (375 high-risk and 125 average-risk) women will be enrolled in Year 1, and 100 additional women will be enrolled in subsequent years.

Women who have completed other research study protocols and have given permission to be contacted about future research opportunities will also be invited to participate in the COE by providing annual blood samples at the time of their mammograms. These women will be approached about potential COE study participation in person or by mail.(see section 8c.2)

In addition, all women undergoing biopsies will be invited to provide a blood specimen prior to biopsy and annually at the time of subsequent mammograms. 100 women undergoing biopsies will be enrolled annually. Women identified and enrolled through the SBCC, and women invited to participate who were identified from other research study protocols, are referred to as the Mammography Cohort (MC).

The second cohort includes women undergoing breast surgery at Swedish Medical Center. The second recruitment source is the approximately 650 women who have surgery for breast cancer at SMC each year. Collaborating surgeons will identify those most likely to have tumors of size > 2 cm and therefore to be candidates for tissue collection. In 1999 there were 124 women who had surgery for breast tumors over 2 cm at SMC. These women will be sampled with probability 1.

Remaining women will be sampled with lower probability to yield desired numbers in the cohort. Based on our experience in the ovarian SPOR, we expect that tissue collection will occur in about 50% of the women sampled. As shown in Table 1, we expect to enroll 25 women in Year 1 and 50 women annually thereafter for donation of both blood and tissue. Fresh tissue specimens will be obtained when it is logistically and ethically appropriate. In addition we expect to enroll 100 women annually beginning in year 2 for donation of blood only. Blood samples will be obtained just prior to or at the time of the surgical procedure. Women identified and enrolled through our collaborations with SMC surgeons are referred to as the Surgical Cohort (SC). Following surgery and treatment, women in the SC will be invited to participate in the MC, providing blood samples at the time of their annual mammograms.

The third recruitment source is women undergoing biopsy by Mammotome® at Cedars Sinai Hospital. Approximately 2,500 women undergo this procedure annually. Of these we will enroll 50 per year, including women with benign lesions, hyperplasia, and in situ disease as well as women with invasive carcinoma. As at SMC, we expect about 20% to be malignant. Both fresh-frozen tissue and blood samples will be donated by women in the Cedars biopsy cohort. Procedures at Cedars Sinai are described in a separate document, which is currently being finalized and reviewed by the local IRB and will be forwarded to DOD for review once local IRB approval is in place. We will forward the updated Cedars documentation as soon as possible.

Table 1. Unique Participants

	Yr 01	Yr 02	Yr 03	Yr 04	Total
Mammography Cohort – High Risk	375	75	75	75	600
Mammography Cohort – Average Risk	125	25	25	25	200
Mammography Cohort – Biopsy	100	100	100	100	400
<i>Subtotal: Mammography Cohort</i>	<i>600</i>	<i>200</i>	<i>200</i>	<i>200</i>	<i>1200</i>
SMC Surgical Cohort: Blood and Tissue	25	50	50	50	175
SMC Surgical Cohort: Blood Only+		100	100	100	300
<i>Subtotal: Surgical Cohort</i>	<i>25</i>	<i>150</i>	<i>150</i>	<i>150</i>	<i>475</i>
Cedars Biopsy Cohort: Blood and Tissue	50	50	50	50	200
Total	675	400	400	400	1875

8. Protocol Design. This protocol outlines the methods for a study to collect blood and tissue specimens from women undergoing mammography and breast-related biopsy and surgery at Swedish Medical Center. Patient approach procedures to be used at Cedars Sinai Medical Center are addressed in a separate document. The study uses the already-established infrastructure in place for the Mammography Tumor Registry Study (MTR). The purpose of the study is to provide a specimen resource to support both breast and ovarian cancer biomarker evaluation. Investigators propose to build a unique resource for multidisciplinary, inter-institutional research on cancer biomarkers including blood samples obtained annually and processed identically in women with and without breast cancer, fresh tissue matched to blood samples on a subset of the women with breast cancer, epidemiological, clinical and follow-up information for women who donate specimens, and a system to facilitate use of the specimens, including state-of-the-art information systems. Collaboration with mammography facilities and surgeons offices is planned to recruit women undergoing screening, biopsy and surgery.

8a. Eligibility Criteria. All women 18+ years of age undergoing mammography or biopsy at the SBCC are potential participants for this research. Women identified and enrolled through the SBCC, including women having both mammograms and biopsies, are referred to as the Mammography Cohort (MC). All women 18+ years of age scheduled for breast surgery by

participating surgeons are potential participants for this research. These women are referred to as the surgical cohort (SC).

Mammography Cohort Risk Stratification. Women having screening mammograms will be invited to complete the **Cancer Research Registry Questionnaire** and the Cancer Research Registry Mammography Results Release form. Of those who respond, study investigators will select a stratified random sample and invite those women to donate blood. Risk stratification will be based on epidemiological data provided on the questionnaire, and on mammogram findings (if the woman gave permission to have these reviewed), as follows:

- A woman will be considered average risk if her mammogram result was assessment code 1 or 2.
- If mammogram results are unknown, a woman will be considered average risk if she does not meet any of the high risk criteria specified below
- Women will be classified as high risk if any of the following apply:
 1. She is referred to biopsy (assessment code 4 or 5); or
 2. The family contains at least two ovarian or breast cancers among the subject and first and second degree relatives of the subject within the same lineage. This condition is satisfied by multiple primary cancers in the same person, where breast cancer is required to meet this criterion, at least one breast cancer must be pre-menopausal (age at diagnosis less than or equal to 50 if age at menopause is unknown).
 3. She is of Ashkenazi Jewish ethnicity with one first-degree or two second-degree relatives with breast or ovarian cancer, or subject is of Ashkenazi ancestry and has had breast cancer. Where breast cancer is required to meet this criterion, at least one breast cancer must be pre-menopausal (age at diagnosis less than or equal to 50 if age at menopause is unknown).
 4. She presents with suspicious mammogram findings (assessment code 3), or has experienced symptoms.

8b. Subject Identification. Potential participants in this study will be identified at the Swedish Medical Center Breast Care Center (SBCC) or through their participation in other research study protocols. The SBCC mammography practice already participates in the Mammography Tumor Registry (IR File #3636), which means they provide regular downloads of mammography data that are routinely linked to the Cancer Surveillance System. The registry is used to support breast cancer research and to provide regular performance reports to participating radiologists. All aspects of the linkage process, including extensive confidentiality procedures, are covered in IR file #3636 and are not discussed here.

8c. Participant Approach, Enrollment, Informed Consent and Specimen Collection. Approach processes are tailored to participant type. All women receiving screening mammograms are asked to sign a consent for future contact. Women receiving biopsies are approached prior to the biopsy procedure. Women from other study protocols are either approached in person at a study appointment or by mail. Women in the surgical cohort are approached at the pre-surgery appointment. All women who consent to participate in the initial blood collection are invited to donate blood at their subsequent mammogram appointment (regardless of cohort).

8c.1 Consent to Contact (Mammography Cohort). All women seen for mammography at SBCC will be asked to join the Women's Cancer Prevention and Detection Network by signing a **Consent to be Contacted for Future Research Studies** for potential participation in women's cancer research. Additional risk factor information will be collected using the **Women's Cancer Prevention and Detection Network Questionnaire**, which will be mailed to the participant after she has completed the Consent to be Contacted form. This mailing will also include a HIPAA compliant medical records release (Women's Cancer Prevention and Detection Network Release), which will allow access only to her mammography records. A broader medical records release will be obtained from women donating specimens, as described in Section 8c2. Within 3 months following the mammogram, data describing mammogram findings will be submitted to FHCRC in accordance with MTR procedures. For women undergoing mammograms, data from the Network Questionnaire in combination with mammogram findings (assessment codes, follow-up recommendation, breast density) will be used to classify women with respect to risk status. A stratified random sample of these women will be invited to donate blood. In cases where mammography data are not available, women will be selected based only on data provided on the **Women's Cancer Prevention and Detection Network Questionnaire**.

8c.2 Women From Other Research Study Protocols

Women who have completed other research protocols, and who have given permission to be contacted about future research opportunities will be approached to participate in the COE. These women may be approached one of two ways. One, they may be approached in person by study staff during their final study appointment and given the COE invitation packet (containing invitation letter, study brochure, COE consent form and medical records release) plus a small incentive item (decorative magnet, Athena Water coupon, etc.). Women will be asked to take the packet home where materials can be reviewed at their convenience. A self addressed stamped envelope will be included in the packet, so that signed consent forms can be returned to the study office. Two, women who have already had their final study appointment will be approached by mail, as described below in section 8c.3.

This group of women will receive an invitation letter appropriately tailored for their population. Several studies conducted by Dr. Urban's group use the same data collection instruments (ex. Baseline questionnaire, Health Status Questionnaire). Accordingly, women who are currently participating in our research studies and represent a potential recruitment source for the COE will not be asked to complete the same instruments twice.

Women who return their signed consent form will receive a **COE Invitation Thank You Letter** (currently under development). The thank you letter will inform study participants that study staff will call them 1-2 months prior to their mammogram to schedule their first COE blood draw appointment.

8c.3 Invitation Letter and Consent for Annual Blood Donation (Mammography Cohort)

Women selected for approach will be contacted by mail several months prior to the next mammogram appointment, using the **Study Brochure**, and the **Invitation Letter**. The letter will describe the study and invite interested women to return a signed **Consent to Participate in the Breast Cancer Early Discovery Study for Women Receiving Mammograms** and a **Medical Records Release Form**. This medical records release is broader than the one previously obtained, and allows general access to a woman's medical records so that the study may obtain history of and treatment of cancer. Upon receipt of the signed consent form and medical records

release form, the study office will call women to schedule their first blood draw appointment. If we are unable to reach a woman by phone, she will be sent the **Not Able to Contact By Phone Letter**, which requests that she call the study office if she would like to participate. If we do not receive any materials or hear from a potential participant within 3 weeks of sending the invitation packet, study staff will call the woman once to follow up with her regarding the study.

Once an appointment has been made, the woman will be sent a **Blood Draw Appointment Confirmation Letter** with directions (**map**) to the blood draw site. All women will have their blood drawn at the Swedish Breast Care Center on the Swedish Medical Center campus unless they are patients at the Swedish Cancer Institute (SCI) and request to have their blood drawn at SCI. If this is the case, study staff will arrange to meet the participant at SCI for her appointment and administer the study questionnaires. At her first blood draw appointment, the participant will complete a **Health Status Questionnaire**. This questionnaire asks about current health information at the time of the draw (ex. Medications). She will also be given a **Baseline Questionnaire** to either complete at her appointment or take home. If she chooses to complete the Baseline Questionnaire at home, she will be given a stamped, self-addressed envelope to return it to the study office. Information from the Baseline Questionnaire will be used to confirm initial risk status and to determine if a woman is at high risk for breast or ovarian cancer based on family history. If a participant does not return the Baseline Questionnaire within 3 weeks, she will be sent a **Reminder Card** and another copy of the questionnaire. If the study office does not receive the questionnaire or hear from the participant 2 weeks after the card was sent, she will receive one follow up call from study staff.

For subsequent blood draws, the study office will send the Annual Blood Draw Reminder Letter one month prior to the next draw and schedule an appointment over the phone. If we cannot reach a woman by phone to schedule her annual appointments, we will send her the **Annual Draw Not Able to Contact by Phone Letter**, which requests that she call the study office with her updated contact information. Once the appointment has been made, the woman will be sent a **Blood Draw Confirmation Letter**. At each draw she will receive a **Health Status Update** questionnaire to complete during her appointment. This questionnaire asks for updated health information. If possible, one draw each year will occur at the time of subsequent mammograms to make it more convenient for participants who receive mammograms at the SBCC. We will provide parking validation for each visit including the blood draw visit that coincides with the annual mammogram.

8c.4 Telephone and In-Person Approach (Women Undergoing Biopsy) All women undergoing biopsies will be invited to provide a blood specimen prior to biopsy and annually at the time of subsequent mammograms. Consent for specimen donation will take place during the biopsy appointment, prior to the biopsy. The SBCC Scheduling Nurse routinely contacts by telephone all women undergoing stereotactic or in some cases ultrasound-guided biopsy 2-3 days prior to the appointment. During this phone call, the scheduling nurse will obtain verbal consent for study staff to contact the woman by phone to discuss study participation. If a woman provides verbal consent, the SBCC nurse will fax the study office the **Biopsy Flowsheet** including the woman's name and the date and time of the biopsy appointment to the confidential fax at the study office. The Scheduling Nurse will check a box that indicates that the woman has given verbal consent to be contacted about study participation. Study staff will then telephone the participant to describe the study and go through the consent materials. Study staff will carefully go over the **Consent to Participate in the Breast Cancer Early Discovery Study for Women Having Breast Biopsies, Medical Records Release Form**, and study questionnaires with the woman. Study staff will also inform the woman that the attending SBCC biopsy nurse will draw

their blood and obtain written consent. Again, only women undergoing pre-scheduled stereotactic or ultrasound guided biopsies will be approached in this manner, women undergoing biopsies on the same day as a suspicious mammogram will not be approached for this study. This process is described in the **Biopsy Consent Procedure Telephone Script**.

The SBCC nurse who attends the biopsy appointment will encourage the woman to ask any questions she may have about participation, and to discuss participation with any family members who are present. The consent process will take place in a private consultation or examination room in the breast care center. Clinical staff at SBCC will serve as witnesses to the informed consent process. If the woman asks a question which the attending biopsy nurse cannot answer, study staff will be available to go to the SBCC and address these questions. If the woman decides to participate, the attending biopsy nurse will obtain written informed consent for the blood donation using the Consent for Data Collection and Blood Donation prior to Biopsy form and draw blood from the participant *prior* to the procedure. A copy of the consent form will be provided to the participant. To allow the study to characterize the donated blood specimens by obtaining the pathology results, women will be asked to complete a Medical Records Release Form. If possible, to obtain information about the woman's health at the time of her blood draw, she will be asked to complete a short **Health Status Questionnaire** before her draw. If this is not feasible, she will be asked to complete the questionnaire as soon as possible after her draw. All consented participants will be provided the **Baseline Questionnaire**, which they may complete immediately or return by mail.

If a participant does not return the Baseline Questionnaire within 3 weeks after her blood draw, she will be sent a **Reminder Card** and another copy of the questionnaire. If the study office does not receive the questionnaire or hear from the participant 2 weeks after the card was sent, study staff will conduct one follow-up call.

Women undergoing biopsy will also be asked to provide blood specimens annually with their subsequent mammograms, regardless of the outcome of their biopsy, using the Reminder Letter as described in Section 8c3. At each subsequent draw they will also be asked to complete the Health Status Update Questionnaire.

8c.5 Approach via Breast Surgeons (Surgical Cohort). Several breast surgeons at Swedish Medical Center have agreed to identify patients that are likely candidates for surgical specimen collection. Women selected for approach based on the surgical schedule will be approached at the pre-surgical appointment for consent to obtain specimens. The informed consent will be conducted by a study Specimen Collection Specialist (SCS) or the Research Nurse. Women will be asked to sign a **Consent for Data Collection and Specimen Donation At Surgery** allowing permission to obtain a blood sample *prior* to surgery, and to donation of breast cancer tissue should there be excess tissue available. Women will also be asked to sign a **Medical Records Release Form**, which allows researchers to access their surgical pathology report and other records related to their cancer diagnosis. This is the procedure that we have used successfully to obtain blood samples and tissue from women undergoing surgery for suspected ovarian cancer at SMC. We will obtain also consent to obtain tissue blocks, which are stored for 10 years at SMC and made available routinely to investigators at the FHCRC.

8c.6 Specimen Collection and Processing

8c.6.1 Blood Collection. In all blood collections, the Specimen Collection Specialist will collect up to 50 ml of whole blood in one 10ml yellow-top tube, two 10 ml red-top tubes and two potassium EDTA 10 ml (purple-top) tubes. The volume of blood drawn may be adjusted

downward as necessary. Tubes will be stored in the refrigerator and processed within 48 hours of receipt. Standard protocols will be followed to process specimens into sera and plasma and to aliquot into cryovials uniquely labeled with study specimen ids. Blood specimens will be stored in very small quantities to avoid freeze-thaw cycles and re-aliquotting. Aliquoted specimens will be transported to the study repository for long-term storage or delivered to laboratory investigators. Times of blood draw, processing and freezing will be recorded.

8c.6.2 Tissue Collection A log of scheduled surgeries for potential tissue donors will be maintained so that the SCS can be present at the surgery. Immediately after the surgeon has removed the necessary tissue and the pathologist has taken what is required for pathologic diagnosis, the SCS will be permitted to collect specimens from the removed tissue for the purposes of the study. When clinically appropriate, a minimum of two and a maximum of ten 1.0ml cryovials, each holding 1 gram, 2cc, or 20mm of breast tissue, will be collected for the study. When feasible, the optimal tissue quantity per case is 6 grams. Tissue collected will include malignant tissue and, if possible, adjacent normal tissue.

During the entire surgical procedure, the treating surgeon and the surgical team will be responsible for monitoring the patient's condition. The surgeon will ultimately remove a surgical specimen and give this to the pathologist. The pathologist will then identify tissue that will not be needed for pathologic diagnosis. All or part of the un-needed tissue will be collected and placed in the labeled cryovials and processed for storage. The pathologist may refuse to provide any specimen for research if they believe that the entire specimen is needed for the subject's clinical care.

The tissue will be snap-frozen, placed into cryovial(s), and stored at -80 degrees C.

8c.6.3 Specimen characterization. For all cases with fresh tissue, Dr. Kiviat will perform histology review.

8c.6.4 Specimen Storage. Each specimen will be labeled with a unique 6-digit numeric label. A duplicate of this label is affixed to a specimen transmittal form identifying the specimen type and participant number, and logged into the database. Examples of these specimen transmittal forms are presented as Instruments 9 and 10. Blood specimens will be stored in a -70° C freezer, and tissue specimens will be stored in a liquid nitrogen freezer.

8c.6.5 Repository Quality Control. A rigorous quality assurance plan is already in place that includes monitoring and maintenance checks of equipment, an eight-hour CO2 back-up system and a temperature-sensitive alarm system that alerts the building maintenance staff when the interior temperature reaches a designated temperature.

8c.6.6 Repository Use. A Specimen Review Committee described in the Communication section will oversee use of specimens in the resource. Advocates will participate in this committee.

8d. Subject Assignment (randomization): Not applicable.

8e. Evaluations Prior to Entry. No clinical evaluations are made prior to entry into the study. If a woman has given us permission to access her mammography records and/or completed and signed the Network Questionnaire, mammogram findings (assessment codes, follow-up recommendation, breast density) and/or family history information from the questionnaire are used to classify women with respect to risk. The mammogram findings are obtained through procedures outlined in the Mammography Tumor Registry (IR#3636). A stratified random sample of women in the mammography cohort are invited to donate blood annually at subsequent mammograms, as described in Section 7.

8f. Evaluations to be made during the conduct of the study. Breast cancer case status will be ascertained on all women using the MTR system of linking to CSS/SEER and Washington State Cancer Registry Data, which include date of diagnosis, stage and grade of disease, histology, age, and race/ethnicity, in addition to individual identifiers. Linkage with high-quality cancer registry data provides passive follow-up for cancer outcomes, including survival. A Certificate of Confidentiality was obtained to protect the linked data from subpoena. These procedures are outlined in detail in IR#3636.

8g. Clinical Assessments. Pathology reports will be obtained routinely for women diagnosed with cancer at SMC to obtain day of diagnosis (CSS records only the month and year) for women in the SC and the subset of women in the MC who have undergone biopsy. This information will be collected using the **Patient Pathology at Diagnosis Form** (currently under development) Additional clinical data will be collected using the **Clinical Status Form** (currently under development). Other data collection instruments include the **Cancer Research Registry Questionnaire**, the **Baseline Questionnaire**, the **Health Status Questionnaire**, the **Health Status Update** which are attached to this protocol.

8g.1 Baseline Questionnaire Reliability and Validity

In an effort to ensure high quality data and to maintain common data elements, investigators have decided to use a Baseline Questionnaire that they are already using in collaborative work in the national Risk of Ovarian Cancer (ROCA) screening trial. Although significant statistical and clinical expertise were involved in questionnaire development, the CGN questionnaire has not been formally tested for validity and reliability. Investigators agree that it is not feasible to assess the validity of the questionnaire because of the substantial personnel effort that would be required to review source documentation such as medical records.

Investigators do plan to plan to assess the reliability of selected measures on the questionnaire, by comparing the responses to variables that are captured on both the Baseline Questionnaire (completed at baseline) to the Health Status Questionnaire (completed at each blood draw). Dr. Garnet Anderson will oversee the design and conduct of a reliability assessment for the Baseline Questionnaire. Dr. Anderson is an investigator at the Women's Health Initiative (WHI) statistical coordinating center, and has significant expertise in this area. WHI investigators have recently completed a study assessing the reliability of selected baseline measures in the WHI Observational Study (Ann Epidemiol 2003; 13:1-15, in press). This study observed that most demographic factors, reproductive variables and family medical history were reliably reported, with kappa or weighted kappa above 0.8. Most of the self-reported medical conditions yielded kappa above 0.75. Investigators anticipate that the Breast Cancer Early Discovery study will observe similar reliability using the Baseline Questionnaire, since many of the measures are the similar to those used in the WHI baseline questionnaires.

8h. Research Intervention/Activity that the Participant will experience

Consent for Contact. Women undergoing mammography will be asked to sign a **Consent to be Contacted for Future Research Studies (Join the Network Form)**, which means that they may be contacted in the future to donate blood for this study, or they may be contacted about other studies for which they are potential candidates. An example of another study that may contact

these participants is the Ovarian Cancer Early Detection Study, which is recruiting high-risk women to participate in an ovarian cancer screening protocol (IR file #5159).

Screening Questionnaire. To ensure consistency in data collection across sites, the **Women's Cancer Prevention and Detection Network Questionnaire** will be used at all locations, including the SBCC. This one-page screening questionnaire is used to collect preliminary medical and family history data. A copy of the questionnaire, along with a HIPAA compliant Medical Records Release (Network Release) will be mailed to women after they return the Consent to be Contacted for Future Research Studies.

Annual Blood Donation. Selected women among those who have undergone screening mammography and consented for future contact will be approached and requested to donate blood at the time of their next annual mammogram and annually thereafter. Women will be approached and consented by mail, as described in section 8c.2. Women who donate blood during biopsy, and well as those in the surgical cohort will also be invited to donate blood annually at the time of subsequent mammograms. All women who donate blood will be asked to complete a **Health Status Questionnaire** at the time of their first blood draw, and a **Health Status Update** at each subsequent draw.

Blood Donation at the Time of Biopsy. Women undergoing biopsy at SBCC will be asked to donate blood specimens at the time of the biopsy. They will also donate blood annually thereafter, at the time of subsequent mammograms.

Blood and Tissue Donation at the Time of Surgery. Women undergoing breast surgery will be invited to donate blood and tissue during surgery. Fresh tissue specimens will be obtained when it is logistically and ethically appropriate. Blood samples will be obtained just prior to or at the time of the surgical procedure. They will also donate blood annually thereafter, at the time of subsequent mammograms.

9. Risk/Benefit Assessment

The results of this research will be used to develop ways to find breast cancer early. Specifically, the study aims to develop a panel of biomarkers that can be used in conjunction with mammography to improve its performance. Although there is no direct benefit to women participating in this study, there may be benefits for other women in the future who are at risk for breast cancer or who are living with breast cancer.

Risks to participants including the potential of feeling uncomfortable due to answering personal questions on study questionnaires. Risks associated with blood draw include the possibility of temporary discomfort or a bruise at the site of the needle puncture. Donation of blood and tissue during surgery will not present any additional risks.

10. Reporting of Serious or Unexpected Adverse Events

Adverse events are expected to be rare on this study. Study personnel will have direct exposure to participants only for a short period of time (eg during the consent and specimen collection process), and will not be monitoring participant's health as they would for a clinical treatment protocol. Therefore, study participants will be asked to report any adverse events that they experience that appear to be related to study participation. This will be done by calling the Research Nurse at: 206-215-6209 or 1-800-328-1124.

An adverse event is any event that occurs during the study, which results in the subject experiencing a new symptom or worsening of an existing symptom. For example, fainting or loss of cognitive function after a blood draw would be considered an adverse event.

A serious adverse event is an event that results in any of the following outcomes:

1. Death
2. Life threatening event
3. Inpatient hospitalization*
4. Persistent or significant disability or incapacity

**Patients undergoing surgery for breast cancer will be approached to donate blood and tissue for the study. Hospitalization associated with this already-planned surgery will not be considered an adverse event.*

Adverse events will be reported to the FHCRC Institutional Review Office (IRO) at the time of annual review for the study. Adverse events that are both serious and unexpected will be immediately (upon the study office notified) reported by telephone to the FHCRC IRO and by telephone to the USAMRMC, Deputy for Regulatory Compliance and Quality (301-619-2165; FAX 301-619-7803). A written report will follow the initial telephone call within 3 working days. The written report will be addressed to:

U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ
504 Scott Street
Fort Detrick, Maryland 21702-5012

11. **Description of Protocol Drugs or Devices:** Not applicable.
12. **Disposition of Data.** All participant materials such as survey responses will be kept in locked cabinets and accessed only by study personnel who have signed a confidentiality pledge. All data will be reported in aggregate format, and will not identify specific participants in any way.

All study materials are stored in locked filing cabinets accessible to study personnel who have signed a confidentiality pledge. All data is stored on a secure network server. Data entry systems are password protected. Access to data files is limited to those study personnel who manage data as part of their job responsibilities and who have signed the confidentiality pledge.

It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research.

13. **Modification of the Protocol.** Any modification to the protocol will follow established protocol modification procedure of the FHCRC Internal Review Office and the HSRRB for review and approval, which include detailed submission of any changes or additions.
14. **Departure from the Protocol.** If the study investigators or staff become aware of any departure from the protocol, the FHCRC Internal Review office will be notified in writing as well as HSRRB office.
15. **Roles and Responsibilities of Study Personnel.**

Nicole Urban, ScD, Principal Investigator (20% FTE) Dr. Urban will be responsible for overall coordination of logistics, facilitation of progress of the scientific teams, and communication at both the investigator and staff level, overall design and conduct of all research activities, and interdisciplinary leadership for the project. She is currently the Principal Investigator for several

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interdisciplinary projects involving scientists from molecular biotechnology and clinical immunology disciplines. She will provide the scientific leadership and framework for the evaluation and application of biomarkers for breast cancer screening. Dr. Urban is responsible for coordination of inter-institutional activities, as well as all activities conducted by investigators and staff at FHCRC, including statistical work on development and validation of the marker panel, and coordination of all recruitment, tracking and specimen collection activities. She will work closely with the statisticians and laboratory scientists in carrying out the proposed workplan and ensuring that study objectives are met. Dr. Urban is a recognized leader in interdisciplinary cancer screening research in the Seattle area with the ability to successfully integrate clinical, basic and public health investigators into a unified research team. She will supervise the Project Manager and meet regularly with all Center Investigators to monitor progress and ensure that interim tasks are completed in a timely manner. Dr. Urban will chair the All- Investigator meetings, co-chair the Interdisciplinary Working Group and participate in the Specimen Review Committee.

Lisa Isozaki, Project Manager (100% FTE) Ms. Isozaki will coordinate all activities of the Center at the staff level and supervise the support staff. She will work closely with project investigators to provide overall coordination for the study, and specifically be responsible for managing the relationship between the clinical, laboratory, and statistical components of the study to ensure interim and final deadlines are met. Ms. Isozaki will develop timelines with clear deliverables that integrate the activities of the laboratory scientists with the statistical scientists and project leadership. She will coordinate communication between study staff and investigators by soliciting regular written updates from the Informatics Manager and Research Nurse whom she will directly supervise. Ms. Isozaki will develop agendas and facilitate staff meetings and investigator meetings. She will provide leadership at the staff level for all study staff, and will directly supervise Kate Watabayashi, Program Assistant. With the assistance of key staff, Ms. Isozaki will compile complete documentation of detailed protocols for participant recruitment and retention, data management, and specimen repository management. Ms. Isozaki will oversee all the administrative activities of the study. Ms. Isozaki will be responsible for all project management activities such as budget preparation and monitoring, managing logistics of subcontractor relationships, human subjects applications including the necessary cooperative files at subcontractors institutions, facilitating investigator meetings and incorporating investigator decisions into the staff workplan.

Kate Watabayashi, Program Assistant (100% FTE) will assist the Project Manager in the overall coordination of research activities. She will arrange staff and investigator meetings, prepare minutes, perform literature searches, conduct word processing/desktop publishing of scientific presentations and manuscripts arising from the study, coordinate investigator travel, and provide overall staff support to the project. Ms. Watabayashi will assist with budget monitoring and securing subcontracts in a timely manner. She will be responsible for all purchasing for the study, including office supplies, laboratory supplies and equipment. Ms. Watabayashi will coordinate all human subjects applications and modifications including oversight of all necessary cooperative files at subcontractors institutions. Ms. Watabayashi will assist the Clinical and Informatics Core staff with participant mailings and development of data entry and study tracking systems as needed.

Advocates

Shannon Marsh, Advocate (25% FTE) Ms. Marsh will coordinate advocate involvement in the research program. She will chair patient advocacy meetings and facilitate ongoing communication among advocates and between the advocate group and study investigators. She will also play a central policy role in evaluating the risks and potential benefits of this research,

and in representing her assessment to the Institutional Review Board (IRB). She will attend Institutional Review Board (IRB) meetings when the study is discussed to educate the IRB about the overall goals of the study, and to provide information about patient approach procedures and the confidentiality and privacy protections in place. In addition, Ms. Marsh will work closely with Drs. Ramsey, and Drucker and Ms. Gough to address consideration of the clinical utility of the marker panel. Ms. Marsh will attend regular scientific meetings including All-Investigator meetings, Specimen Review Committee meetings, and Interdisciplinary Working Group Meetings. She will represent the research study at local and national advocacy meetings.

Julia Cañas. Julia Cañas will be responsible for coordinating minority recruitment. Ms. Cañas will work through established contacts to disseminate study information and will collaborate with Shin-Ping Tu, a UW investigator responsible for minority recruitment for the ovarian SPORE, to develop culturally appropriate approach protocols for minority populations.

Mona Bailey. Mona Bailey will be responsible for educational outreach. Ms. Bailey will work with Ms. Cañas to develop a study brochure specifically targeting minority groups. She will also coordinate the development and implementation of educational outreach programs geared toward the African American, Asian, and Hispanic communities.

Barbara Bridge. Barbara Bridge will be responsible for development of patient retention materials, and programs to empower breast cancer survivors to be active participants in a research program. Ms. Bridge will work with study investigators and clinical staff on creating survivor-to-survivor letters and reminder cards. She will also coordinate efforts to develop a study brochure and an advocacy newsletter.

Scientists

Martin McIntosh, PhD, Statistician (20% FTE) will be responsible for the data that describes the laboratory analyses and for the data analysis relating to the validation of markers that may be added to a breast biomarker panel. He will work closely with Ms. Guay to develop analysis sets for use by the investigators. He will work with the other investigators to solve methodological problems associated with collected variables and data analysis. Dr. McIntosh will collaborate with Drs. Urban and Anderson in this methodological work. He will also participate in manuscript and report preparation.

Garnet Anderson, PhD, Statistician (10% FTE) Dr. Anderson is responsible for the Patient Registry, including epidemiological, clinical and follow-up information about the women. She will collaborate with Drs. Mandelson and Clarfeld to develop risk assessment and sampling measures that incorporate breast density, mammography outcome, pedigree and other risk factor data, and participate in the development of study questionnaires and other data collection instruments. Dr. Anderson will provide scientific leadership to Shirley Gough in the management of patient contact, data collection and the patient tracking system. She will develop statistical methods for measuring risk using data available from consenting women and associated mammography data. She will work closely with Dr. McIntosh and will coordinate with other investigators in the development and evaluation of potential marker panels resulting from the assays performed on the Panel Validation Set. Together with Dr. Kiviat, Dr. Anderson will co-chair the Specimen Review Committee. Dr. Anderson will participate in manuscript and report preparation.

Nancy Kiviat, MD, Pathologist (10% FTE) Dr. Kiviat will serve as co-PI, responsible for the Specimen Repository. She will be supported by Ms. O'Briant who will manage all activities surrounding specimens from the time of collection to analysis. Dr. Kiviat and Ms. O'Briant will be responsible for specimen inventory control, the specimen tracking system and the Specimen Review Committee. Dr. Kiviat will be responsible for ensuring that the common data elements

used to describe stored specimens that are currently being developed by other research networks including SPORE's and the EDRN will be used in this study. She will also be responsible for blood processing protocols and characterization of specimens in the repository. Dr. Kiviat will measure mammaglobin using PCR in DNA from cells obtained from blood. She will work closely with Drs. Schummer and Karlan on methods for extraction, amplification and preservation of mRNA from tissue for molecular profiling work. Dr. Kiviat will also collaborate with Drs. Hellstrom, Mills and Schummer to investigate gene expression in breast tissues. Dr. Kiviat will be responsible for all activities conducted by investigators and staff at the UW. The UW contributes laboratory-based clinical scientists with an understanding of the biology of the disease as well as the needs of the patients. Dr. Kiviat will facilitate communication among the UW laboratory scientists and provide leadership and guidance for the assay development and biomarker measurement activities.

Scott Ramsey, MD, PhD, Health Economist (5% FTE) Dr. Ramsey is an internist and health economist who oversees the Mammography Tumor Registry at FHCRC. He will lead the scientific team evaluating the clinical utility of study results and the feasibility of integrating a marker panel routinely into clinical care. He will work with the team to develop standards to evaluate markers. Dr. Ramsey will participate in the development of data collection instruments, to ensure that adequate data are collected for future cost-effectiveness analyses that would be conducted as part of translating study results into clinical practice. In addition, he will assist with general analysis and participate in manuscript and report preparation. Because Dr. Ramsey is a recipient of a National Cancer Institute career development award he will donate his salary until February 1, 2003.

Meg Mandelson, PhD, Epidemiologist, (5% FTE) Dr. Mandelson has investigated the characteristics, including breast density, of breast cancers that are not detected by mammography, and will collaborate with Dr. McIntosh in investigating candidate biomarkers that may complement mammography and improve screening performance. She will collaborate with Drs. Anderson and Clarfeld to develop risk assessment and sampling measures that incorporate breast density, mammography outcome, pedigree and other risk factor data, and participate in the development of study questionnaires and other data collection instruments.

Allen Gown, MD, Breast Pathologist (5% FTE) Dr. Gown is an internationally recognized expert in breast pathology and in the diagnostic and research applications of immunohistochemistry. He will provide expertise in expression at the tissue level of angiogenesis and other markers. He will work closely with Drs. Yaziji, Rivkin and Schummer to identify breast cancer subtypes and "bad actors". He will interpret results from IHC studies of biomarkers on breast tissue samples and provide input on which biomarkers might have utility as diagnostic and prognostic indicators.

Hadi Yaziji, MD, Breast Pathologist (5% FTE) Dr. Yaziji is a breast pathologist with extensive experience in immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). He will be responsible for activities in the PhenoPath laboratory. Dr. Yaziji will evaluate breast biopsies from study participants and work with Dr. Gown to interpret results from IHC studies of biomarkers on breast tissue samples. He will work closely with Drs. Gown, Rivkin and Schummer to identify breast cancer subtypes and "bad actors". Dr. Yaziji will evaluate tissue donated by participants for histologic prognosticators, as well as selecting foci of interest on the tissue sections for potential ancillary studies. He will work with Dr. Gown to interpret results from IHC studies of biomarkers on breast tissue samples and provide input on which biomarkers might have utility as prognostic indicators.

Brad Nelson, PhD, Immunologist (Contributed Consultant) Dr. Nelson has identified a panel of 12 tumor antigens that together are recognized by serum antibodies from 18/30 ovarian cancer

patients compared to 0/20 normal controls. Preliminary results using a small number of early-stage breast cancer sera (n=12) indicate that several of these antigens are also immunogenic in breast cancer. Dr. Nelson is currently developing assays for these markers. Dr. Nelson will collaborate with Dr. Mann to explore markers that continue to look promising for potential inclusion in the biomarker panel.

Michel Schummer, PhD, Molecular Biotechnologist (Consultant 20% FTE Years 01-02; 20% FTE Years 03-04) Dr. Schummer is a Senior Research Scientist at the Institute for Systems Biology, and has experience conducting laboratory procedures to measure gene expression. Dr. Schummer will collaborate with Dr. Kiviat to ensure integration of the newest molecular approaches to genomics and proteomics in the laboratory work. Dr. Schummer will maintain ongoing communication with Dr. Kiviat regarding additional PCR markers that become available over the period of the grant, so that they can be incorporated into this study. He and will work closely with Drs. Kiviat and Karlan on methods for extraction, amplification and preservation of mRNA from tissue for molecular profiling work in Years 1-2 and will be responsible for molecular profiling of breast cancer tissues in Years 3-4. Dr. Schummer will also collaborate with Drs. Hellstrom, Mills and Kiviat to investigate gene expression in breast tissues. He will work closely with Drs. Gown, Yaziji and Rivkin to identify breast cancer subtypes and "bad actors". Dr. Schummer will help ensure that the protocols for processing and handling of macrodissected tissues will preserve the integrity of the molecules that will later be extracted from tissue specimens, including RNA, DNA and protein.

Ingegerd Hellstrom, PhD, Immunologist (5% FTE) Dr. Hellstrom is an expert in the development of antibody-based tests to detect shed and secreted proteins expressed by tumor, and organ-specific antigens that are amplified by tumor growth. She will work closely Drs. Mills and Kiviat to develop assays for genes identified in breast cancer pathways. Dr. Hellstrom will test an assay to measure mesothelin using the Assay Refinement/Triage set of specimens. If it appears useful for the panel, she will then measure mesothelin and other proteins that meet the criteria for initially promising results in the Panel Definition Set. She will collaborate with Dr. Mills to develop ELISA assays necessary to facilitate his work in lipid markers, and with Dr. Kiviat on an antibody for mammaglobin.

Gordon Mills, MD, PhD, Molecular Oncologist (5%) Dr. Mills will be responsible for laboratory science conducted at MD Anderson Cancer Center. His overall responsibility will be to study lipid markers that may complement mammography. He will use serum samples from the Assay Refinement/Triage Set to refine the assay to measure LPA and other lipid markers. In addition, he will measure the lipid markers in the panel development set of serum samples. Dr. Mills will provide leadership and guidance for the development of detailed specimen processing protocols to ensure consistent measurement of lipid markers in serum samples. He will also collaborate with Drs. Schummer, Hellstrom, and Kiviat to investigate gene expression in breast tissues.

Gary Mann, MD, Immunologist (5% FTE) Dr. Mann will be responsible for activities in the Tumor Immunology Laboratory at the UW. He will use serum samples from the Assay Refinement/Triage Set and Panel Development Set to refine the assays to measure for antibodies to HER2, p53, and IGFBP-2. He will participate in the evaluation of laboratory results and the development and validation of the marker panel.

Irena King, PhD, Lab Director (5% FTE) Dr. King will be responsible for activities in the PHS Core Lab. She will measure VEGF and HGF in both the Assay Refinement/Triage Set and Panel Development set of plasma samples. In addition, Dr. King will oversee all scientific and quality control activities of the project as they relate to blood processing, storage and analysis. Dr. King will supervise Kathy O'Briant, the Research Technician who will provide assistance in all of the study laboratories in Years 1-3, and who will conduct the assays for the Validation Panel Set in

Dr. King's laboratory in Years 3 and 4. Dr. King will be responsible for ensuring identical processing and storage of all specimens as well as coordinating the completion of serum-assays performed in off-site laboratories. Dr. King will also manage and coordinate the transfer of serum specimens between study sites when necessary. She will work with Dr. Urban and Ms. O'Briant to develop a protocol for the transfer and tracking of specimens from designated study freezers to other laboratories for their initial and on-going assay analysis. She will also lend her expertise to the evaluation of serum assays and will participate in manuscript preparation.

Clinicians

Scott Karlan, MD, Cedars-Sinai Breast Surgeon (Consultant 20% FTE) Dr. Karlan is a leading breast surgeon who has participated in research activities at Cedars-Sinai involving tissue collection and biomarker development. Dr. Karlan will oversee recruitment, enrollment and specimen collection from women undergoing biopsy for suspected breast cancer at Cedars Sinai Medical Center. He will travel to Seattle once in each year for an All-Investigator Meeting and will participate in additional All-Investigator meetings via conference call or web interface. See Cedars-Sinai subcontract.

Beth Karlan, MD, Gynecologic Oncologist (5%FTE; 1% compensated, 4% donated) Dr. Karlan has extensive experience in cancer screening and has collaborated with Dr. McIntosh in the past on the evaluation of markers for ovarian cancer screening. She will participate in the evaluation of laboratory results and the development and validation of the marker panel. Dr. Karlan will work closely with Drs. Schummer and Kiviat on methods for extraction, amplification and preservation of mRNA from tissue for molecular profiling work. Dr. Karlan will participate in conference calls and be available via email to collaborate with investigators in Seattle. She will travel to Seattle annually to participate in an All-Investigator Meeting and will participate in additional Investigator meetings via conference call or web interface. She will participate in manuscript and report preparation. See Cedars-Sinai subcontract.

Mariann Drucker, MD, Swedish Medical Center Radiologist (5% FTE). Dr. Drucker is a highly experienced mammographer in the Swedish Breast Care Center. She will provide clinical guidance and expertise to the project about breast cancer screening and will help interpret mammography data. She has been an investigator on the Mammography Tumor Registry (MTR) since 1994 and has served as the liaison to the medical community in Washington State and as the primary contact for radiologists participating in the MTR project. She will supervise interactions between project staff and radiologists and their staff. Dr. Drucker, her associates and their staff, will administer the consent to contact form and Screening Questionnaire to patients and will invite women undergoing stereotactic biopsies to participate. She will work with Drs. Ramsey and Kessler and Ms. McAree to address the clinical utility of the panel of biomarkers. She will attend Investigator and Interdisciplinary Working Group meetings and provide leadership in interpreting the clinical relevance of mammography findings.

Saul Rivkin, MD, Oncologist (3% FTE) Dr. Rivkin is a well-known breast cancer oncologist in the Seattle community, practicing at Swedish Medical Center. Dr. Rivkin will serve as a liaison between study investigators and the clinical community, especially clinicians providing breast cancer care. In this role, Dr. Rivkin will facilitate and encourage participation by clinicians in the Interdisciplinary Working Group for which he will serve as Co-Chair. Dr. Rivkin has a similar role for an ovarian cancer research program in Seattle, and has been successful in bringing the clinical perspective to scientific studies. He will work closely with Drs. Gown, Yaziji, and Schummer to identify breast cancer subtypes and "bad actors". Dr. Rivkin will also provide scientific leadership for the evaluation of VEGF as a candidate for inclusion in the biomarker panel.

David Beatty, MD, Swedish Medical Center Breast Surgeon (Contributed Consultant) Dr. Beatty is a leading Seattle breast surgeon who has been an investigator on other FHCRC breast studies involving tissue collection. He will notify the study of patients scheduled for breast biopsy or surgery so the SCS can obtain informed consent pre-operatively, draw blood and attend surgeries to collect tissue on patients with large tumors that could potentially yield tissue for study purposes. He will collaborate with Drs. Anderson and Mandelson to develop risk assessment and sampling measures that incorporate breast density, mammography outcome, pedigree and other risk factor data, and participate in the development of study questionnaires and other data collection instruments. He will be a member of the Interdisciplinary Working Group.

Marc Horton, MD, Swedish Medical Center Breast Surgeon (Contributed Consultant) Dr. Horton is an experienced breast surgeon. His surgical practice is located on the same floor as the blood collection clinic for the Marsha Rivkin Ovarian Cancer Research Center, which can be used for this Center's blood draws. Dr. Horton and his partners will notify the study of patients scheduled for breast biopsy or surgery so a SCS can obtain informed consent pre-operatively, draw blood and attend surgeries to collect tissue on patients with large tumors that could potentially yield tissue for study purposes. He will be a member of the Interdisciplinary Working Group.

David Needle, MD, Swedish Medical Center Breast Surgeon (Contributed Consultant) Dr. Needle is an experienced breast surgeon and member of a large surgical practice. Surgery office staff will work closely with the SCS and will notify the study of patients scheduled for breast biopsy or surgery so the SCS can obtain informed consent pre-operatively, draw blood and attend surgeries to collect tissue on patients in their practice with large tumors that could potentially yield tissue for study purposes.

Janice Stracener, MD, Swedish Medical Center Radiologist (Contributed Consultant) Dr. Stracener is a highly experienced mammographer in the Swedish Breast Care Center and is currently the SBC liaison to the Mammography Tumor Registry, participating in the Radiologist Advisory Committee. Dr. Stracener, her associates and their staff, will administer the consent to contact form and Screening Questionnaire to patients and will invite women undergoing stereotactic biopsies to participate. She will attend Investigator and Interdisciplinary Working Group meetings and assist in interpreting the clinical relevance of mammography findings.

Patient Registry and Specimen Repository Staff

Shirley Gough, RN, Research Nurse, (50% FTE) Ms. Gough has extensive experience in the breast cancer care clinical setting, and will manage the Patient Registry, responsible for all activities that involve contact with women or their physicians or the data that describes them, including patient contact, data collection activities and the patient tracking system. She will be responsible for implementing the components of this study involving physician and participant interaction, including participant recruitment, retention, and compliance. Ms. Gough will facilitate relationships with the breast cancer surgeons at SMC whose patients will be approached, and work with these physicians to develop efficient enrollment procedures to minimize impact on patient flow in the clinics. She will work with the Breast Care Center to coordinate enrollment of women undergoing mammograms and biopsies. She will work closely with Ms. McAree and Drs. Ramsey, Kessler and Drucker to address the clinical utility of the panel of biomarkers. She will oversee and monitor the recruitment process, and work with Ms. Shaw to develop standardized recruitment and compliance reports accessible to all investigators via the Flex KB collaborative site. Ms. Gough will attend biopsy appointments of women who have provided permission, conduct informed consent, and perform blood draw. Ms. Gough will oversee weekly transfer of serum specimens from Dynacare laboratories to study freezers. She will conduct quality assurance checks on specimen collection forms, pathology data forms, and freezer

inventory. Ms. Gough will also review the pathology reports for patients who develop cancer to collect information on estrogen and progesterone receptor assays, HER2, p53 and other markers. She will review the reports of in situ cancers to ascertain the histologic subtypes of DCIS because CSS and WSCR coding guidelines for histology lead to a broad grouping of DCIS and lose some of the more specific information on subtypes which are of interest to investigators. Ms. Gough will supervise the Specimen Collection Specialists and Alisa Larson, Program Assistant.

Kathy O'Briant, Research Technician (100% FTE) Ms. O'Briant is very experienced in all of the laboratory procedures required for the proposed work. She will manage the Specimen Repository, including all activities surrounding specimens from the time of collection to analysis and will be the contact person for all requests and communication. Under the direction of Dr. Kiviat, she will be responsible for specimen inventory control, the specimen tracking system and the Specimen Review Committee. To promote good communication between laboratories, Kathy O'Briant will serve as liaison between the laboratory scientists and statisticians and will supervise the TBN Research Technician who will work in the various laboratories. She will provide assistance with assay development, refinement, and validation in all of the collaborating laboratories. She will compile complete documentation of laboratory procedures and protocols. She will work with Dr. Kiviat to develop lab procedures to extract RNA from small amounts of breast tissue. She will work closely with the laboratory scientists on the development of assays for genes identified in breast cancer pathways and the identification of breast cancer subtypes and "bad actors". Ms. O'Briant will conduct the assays on the Panel Validation Set in Dr. King's laboratory (Years 3 and 4). She will work closely with Ms. Gough to develop and monitor collection procedures. She will also work closely with the Informatics staff on the redesign and maintenance of the specimen tracking system (STS) and the implementation of the FlexKB to ensure both systems meet the needs of the laboratory scientists. Ms. O'Briant will supervise the Research Technician hired in Year 03.

Meghan Crawford, Research Technician (100% FTE in Years 03 and 04) The Laboratory Research Technician will provide assistance in all of the study laboratories and, along with Ms. O'Briant, will conduct assays on the Panel Validation Set in Dr. King's laboratory. Ms. Crawford will also be responsible for facilitating communication among laboratories and documenting lab procedures. All activities will be coordinated by Ms. O'Briant.

Heather Aiosa, Specimen Collection Specialist (50% FTE Year 01, 100% FTE Year 02-04) Ms. Aiosa is a trained phlebotomist and experienced Specimen Collection Specialist, She will be assigned to Dr. Beatty's surgical practice and be responsible for conducting informed consent for donation of blood and tissue specimens for patients enrolled at that practice. To facilitate this process, work space for the SCS will be provided in Dr. Beatty's practice. Ms. Aiosa will perform blood draw on consenting patients for whom tissue will not be collected. She will monitor the surgical schedule, and attend surgeries of enrolled women when the surgeon has indicated that excess tissue may be available. In these cases, she will collect blood and tissue in the operating room. Although her principal assignment is in Dr. Beatty's practice, his office is within walking distance of the offices of Dr. Horton and the SBC and she will be available for collections at other locations. When time allows, Ms. Aiosa will assist with the substantial data entry volume that will be required to enter the 1-page screening questionnaire completed by women undergoing mammograms at the Breast Care Center. Ms. Aiosa will also assist with data entry of the epidemiologic Baseline Questionnaires, and the annual health status forms from women donating specimens. For each specimen collection, Ms. Aiosa will complete a detailed specimen collection form which indicates the specimen type and tracking number, date and time of collection, patient UPN, and associated data. She will use this form to enter collected specimens into the computerized inventory system.

(TBN?) Josh Sallin, Specimen Collection Specialist (50%FTE Year 01, 100% FTE Years 02-04)

Mr. Sallin is a trained phlebotomist and experienced Specimen Collection Specialist, currently performing these duties for the Ovarian SPORE. He will be assigned to Dr. Needle's surgical practice and be responsible for conducting informed consent for donation of blood and tissue specimens for patients enrolled at that practice. To facilitate this process, work space for the SCS will be provided in Dr. Needle's practice. Mr. Sallin will perform blood draw on consenting patients for whom tissue will not be collected. He will monitor the surgical schedule, and attend surgeries of enrolled women when the surgeon has indicated that excess tissue may be available. In these cases, he will collect blood and tissue in the operating room. Although his principal assignment is at the PacMed Clinic, the clinic is located within .3 miles of SMC and the offices of Dr. Clarfeld, Dr. Horton and the SBC and Mr. Sallin will be available for collections at other locations. When time allows, Mr. Sallin will assist with the substantial data entry volume that will be required to enter the 1-page screening questionnaire completed by women undergoing mammograms at the Breast Care Center. Mr. Sallin will also assist with data entry of the epidemiologic Baseline Questionnaires, and the annual health status forms from women donating specimens. For each specimen collection, Mr. Sallin will complete a detailed specimen collection form which indicates the specimen type and tracking number, data and time of collection, patient UPN, and associated data. He will use this form to enter collected specimens into the computerized inventory system.

Leah Sabacan, Program Assistant (50% FTE Year 01; 75% FTE Years 02-04) Ms. Sabacan will provide support to all recruitment and intervention activities, including assembly and distribution of recruitment and enrollment materials, data entry of participant questionnaires, assembly and distribution of blood collection kits, assisting with specimen transfers and freezer inventory, conducting follow-up and reminder calls for all participants who are overdue for annual blood collections. 8,600 women will be asked to complete the Consent to Contact and 1-page screening questionnaire each year, and Ms. Sabacan will be responsible for data entry of those questionnaires from women who return them. She will be responsible for preparing enrollment/blood collection packets for 675 participants in year 1, and 400 participants in each subsequent year. She will conduct follow-up calls with participants who fail to complete their blood draws within the expected time frame. Ms. Sabacan will provide overall support to the staff leadership, coordinating special projects as needed. In particular, she will be available to assist Ms. Gough with special projects related to recruitment, and to assist Ms. O'Briant with Specimen Repository management tasks.

Informatics Staff

Steve Zeliadt, Informatics Manager, (50% FTE) Mr. Zeliadt has extensive experience in database development. He manages the Mammography Tumor Registry (MTR). Mr. Zeliadt will be responsible for managing informatics including the Specimen Tracking System (STS), access to and analysis of data, report generation and web-based communication tools (FlexKB). The broad scope of his responsibility will include database design and development, maintenance and updates of the linked mammography tumor registry, design and development of data collection instruments, coordinating investigator requests for analysis datasets, development of standardized reports describing the Specimen Repository, and management of the STS. Mr. Zeliadt will coordinate quarterly data transfers from radiology facilities to the study office and identification of high risk patients based on mammography and questionnaire data, and linkage of mammography data to the SEER/WSCR registries to identify cancers in the screening population. Mr. Zeliadt will develop task lists and timelines for the database development work, and work with Carole Shaw, the Database Manager, and programmers to ensure that study requirements for informatics support are met. Mr. Zeliadt will serve as liaison with Lauren Clarke, the consultant developing the FlexKB system to support real time inter-institutional communication and project

updates between investigators. He will work with Ms. O'Briant to support the Specimen Review Committee, and will be responsible for compiling detailed specimen inventory information for the committee's reference in making specimen allocation decisions. Mr. Zeliadt will work with Carole Shaw to identify specimens to be transferred to project investigators, and will ensure that all appropriate scientific approvals are in place. Mr. Zeliadt will supervise the Database Manager and Informatics Specialist.

Michael O'Donnell, Statistical Research Associate (50% FTE) Mr. O'Donnell will be responsible for statistical procedures including data quality control, dataset cleaning and analysis for all study data. He will work closely with Drs. McIntosh and Anderson to evaluate the results of surveys and questionnaires, and will provide statistical analysis support to study investigators. He will also work closely with Mr. Zeliadt to manage the mammography data obtained from the Swedish Breast Care Center following approved Mammography Tumor Registry procedures.

Carole Shaw, Database Manager (50% FTE) Ms. Shaw currently has responsibility for two databases which will be used for the study: the linked mammography tumor registry, and the STS which is used to track inventory and laboratory results for biological specimens for the ovarian SPORE. Ms. Shaw will continue to manage and oversee all database activities. She will develop a study database to identify all subjects who have agreed to participate and routines to select and identify eligible participants. Other features of the database will include reports documenting the status of participants and generation of follow-up letters for serial blood draws. She will analyze the current specimen tracking system and develop revised software design specifications necessary for this study and a plan for porting existing data in the legacy system to the new data structure. She will be responsible for ongoing database design and management, including data collection, data validation, and quality assurance checks on the linkage process as the database becomes more complex. She will be responsible for resolving disparity among linked data items, and for ensuring confidentiality. Ms. Shaw will make any adaptations to the STS to ensure that it meets the needs of this study, and for development of reports documenting the status of specimens collected for the study, including inventory, tracking, and laboratory value reporting. Ms. Shaw will supervise the Programmer, Shelly Hager, and Data Coordinator, Caroline Smith, and will be the primary contact for data management personnel for the exchange of data between participating laboratories and mammography facilities.

Appendix C
Cedars Clinical/Recruitment Protocol

**Center for the Evaluation of Biomarkers for Early Detection of Breast
Cancer**

Funded by the Department of Defense as a Breast Cancer Center of Excellence

Award Number: DAMD 17-02-1-0691

proposal Number: BC013002

Main Grant Recipient: Fred Hutchinson Cancer Research Center

Subcontractor: Cedars-Sinai Medical Center

**Recruitment and Specimen Collection Protocol for Cedars Sinai Medical
Center (CSMC IR#4321-01)**

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1. **Protocol Title:** Biomarkers for the Early Detection of Breast Cancer.
2. **Phase.** Not applicable
3. **Principal Investigator:** Nicole Urban, ScD
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Medical Monitor: This study has been determined to be minimal risk by the Department of Defense Human Subject Reviewer, so identification of a medical monitor is not necessary.

4. Locations of Study:

Cedars-Sinai Medical Center, 8700 Beverly Blvd. Los Angeles, CA 90048-1804	Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North, MP-900 P. O. Box 19024 Seattle, WA 98109
Group Health Cooperative Center for Health Studies 1730 Minor Avenue Suite 1600 Seattle, WA 98101	PhenoPath Laboratories 3000 First Avenue #1 Seattle, WA 98121
Virginia Mason Research Center 1201 Ninth Ave.	MacroGenics 1441 N 34th St

Seattle, WA 98101	Seattle, WA 98103
Pacific Northwest Research Institute 720 Broadway Seattle, WA 98122	University of Texas MD Anderson Cancer Center 1515 Holcombe Blvd. Houston, TX 77030-4095
University of Washington Medical Center 1959 N.E. Pacific Seattle, Washington 98195	
Swedish Medical Center Breast Care Center Dr. Dwyer (Radiologist) Dr. Stracener (Radiologist) 1101 Madison St., Suite 310 Seattle, WA 98104	Swedish Medical Center Drs. Hart, Florence and Horton (Breast Surgeons) Arnold Pavilion 1221 Madison, Suite 1411 Seattle, WA 98104-1360
PacMed Clinics Dr. Needle (Breast Surgeon) 1200 12 th Avenue South Seattle, WA 98144	University of Washington (Kiviat Laboratory) Harborview Medical Center Dept. of Pathology Box 359791 325 Ninth Ave. Seattle, WA 98104

5. **Expected Start and Completion Dates:** 10/1/2002-9/30/2006

6. Purpose and Objectives:

Purpose. The purpose of the Center is to assemble the team and the infrastructure needed to accelerate progress in breast cancer early detection biomarker research. We will develop a unique resource for inter-institutional collaborative breast biomarker research, and evaluate the potential of biomarkers detectable in serum or plasma to improve existing breast cancer early detection strategies. We will use the resource to evaluate the performance of candidate breast cancer biomarkers in a cohort of women participating in mammography.

Our vision is that a simple blood test could be used in conjunction with mammography to detect all breast cancer early in the disease process. For example, one clinical scenario might work as follows: at the time of her annual physician visit, a woman could have her blood drawn and tested for a panel of breast cancer markers. If the mammogram were clearly positive, she would be referred for biopsy. If the mammogram were equivocal, she would be referred to biopsy only if the marker panel suggested a malignancy. If the mammogram was negative, but the marker panel suggested malignancy, she would be referred for additional imaging such as MRI. Other scenarios may be preferable, and indeed one of the purposes of our study is to explore other possibilities. For example, use of the marker panel between annual mammograms might identify women with fast-growing tumors.

The expected result of the proposed Center is a panel of markers and decision rules for its use. The panel will be useful clinically, to improve the performance of mammography. Our comprehensive approach and access to an appropriate specimen repository increases the probability of our success. 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 (i.e. intraclass correlation), 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. Because high-quality specimens are frequently not available, investigators often rely on samples that were obtained from different sources for cases and healthy women. They may have been obtained during remission or even during treatment, or processed and stored differently in ways that affect marker levels. As a result, many markers that appear initially to be very promising prove later not to be useful, and the development process is characterized by false starts and missed opportunities. The scientific community is often skeptical about the claims made for new markers, in part because many initially promising results cannot be replicated in different laboratories.

Another barrier is the clinical challenge we will face if we are successful. Markers could be ordered before, at the same time as, or after a mammogram, by the primary care physician, a radiologist, or the specialist who evaluates suspicious findings. Each strategy

will affect the sensitivity and specificity of the combination of tests. If markers identify cancers that cannot be seen on a mammogram, clinical work up to identify the location of the tumor will be required. Cost-effective strategies will be needed. As we will obtain serum for women in several stages of evaluation—prior to screening, just prior to biopsy, and just prior to surgery—we will be in a unique position to evaluate the clinical utility of markers at all these potential stages of screening.

Objectives. Our goal is to evaluate breast cancer biomarkers for their contribution to early detection of breast cancer. Subsets of breast cancer that are missed by mammography, or that grow too quickly to be detected in early stage by annual mammography, are of particular interest. Our aims are:

1. To validate and refine the ability of candidate biomarkers to predict disease status;
2. To evaluate panels of biomarkers 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 subsets of in situ and invasive breast cancers and explore their associations with biomarkers in the panel.

To support the research goals we will build a unique resource for multidisciplinary, inter-institutional research on breast cancer biomarkers including

1. Blood samples obtained annually and processed identically in women with and without breast cancer,
2. Fresh tissue matched to blood samples on a subset of the women with and without breast cancer,
3. Epidemiological, clinical and follow-up information for women who donate specimens, and
4. A system to facilitate use of the specimens, including state-of-the-art information systems.

We will develop a specimen resource from a well-characterized population, with associated risk factor information, mammography findings and follow-up data on cancer outcomes. It will include blood samples obtained from selected women who have mammograms, biopsy or breast cancer surgery over the 4-year period of the grant. We will evaluate candidate biomarkers for their ability to distinguish among women with healthy breasts and women with various breast conditions, including both invasive and in-situ forms of breast cancer, premalignant breast diseases, and benign lesions. We will evaluate the role of biomarkers detectable in serum or plasma in improving our current breast cancer early detection strategies.

For selected women, we will explore the feasibility of collection and analysis of fresh-frozen tissue in order to characterize malignant conditions at the molecular level. This will allow us to correlate biomarkers included in the panel with subsets of breast tumors identified through molecular profiling.

Our hypotheses are:

- (a) Used alone, biomarkers detectable in blood products can detect subsets of, but not all, breast cancer;
- (b) Use of a breast cancer biomarker panel can improve the performance of mammography in early detection of breast cancer.

7. Study Population.

Recruitment for this study will take place in Seattle, at Swedish Medical Center, and in Los Angeles, at Cedars Sinai Medical Center. The overall study population is described below.

The study population includes three cohorts defined by recruitment source. The first recruitment source is women undergoing biopsy or surgery for breast cancer at Cedars Sinai Medical Center. Approximately 1,500 women undergo this procedure annually. Of these we will enroll 50 per year, including women with benign lesions and premalignant breast diseases, as well as women with in-situ and invasive carcinoma (see table 1). 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. Patients are not scheduled for surgical procedures for the purpose of this study alone.

The second source is the approximately 8,600 women who obtain mammograms and undergo biopsies at the Swedish Medical Center Breast Care Center in Seattle each year. As shown in Table 1, 500 (375 high-risk and 125 average-risk) women will be enrolled in Year 1, and 100 additional women will be enrolled in subsequent years. In addition, all women undergoing biopsies will be invited to provide a blood specimen prior to biopsy and annually at the time of subsequent mammograms. 100 women undergoing biopsies will be enrolled annually. Women identified and enrolled through the breast care center including women having both mammograms and biopsies, are referred to as the Mammography Cohort (MC).

The third cohort includes women undergoing breast surgery at Swedish Medical Center. The second recruitment source is the approximately 650 women who have surgery for breast cancer at SMC each year. As shown in Table 1, we expect to enroll 25 women in Year 1 and 50 women annually thereafter for donation of both blood and tissue. Fresh tissue specimens will be obtained when it is logistically and ethically appropriate. In addition we expect to enroll 100 women annually beginning in year 2 for donation of blood only. Blood samples will be obtained just prior to or at the time of the surgical procedure. Women identified and enrolled through our collaborations with SMC surgeons are referred to as the Surgical Cohort (SC). Following surgery and treatment, women in the SC will be invited to participate in the MC, providing blood samples at the time of their annual mammograms.

Table 1. Unique Participants

	Yr 01	Yr 02	Yr 03	Yr 04	Total
Mammography Cohort – High Risk	375	75	75	75	600
Mammography Cohort – Average Risk	125	25	25	25	200
Mammography Cohort – Biopsy	100	100	100	100	400
<i>Subtotal: Mammography Cohort</i>	<i>600</i>	<i>200</i>	<i>200</i>	<i>200</i>	<i>1200</i>
SMC Surgical Cohort: Blood and Tissue	25	50	50	50	175
SMC Surgical Cohort: Blood Only+		100	100	100	300
<i>Subtotal: Surgical Cohort</i>	<i>25</i>	<i>150</i>	<i>150</i>	<i>150</i>	<i>475</i>
Cedars Surgical Cohort: Blood and Tissue (CSC)	50	50	50	50	200
Total	675	400	400	400	1875

8. Protocol Design. This document outlines the methods for collection of blood and tissue from women undergoing surgical biopsy procedures at Cedars-Sinai Medical Center. Methods for recruitment and enrollment of the Seattle study population are described in a separate document.

8a. Eligibility Criteria.

Inclusion Criteria

Women 18+ years of age

Scheduled for breast surgical procedure for a benign or malignant condition

Exclusion Criteria

Breast abnormalities less than 15mm (for procedures using a mammotome)

Breast abnormalities less than 20mm (when using an open surgical technique)

Women enrolled at Cedars-Sinai are referred to as the Cedars Sinai Cohort (CSC). Surgical procedures will be performed in the Cedars-Sinai Medical Center hospital operating suites, the Saul and Joyce Brandman Breast Center, or the Cedars-Sinai Outpatient Surgery Center.

8b. Recruitment (Subject Identification)

After approval from the IRB, we intend to approach physicians who attend Breast Center conferences, to educate them about available research protocols for interested patients. Recruitment flyers will also be posted and made available to raise patient awareness, and we expect some patients to self-refer. This study will also be listed on the Cedars-Sinai web site.

Blood and tissue donors 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.

8c. Participant Approach, Enrollment, Informed Consent and Procedures

8c1. Participant Approach, Enrollment and Informed Consent

Physicians will identify patients who meet eligibility criteria at the time their patient is scheduled for breast surgery. The treating physician (or a member of their staff) will ascertain whether the patient is interested in learning more about the research protocol. The treating physician may be the principal investigator, a co-investigator or a non-investigator. Patients who express an interest will be referred to and ultimately contacted by a member of the research team, usually the study coordinator. The study will be described in detail, including the risks and benefits of study participation. The patient will be given an informed consent form to take home and review. The patient will have ample time to consider the study. Coercion and conflict of interest will be avoided by clearly explaining that this study plays no role in their clinical care, that participation in this study is strictly voluntary, and that declining to participate will not affect their treatment in any way. The investigator or co-investigator will obtain a signed informed consent prior to the collection of data, blood and tissue.

8c2 Research Procedures /Activity that the Participant will experience

Women undergoing breast surgery will be invited to donate blood and tissue during surgery and to complete two questionnaires. Tissue specimens and blood specimens will be obtained when it is logistically and ethically appropriate.

Questionnaire and data

After signed consent is obtained, study participants will be given the "Baseline Questionnaire" and "Health Status Questionnaire" and a stamped self-addressed return envelope. Study participants will be asked to return the Baseline Questionnaire within four weeks of their procedure, and asked to complete the Health Status Questionnaire just prior to their procedure. Participants who do not return the Baseline Questionnaire will be contacted by phone six weeks after their procedure.

Patient demographic data and pathologic classification will be acquired from the patient's medical records and anatomic pathology reports respectively. This information will be stored in the database and identified by the use of the assigned numeric identifier. Clinical assessments of the donors for the purpose of this study will be required.

Blood Collection:

Prior to each surgery, patient consent will be obtained to collect blood. The research collection team will notify and work with the operating room staff prior to the beginning of surgery that a patient is participating in the research study. Up to 50cc of blood will be obtained prior to or at the time of surgery, or at a time when blood is drawn for other laboratory tests. Priority of blood collection is: 1) four 10 ml red top tubes for serum specimens, 2) one 10 ml lavender top EDTA or yellow top tube for plasma. The volume of blood drawn may be adjusted downward as necessary if a clinical draw is being conducted on the same day.

Blood Storage:

10/22/04
Cedars Protocol 11_20_2003

Standard protocols will be followed to process specimens into sera and plasma and to aliquot into cryovials uniquely labeled with study specimen ids. Tubes will be stored in the refrigerator and processed within 48 hours of receipt. After processing, blood specimens will be aliquotted into 1.8 mL pre-labeled cryovials or very small quantities to avoid freeze-thaw cycles. Aliquoted specimens will be transported to the Core Tissue Bank for long-term storage or delivered to laboratory investigators. Times of blood draw, processing and freezing will be recorded.

Tissue Collection:

The amount of tissue collected for the purposes of the research study will vary. Tissue will be collected only if it is not needed for pathologic diagnosis. The clinical pathologist involved in the participant's case will work with the treating surgeon to identify the location and the amount of tissue available for research purposes. When clinically appropriate, a minimum of two and a maximum of ten 1.0mL cryovials (each holding 1 gram of breast tissue) will be collected for the study. When feasible, the optimal tissue quantity per case is 6 grams.

Tissue collected will include malignant tissue and, if possible, adjacent normal tissue.

For each tissue collection, a packet containing a "Dr. Karlan's Lab - Specimen Pickup/Documentation" form, the original and a copy of the signed informed consent form, a Cedars-Sinai Department of Pathology "Request for Tissue for Research" form, and labeled cryovials will be assembled. The study coordinator or designee will (1.) take this packet to the surgical suite for tissue collection, (2.) ensure that the original signed informed consent for study participation is placed in the subject's medical record prior to the surgical procedure, and (3.) work with the surgeon and operating room personnel to assure that they are aware of the patient's participation in this research project prior to the beginning of the patient's surgery. During the entire surgical procedure, the treating surgeon and the surgical team will be responsible for monitoring the patient's condition. The surgeon will ultimately remove a surgical specimen and give this to the pathologist. The pathologist will then identify tissue that will not be needed for pathologic diagnosis. All or part of the un-needed tissue will be collected and placed in the labeled cryovials and processed for storage. The pathologist may refuse to provide any specimen for research if they believe that the entire specimen is needed for the subject's clinical care.

Tissue Storage:

It is anticipated that only a small amount of tissue will be available per patient. After this tissue has been placed in cryovials, the study coordinator or designee will transfer the cryovials to the histobath located in the 3rd floor OR (for procedures performed in the hospital operating room suites) or the C-S Outpatient Surgery Center 1st floor OR (for procedures performed in the C-S Outpatient Surgery Center or the Joyce and Saul Brandman Breast Center).

The tissue will be snap-frozen in the histobath. Once a week, cryovials will be transported to the Core Tissue Bank. Specimens will be stored at -80 degrees C.

8d. Subject Assignment (randomization): Not applicable.

8e. Evaluations Prior to Entry.

No clinical evaluations are made prior to entry into the study.

8f. Evaluations to be made during the conduct of the study. Breast cancer case status will be ascertained on all women by abstracting information from participant medical records.

8g. Clinical Assessments. Pathology reports will be obtained and abstracted using the **Patient Pathology at Diagnosis Form**. Additional clinical data will be abstracted from medical records using the **Patient Clinical Status at Dx Form** and the **Clinical Follow Up Form** (for women diagnosed with breast cancer as a result of their biopsy). Mammography results will be abstracted from the medical records using the **Mammography Results Form**. All of these forms are currently under development and will be submitted to IRB at a later date.

9. Risk/Benefit Assessment

This research is intended to improve our ability to diagnose breast cancer at an early stage. Specifically, this study aims to develop a panel of biomarkers that can be used in conjunction with mammography to improve the clinical detection rate (true sensitivity) of mammography. Although there is no direct benefit to women participating in this study, there may be benefits for other women in the future who are at risk for developing breast cancer or who are living with breast cancer.

Risks to participants including the potential of feeling uncomfortable as a result of answering personal questions on study questionnaires. Participants may or may not be concerned about not knowing results of studies conducted on their blood and tissue. Risks associated with blood drawing include the possibility of temporary discomfort or a bruise at the site of the needle puncture. Donation of blood and tissue during surgery will not present any additional risks.

10. Reporting of Serious or Unexpected Adverse Events

Adverse events are expected to be rare in this study. Study personnel will have direct exposure to participants only for a short period of time (e.g., during the consent and specimen collection process), and will not be monitoring participant's health as they would for a clinical treatment protocol. Therefore, study participants will be asked to report any adverse events that they experience that appear to be related to study participation. This will be done by calling the Study Coordinator / Research Nurse.

An adverse event is any event that occurs during the study, which results in the subject experiencing a new symptom or worsening of an existing symptom. For example, fainting or loss of cognitive function after a blood draw would be considered an adverse event.

A serious adverse event is an event that results in any of the following outcomes:

1. Death
2. Life threatening event
3. Inpatient hospitalization*
4. Persistent or significant disability or incapacity

**Patients undergoing surgery for breast cancer will be approached to donate blood and tissue for the study. Hospitalization associated with this already-planned surgery will not be considered an adverse event.*

Adverse events will be reported to the local Institutional Review Board (IRB) as per institutional policy.

Adverse events that are both serious and unexpected will be immediately (upon the study office notified) reported by telephone to the local IRO and by telephone to Nicole Urban, FHCRC Principal Investigator. Dr. Urban will be responsible for reporting these events to the USAMRMC, Deputy for Regulatory Compliance and Quality (301-619-2165; FAX 301-619-7803). A written report will follow the initial telephone call within 3 working days. The written report will be addressed to:

U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ
504 Scott Street
Fort Detrick, Maryland 21702-5012

11. Description of Protocol Drugs or Devices: Not applicable.

12. Disposition of Data.

To maintain human subject anonymity, specimens and data are retrieved through the use of the numeric identifier only. Patient demographic data and pathologic classification will be acquired from the patient's medical records and anatomic pathology reports respectively. This information will be stored in the database and identified by the use of the assigned numeric identifier. Access to information linking the donors' real names with the numeric identifier will be restricted to study staff members.

13. Modification of the Protocol.

Any modification to the protocol will follow established protocol modification procedure of the local Internal Review Office and the HSRRB for review and approval, which include detailed submission of any changes or additions.

14. Departure from the Protocol. If the study investigators or staff become aware of any departure from the protocol, the local Internal Review office will be notified in writing as well as HSRRB office.

15. Roles and Responsibilities of Study Personnel at Cedars Sinai Medical Center

Scott Karlan, MD, Cedars-Sinai Breast Surgeon (Consultant 20% FTE) Dr. S. Karlan is a leading breast surgeon who has participated in research activities at Cedars-Sinai involving tissue collection and biomarker development. Dr. S. Karlan will oversee recruitment, enrollment and specimen collection from women undergoing biopsy or surgery for breast cancer at Cedars Sinai Medical Center. He will travel to Seattle annually for an All-Investigator Meeting and will participate in additional Investigator meetings via conference call or web interface.

Beth Karlan, MD, Gynecologic Oncologist (5%FTE; 1% compensated, 4% donated) Dr. B. Karlan has extensive experience in cancer screening and has collaborated with Dr. McIntosh in the past on the evaluation of markers for ovarian cancer screening. She will participate in the evaluation of laboratory results and the development and validation of the marker panel. Dr. B. Karlan will work closely with Drs. Schummer and Kiviat on methods for extraction, amplification and preservation of mRNA from tissue for molecular profiling work. Dr. B. Karlan will participate in conference calls and be available via email to collaborate with investigators in Seattle. She will travel to Seattle annually for an All-Investigator Meeting and will participate in additional Investigator meetings via conference call or web interface. She will participate in manuscript and report preparation.

The Study Coordinator / Research Nurse will work closely with project investigators to provide overall coordination for the study. (S)he will oversee administrative and project management activities, which include preparing and monitoring budgets, submitting and modifying IRB and Human Subjects applications, facilitating investigator meetings and incorporating investigator decisions into staff workplans. The Study Coordinator/Research Nurse will be responsible for implementing the components of this study that involve physician and participant interaction, participant recruitment, retention, and compliance. The Study Coordinator/Research Nurse will also review subject medical records to obtain data needed as described in the protocol.

Appendix D
Surgeon and Pathologist meeting minutes

Breast Cancer Early Discovery Meeting Summary
June 14, 2004
5:00pm-6:30pm
A-West level A & B conference rooms
Swedish Medical Center

Distribution List: J. David Beatty, Nicole Urban, Patricia Dawson, Christine Lee, Charles Drescher, Toni Oien, Patra Grevstad, John Dawson, Ron Tickman, Nan Ping Wang, Lisa Isozaki, Ksenia Koon, Shirley Gough, Kate Watabayashi, Kathy O'Briant

Consenting patients:

Consenting patients would be most practical at the pre-surgical visit and it was suggested by some that the surgeon introduce the study to their patients. By doing this, the patient may be more willing to consent if it appears her surgeon approves of the study. Then a study staff can proceed by providing detailed information about what the study will require from a participant. It was agreed that women should be consented for both blood and tissue donation, but that it would be decided later by the surgeons and pathologists whether tissue would be collected for research.

Blood draw:

Dr. Urban prefers that conditions at the time of blood draw mimic those of a woman who goes for screening, to avoid conditions such as fasting. Collections should be done at the pre-surgical visit rather than the OR

Dr. Lee believes that this is feasible, because if a woman consents to the study, she most likely will allow blood to be drawn at the pre-surgical visit.

Tissue:

All were concerned by the amount of tissue requested for the study. Dr. Tickman believes that the study will not receive grams of tissue, but rather millimeter tissue slices from the center of the tumor which, implying that the tumor tissue requirement must be reduced to 1 or 1.5 cm diameter. Dr. Urban is comfortable with this if the tissue is OCT-embedded for the purposes of RNA extraction by laser capture microdissection (LCM).

Tissue collection at surgical procedures:

There was much discussion regarding the challenges of obtaining breast cancer tissue from surgical procedures.

The major challenges include:

1. The current practice is to place all breast tissue in formalin at the time of surgery, and, at a later time, cut, section, and evaluate the tissue. To provide fresh tissue, pathology would need to add a step in their procedure whereby a pathologist or the gross PA, would cut the fresh breast tissue and give samples to study staff immediately following surgery.
2. The current practice does not support obtaining tissue from lumpectomy specimens in a timely manner. In lumpectomy cases, surgically removed tissue is sent to the breast center to determine if the excision is complete. Until a radiologist reviews the tissue radiograph to determine that the breast lesion and localizing wires are removed, no tissue can be collected for research. This procedure can take up to 40 minutes and would need to be expedited for us to obtain lumpectomy tissues for our study.
3. It is critical that tissue collected for research does not compromise the ultimate diagnosis of a patient. The Center of Excellence study protocol describes the collection of 1 to 10 grams of breast tissue with an optimal amount of 6 grams. Dr. Beatty believes that this may be feasible from total mastectomies, which account for about 30% of the breast cancer patients seen at SMC. In some cases, however, the majority of the malignant tissue may have already been excised at biopsy.

To begin, Dr. Beatty suggests tissue be collected from women scheduled for a total mastectomy and, once surgeons and pathologists are comfortable with the procedure and the donation of tissue to the study, that tissue from a lumpectomy procedure and other types of surgery be considered. The protocol criteria state that we will obtain tissue from women who have a 2 cm or greater sized tumor.

Dr. Wang stated he agrees with the study criteria, which restricts collection of tissue on lesions smaller than 2 cm. Dr. Lee suggests that surgeons and pathologists begin with tissue collection on 2cm-sized tumors and, once everyone is comfortable with the procedure, smaller tumor sizes be considered.

4. Breast tissue collection via mammotome device was briefly discussed. Dr. Beatty is interested in the possibility of using a hand held mammotome device to biopsy solid masses and to potentially collect samples for research. All agreed obtaining stereotactic mammotome samples should be discussed at another time with radiologists in attendance.

Tissue to pathologists:

In order to expedite the transfer of tissue to the pathologist and subsequent donation to the study, Drs. Tickman and Wang made several suggestions:

1. Request that a dedicated pathologist at SMC, 1st Hill and Providence campus, work with the study and assist with development of an acceptable procedure.
2. Alter the pathology procedure for study participants by implementing fresh sectioning of breast tissue by a pathologist or Gross PA, including tissue samples provided directly to study staff
3. Research staff to provide advanced notice to pathology that a study participant is scheduled for surgery
4. Have a Specimen Collection Specialist present at the surgery and transfer tissue quickly to the participating pathologist or gross PA.
5. Study staff to provide transport of lumpectomy tissue from surgery to SBCC and back again in an effort to expedite the process.

Dr. Urban is particularly interested in obtaining DCIS tissue in order to characterize the different DCIS histology types using biomarkers and to perhaps learn which DCIS may become invasive and which may not. However, it was said that the tissue removed might not be determined as DCIS because some cases of DCIS do not have distinctive gross findings.

Action items:

1. Distribute protocol and consent form for surgical cohort to surgeons and pathologist.
Updated, June 18, 2004: Materials distributed.
2. Provide study staff contact list to participating surgeons.
Updated, June 21, 2004: Heather Aiosa will be the main contact and specimen collection person. She will begin by spending Monday afternoons in Christine Lee's clinic beginning in mid-July. We anticipate that other surgeons may have slightly different procedures for their clinics and we will work with them to develop an approach procedure.
3. Identify a dedicated pathologist at SMC and Providence
4. Request space for a Specimen Collection Specialist at Providence.

In Attendance: Heather Aiosa, Sarika Bhatia, Meghan Crawford, Dr. John Dawson, Dr. Chuck Drescher, Marcia Gaul, Shirley Gough, Samantha Hoyt-Schmid, Lisa Isozaki, Ksenia Koon, Jennifer Lange, Dr. Christine Lee, Elizabeth Murphy, Kathy O'Briant, Anamaria Prosser, Leah Sabacan, Dr. Ron Tickman

Distribution: SPORE Staff, Dr. John Dawson, Dr. Chuck Drescher, Dr. Christine Lee, Dr. Pam Paley, Dr. Ron Tickman, Nicole Urban

BCEDS surgery specimen collection

Currently we are working in conjunction with Dr. Christine Lee to enroll patients into BCEDS from her breast surgery practice at the Providence Comprehensive Breast Center on Monday afternoons. We hope to expand the enrollment population to include other physicians at Providence as well as at Swedish. Dr. John Dawson is interested in participating and has asked for the required enrollment materials for review.

Deb Forman, Dr. Lee's nurse, is an integral part of the enrollment process at Providence. Each Friday, she identifies and informs Heather or Elizabeth of potential study participants who will be coming to their pre-surgical clinic visit the following Monday. This gives Heather or Elizabeth ample time to be at Providence to meet with the potential participant, immediately following her clinic visit, in hopes of enrolling her. To date, one woman has been consented and two others have been approached.

Dr. Dawson has indicated an interest in approaching and possibly enrolling the patients himself. In such cases, patients can go to Dynacare to have their blood drawn so study staff will supply Dr. Dawson with blood draw packets. Alternatively, Heather and Elizabeth will be available to come for the blood draw portion only. Heather and Elizabeth will also be available to consent those women that Dr. Dawson doesn't enroll, but who are interested in the study. Since Dr. Dawson's practice is at Swedish Medical Center, Heather and Elizabeth will be on-call. That is, they will go over to Dr. Dawson's office, when contacted, to enroll women who are interested. Dr. Dawson and his nurse will be given the study cell phone number to call in such situations.

We are asking women to donate blood pre-surgery, during surgery, and also to donate a sample of their breast tissue when clinically appropriate, as determined by the pathologist. The study calls for a draw at the pre-surgical appointment so that the blood will be drawn under similar circumstances to that of a blood draw on a healthy woman. In terms of the draw that happens during (or right around the time of surgery), we discussed the option of having the draw immediately prior to surgery. Due to the new SMC protocol, which requires nursing staff to place an antibiotic IV and administer a beta-blocker before surgery, it was decided to draw the surgery blood when the woman is in the operating room instead of in the transfer area. This will be done when the woman is under general anesthesia, but just before the time that the blue dye is administered.

Initially, women undergoing mastectomies, new patients that are undergoing neoadjuvant therapy, and those patients that are undergoing surgery who are T2 will be approached for the tissue collection portion of the protocol, in addition to the standard blood collection portion of the protocol.

We discussed how much tissue will be collected from each participant. At least a core biopsy must be obtained, but we are looking for a half-gram of tissue or more. It is feasible that women undergoing

neoadjuvant therapy may have a tissue sample removed at the same time as the T-clip instead of during surgery.

There are still barriers that need to be worked out as far as collecting tissue and being able to fresh freeze it within the twenty-minute time frame. We will look at the first five surgical patients or so to determine what is feasible.

Drs. Dawson, Lee, and Tickman will attend the informal SPORE staff meetings, held every other month, beginning September 27, 2004.

Appendix E
Blood and tissue
collection and processing procedures

Breast Cancer Early Discovery Study
Blood and tissue collection and processing procedures

Blood draw:

Women will be asked to donate blood prior to and during surgery. The pre-surgical blood draw will be obtained preferably at the pre-surgical visit, although a woman can have this sample drawn any time before surgery (for example, if a woman has a scheduled blood draw for other reasons on another day before surgery, the research staff can be available to capture blood for the purposes of the study at that time). The blood draw during surgery will be performed in the operating room. Because of a new SMC protocol, nursing staff is required to place an IV to administer a beta-blocker and antibiotic prior to surgery. Therefore, the anesthesiologist or research staff will perform this blood draw in the operating room after the insertion of the IV and beta-blocker. At this time, the woman will be under general anesthesia and no blue dye will have yet been administered.

For each draw, 50 mL of blood will be taken:

- 3 10 ml Serum Separator Tubes (SST) or red-top tubes
- 1 10 ml EDTA Tube (Lavender-top) tube
- 1 10 ml ACD Tube (Yellow top-tube)

Tissue collection from surgery:

In addition to the blood draws from women undergoing surgery, women will also be asked to consent to donate tissue, but only if clinically feasible or deemed appropriate by the pathologist. Initially, patients undergoing full and partial mastectomies, patients who have been diagnosed with stage T2 disease, and new patients undergoing neo-adjuvant therapy will be approached for the tissue collection portion of the protocol along with the blood collection portion of the protocol. A minimum of 0.1 g of tumor tissue will be collected for the study. In addition, 0.1 g to 1 g of normal breast tissue will be collected when it is available. For women undergoing neo-adjuvant therapy, it may be feasible for a tissue sample to be removed at the time the surgical clip is inserted instead of during surgery.

Summary:

Condition	Tissue requirement	Note
Full Mastectomy	\geq 0.1 g tumor \geq 0.1g normal	
Partial Mastectomy	\geq 0.1 g tumor \geq 0.1 g normal	
Neoadjuvant therapy	\geq 0.1 g tumor \geq 0.1 g normal	Tissue sample may be removed at the time the surgical clip is inserted.

Stage T2 disease	\geq 0.1 g tumor \geq 0.1 g normal	
------------------	---	--

Tissue processing:

Once the pathologist has determined that tissue will be available for the study, the research staff will process the tissue as follows:

If < 0.5 g tissue:

- Embed the entire tissue section in OCT

If 0.5 g – 1 g tissue:

- Divide the tissue into 2 sections and embed both in OCT

If > 1 g tissue:

- Divide into section ~0.5 g each
- If 3 sections, embed and freeze 2 sections in OCT and snap freeze the other by placing in a cryovial and dropping in liquid nitrogen
- If > 3 sections, embed 3 sections in OCT and snap freeze all remaining sections by placing in a cryovial and dropping in liquid nitrogen

Tissue should be placed in liquid nitrogen within a 20-minute time frame. In order to stay within the time allowed, the study staff will expedite transport of tissue to the pathologist or gross pathology assistant who will provide tissue to the research staff.

Appendix F
Pathology data collection instruments

UPN _____

BREAST CANCER EARLY DISCOVERY STUDY

Patient Level Clinical Diagnosis

Date: ____ / ____ / ____

Form completed by: _____

UPN: _____

Form QC by: _____

SECTION A: Patient Reports Obtained

Reports Received:

	Date report completed	Date report received
<input type="checkbox"/> Pathology Report (from biopsy)	_____	_____
<input type="checkbox"/> Chemistry Report (from biopsy)	_____	_____
<input type="checkbox"/> Pathology Report (from surgery)	_____	_____
<input type="checkbox"/> Chemistry Report (from surgery)	_____	_____
<input type="checkbox"/> Operative Notes	_____	_____
<input type="checkbox"/> Progress Reports	_____	_____
<input type="checkbox"/> Oncology/ Treatment Notes	_____	_____
<input type="checkbox"/> Other Reports, specify _____	_____	_____
<input type="checkbox"/> Other Reports, specify _____	_____	_____

SECTION B: Specimen Collection Information**B1. Specimen collected from the following procedure if only one type of procedure performed:**

- | | |
|--|---|
| <input type="checkbox"/> ₁ Fine needle aspiration | <input type="checkbox"/> ₄ Surgical biopsy/Lumpectomy |
| <input type="checkbox"/> ₂ Core biopsy | <input type="checkbox"/> ₅ Mastectomy |
| <input type="checkbox"/> ₃ Vacuum assisted/ Mammotome | <input type="checkbox"/> ₆ Other, <i>specify</i> _____ |

B2. Histologic cell types that have been identified in this patient to date

- ₁ Benign
₂ Atypia
₃ In-situ
₄ Invasive

SECTION C: Tissue Characteristics – Assessment of Benign**C1. Please indicate laterality of the procedure:**

- | | | | |
|---|---|--|---|
| <input type="checkbox"/> ₁ Left breast | <input type="checkbox"/> ₁ Upper Outer (UO) | <input type="checkbox"/> ₂ Right breast | <input type="checkbox"/> ₁ Upper Outer (UO) |
| | <input type="checkbox"/> ₂ Upper Inner (UI) | | <input type="checkbox"/> ₂ Upper Inner (UI) |
| | <input type="checkbox"/> ₃ Lower Outer (LO) | | <input type="checkbox"/> ₃ Lower Outer (LO) |
| | <input type="checkbox"/> ₄ Lower Inner (LI) | | <input type="checkbox"/> ₄ Lower Inner (LI) |
| | <input type="checkbox"/> ₅ Breast, NOS | | <input type="checkbox"/> ₅ Breast, NOS |
| | <input type="checkbox"/> ₆ Other, <i>specify</i> _____ | | <input type="checkbox"/> ₆ Other, <i>specify</i> _____ |
| | <input type="checkbox"/> ₉₀ Unknown | | <input type="checkbox"/> ₉₀ Unknown |

C2. Cores/Specimen collected and described:

C2a. Core/Specimen description:

C2b. Core/Specimen size:

C3. Histology type: (Check all that apply)

- | | |
|---|--|
| <input type="checkbox"/> ₁ No specific pathologic change | <input type="checkbox"/> ₉ Fibrocystic changes, NOS |
| <input type="checkbox"/> ₂ Ductal hyperplasia (w/o atypia), NOS | <input type="checkbox"/> ₁₀ Fibrocystic changes, <i>specified</i> _____ |
| <input type="checkbox"/> ₃ Ductal hyperplasia (w/o atypia), <i>specified</i> _____ | <input type="checkbox"/> ₁₁ Radial scar |
| <input type="checkbox"/> ₄ Sclerosing adenosis | <input type="checkbox"/> ₁₂ Columnar cell change (without atypia) |
| <input type="checkbox"/> ₅ Fibroadenoma | <input type="checkbox"/> ₁₃ Cyst |
| <input type="checkbox"/> ₆ Cellular fibroadenoma | <input type="checkbox"/> ₁₄ Phylloides |
| <input type="checkbox"/> ₇ Intraductal papilloma | <input type="checkbox"/> ₁₅ Other, <i>specify</i> _____ |
| <input type="checkbox"/> ₈ Micropapilloma | <input type="checkbox"/> ₉₀ Indeterminate/Unknown |

C4. Presence of microcalcification:

- ₁ No
₂ Yes
₉₀ Indeterminate/Unknown
₉₉ Not assessed

C5. Additional information for benign histology

SECTION D: TISSUE CHARACTERISTICS – Assessment of Atypia

Please duplicate section D for each atypical histologic cell type present.

D1. Please indicate laterality of the procedure:

- | | | | |
|---|--|--|--|
| <input type="checkbox"/> ₁ Left breast | <input type="checkbox"/> ₁ Upper Outer (UO) | <input type="checkbox"/> ₂ Right breast | <input type="checkbox"/> ₁ Upper Outer (UO) |
| | <input type="checkbox"/> ₂ Upper Inner (UI) | | <input type="checkbox"/> ₂ Upper Inner (UI) |
| | <input type="checkbox"/> ₃ Lower Outer (LO) | | <input type="checkbox"/> ₃ Lower Outer (LO) |
| | <input type="checkbox"/> ₄ Lower Inner (LI) | | <input type="checkbox"/> ₄ Lower Inner (LI) |
| | <input type="checkbox"/> ₅ Breast, NOS | | <input type="checkbox"/> ₅ Breast, NOS |
| | <input type="checkbox"/> ₆ Other, specify _____ | | <input type="checkbox"/> ₆ Other, specify _____ |
| | <input type="checkbox"/> ₉₀ Unknown | | <input type="checkbox"/> ₉₀ Unknown |

D2. Cores/Specimen collected and described:

D2a. Core/Specimen description:

D2b. Core/Specimen size:

D3. Histology Type: (Check all that apply)

- ₁₅ Ductal hyperplasia with atypia (ADH)
₁₆ Lobular hyperplasia with atypia (ALH)
₁₇ Intraductal papilloma with atypia
₁₈ Columnar cell change/hyperplasia with atypia
₁₉ Other, specify _____
₉₀ Indeterminate/Unknown

D4. Presence of microcalcification:

- ₁ No
₂ Yes, NOS
₃ Yes, involving atypia
₉₀ Indeterminate/Unknown
₉₉ Not assessed

D5. Additional information for atypia

SECTION E: Tissue Characteristics – Assessment of In-Situ Carcinoma

Please duplicate section E for each in-situ histologic cell type present.

E1. Please indicate laterality of the procedure:

- | | | | |
|---|--|--|--|
| <input type="checkbox"/> ₁ Left breast | <input type="checkbox"/> ₁ Upper Outer (UO) | <input type="checkbox"/> ₂ Right breast | <input type="checkbox"/> ₁ Upper Outer (UO) |
| | <input type="checkbox"/> ₂ Upper Inner (UI) | | <input type="checkbox"/> ₂ Upper Inner (UI) |
| | <input type="checkbox"/> ₃ Lower Outer (LO) | | <input type="checkbox"/> ₃ Lower Outer (LO) |
| | <input type="checkbox"/> ₄ Lower Inner (LI) | | <input type="checkbox"/> ₄ Lower Inner (LI) |
| | <input type="checkbox"/> ₅ Breast, NOS | | <input type="checkbox"/> ₅ Breast, NOS |
| | <input type="checkbox"/> ₆ Other, specify _____ | | <input type="checkbox"/> ₆ Other, specify _____ |
| | <input type="checkbox"/> ₉₀ Unknown | | <input type="checkbox"/> ₉₀ Unknown |

E2. Cores/Specimen collected and described:

E2a. Core/Specimen description:

E2b. Core/Specimen size:

E3. Tumor size estimated by:

- ₁ Palpation
₂ Ultrasound
₃ Mammography
₄ MRI
₅ Measurement of gross specimen
₆ Measurement of specimen on pathology report
₉₉ Assessment not performed

E4. Histology type:

- | | |
|--|--|
| <input type="checkbox"/> ₁ Ductal | |
| <input type="checkbox"/> ₂₀ Comedo | <input type="checkbox"/> ₂₄ Apocrine |
| <input type="checkbox"/> ₂₁ Solid | <input type="checkbox"/> ₂₅ Intracystic |
| <input type="checkbox"/> ₂₂ Cribriform | <input type="checkbox"/> ₂₆ Papillary |
| <input type="checkbox"/> ₂₃ Micropapillary | <input type="checkbox"/> ₂₇ Clinging |
| <input type="checkbox"/> ₂₈ Lobular | |
| <input type="checkbox"/> ₂₉ Other, specify _____ | |
| <input type="checkbox"/> ₉₀ Indeterminate/Unknown | |

E5. Margin involvement (closest margin to in-situ component):

- | | |
|--|--|
| <input type="checkbox"/> ₁ < than 5mm | <input type="checkbox"/> ₅ Involved, NOS |
| <input type="checkbox"/> ₂ From 5mm to 10mm | <input type="checkbox"/> ₆ Not involved, NOS |
| <input type="checkbox"/> ₃ > 10mm | <input type="checkbox"/> ₉₀ Indeterminate/Unknown |
| <input type="checkbox"/> ₄ Actual margin, if known: _____.__ mm | <input type="checkbox"/> ₉₉ Not assessed |

E6. Nuclear Grade:

- ₁ Low nuclear grade
₂ Intermediate nuclear grade
₃ High nuclear grade
₉₀ Indeterminate/Unknown
₉₉ Not assessed

SECTION E: Assessment of In-Situ Carcinoma (Continued)

Please duplicate section E for each in-situ histologic cell type present.

E7. Presence of necrosis:

- ₁ No
₂ Yes
₉₀ Indeterminate/Unknown
₉₉ Not assessed

E8. Presence of microinvasion:

- ₁ No
₂ Yes
₉₀ Indeterminate/Unknown
₉₉ Not assessed

E9. Presence of microcalcifications:

- ₁ No
₂ Yes, NOS
₃ Yes, involving benign ducts
₄ Yes, involving atypia
₅ Yes, involving both benign ducts and DCIS
₆ Yes, involving DCIS
₇ Other, *specify* _____
₉₀ Indeterminate/Unknown
₉₉ Not assessed

E10. Presence of Paget's disease of the nipple:

- ₁ No
₂ Yes
₉₀ Indeterminate/Unknown
₉₉ Not assessed

E11. Additional information in-situ carcinoma

SECTION F: Tissue Characteristics – Assessment of Invasive Carcinoma

Please duplicate section F for each invasive histologic cell type present.

F1. Please indicate laterality of the procedure:

- | | | | |
|---|--|--|--|
| <input type="checkbox"/> ₁ Left breast | <input type="checkbox"/> ₁ Upper Outer (UO) | <input type="checkbox"/> ₂ Right breast | <input type="checkbox"/> ₁ Upper Outer (UO) |
| | <input type="checkbox"/> ₂ Upper Inner (UI) | | <input type="checkbox"/> ₂ Upper Inner (UI) |
| | <input type="checkbox"/> ₃ Lower Outer (LO) | | <input type="checkbox"/> ₃ Lower Outer (LO) |
| | <input type="checkbox"/> ₄ Lower Inner (LI) | | <input type="checkbox"/> ₄ Lower Inner (LI) |
| | <input type="checkbox"/> ₅ Breast, NOS | | <input type="checkbox"/> ₅ Breast, NOS |
| | <input type="checkbox"/> ₆ Other, specify _____ | | <input type="checkbox"/> ₆ Other, specify _____ |
| | <input type="checkbox"/> ₉₀ Unknown | | <input type="checkbox"/> ₉₀ Unknown |

F2. Cores/Specimen collected and described:

F2a. Core/Specimen description:

F2b. Core/Specimen size:

F3. Tumor size estimated by:

- ₁ Palpation
₂ Ultrasound
₃ Mammography
₄ MRI
₅ Measurement of gross specimen
₆ Measurement of specimen on pathology report
₉₉ Assessment not performed

F4. Histology type:

- Epithelial
- ₃₀ Ductal
 - ₃₁ Lobular
 - ₃₂ Mixed lobular/ductal
 - ₃₃ Medullary
 - ₃₄ Atypical Medullary
 - ₃₅ Tubular
 - ₃₆ Mixed tubular/lobular
 - ₃₇ Mucinous
 - ₃₈ Papillary
 - ₃₉ Adenoid cystic
 - ₄₀ Metaplastic
 - ₄₁ Squamous
 - ₄₂ Inflammatory (IBC)
- Stromal
- ₄₃ Phylloides
 - ₄₄ Sarcoma, *specify type* _____
- ₄₅ Other, *specify* _____
- ₉₀ Indeterminate/Unknown

SECTION F: Assessment of Invasive Carcinoma (Continued)

Please duplicate section F for each invasive histologic cell type present.

F5. Nuclear Grade:

- ₁ Low nuclear grade
₂ Intermediate nuclear grade
₃ High nuclear grade
₉₀ Indeterminate/Unknown
₉₉ Not assessed

F6. Nuclear pleomorphism:

- ₁ Small variation in size and shape
₂ Moderate variation in size and shape
₃ Marked variation in size and shape
₉₀ Indeterminate/Unknown
₉₉ Not assessed

F7. Mitotic Rate:

- ₁ Low
₂ Intermediate
₃ High
₄ Mitotic rate, specified _____
₉₀ Indeterminate/Unknown
₉₉ Not assessed

F8. Tubule differentiation:

- ₁ Majority of tumor, > 75% of tumor
₂ Moderate, > 10 – 75% of tumor
₃ Minimal, < 10% of tumor
₉₀ Indeterminate/Unknown
₉₉ Not assessed

F9. Histologic grade: Specify scheme _____

- ₁ Low
₂ Intermediate
₃ High
₉₀ Indeterminate/Unknown
₉₉ Not Assessed
₄ Other, specify _____

F10. Presence of lymphatic or vascular invasion:

- ₁ No
₂ Yes
₉₀ Indeterminate/Unknown
₉₉ Not assessed

F11. Tumor Necrosis:

- ₁ Scant
₂ Moderate
₃ Extensive
₄ None
₉₀ Indeterminate/Unknown
₉₉ Not assessed

SECTION F: Assessment of Invasive Carcinoma (Continued)

Please duplicate section F for each invasive histologic cell type present.

F12. Stromal Response:

- ₁ No
- ₂ Yes
- ₉₀ Indeterminate/Unknown
- ₉₉ Not assessed

F13. Presence of microcalcifications:

- ₁ No
- ₂ Yes, NOS
- ₃ Yes, involving invasive carcinoma
- ₉ Yes, involving benign and invasive
- ₉₀ Indeterminate/Unknown
- ₉₉ Not assessed

F14. Margin involvement (closest margin to tumor):

- ₁ < than 1mm
- ₂ From 1mm to 10mm
- ₃ > 10mm
- ₄ Actual margin, if known: _____.__ mm
- ₅ Involved, NOS
- ₆ Not involved, NOS
- ₉₀ Indeterminate/Unknown
- ₉₉ Not assessed

F15. Skin involvement:

- ₁ Nipple retraction
- ₂ Paget's disease of the nipple
- ₃ Skin retraction
- ₄ Skin dimpling
- ₅ Peau d'orange
- ₆ Erythema
- ₇ Ulceration
- ₉₀ Indeterminate/Unknown
- ₉₉ Not assessed

F16. Disease Staging:

P = Pathologic; C = Clinical (Indicate highest stage)

T Stage	<input type="checkbox"/> <input type="checkbox"/> T0	<input type="checkbox"/> <input type="checkbox"/> Tis	<input type="checkbox"/> <input type="checkbox"/> T1mic	<input type="checkbox"/> <input type="checkbox"/> T1a	<input type="checkbox"/> <input type="checkbox"/> T1b	<input type="checkbox"/> <input type="checkbox"/> T1c	<input type="checkbox"/> <input type="checkbox"/> T2
	<input type="checkbox"/> <input type="checkbox"/> T3	<input type="checkbox"/> <input type="checkbox"/> T4	<input type="checkbox"/> <input type="checkbox"/> T4a	<input type="checkbox"/> <input type="checkbox"/> T4b	<input type="checkbox"/> <input type="checkbox"/> T4c	<input type="checkbox"/> <input type="checkbox"/> T4d	<input type="checkbox"/> <input type="checkbox"/> TX

N Stage	<input type="checkbox"/> <input type="checkbox"/> N0	<input type="checkbox"/> <input type="checkbox"/> N1	<input type="checkbox"/> <input type="checkbox"/> N1a	<input type="checkbox"/> <input type="checkbox"/> N1b	<input type="checkbox"/> <input type="checkbox"/> N1bi	<input type="checkbox"/> <input type="checkbox"/> N1bii
	<input type="checkbox"/> <input type="checkbox"/> N1biii	<input type="checkbox"/> <input type="checkbox"/> N1biv	<input type="checkbox"/> <input type="checkbox"/> N2	<input type="checkbox"/> <input type="checkbox"/> N2a	<input type="checkbox"/> <input type="checkbox"/> N2b	<input type="checkbox"/> <input type="checkbox"/> N3
	<input type="checkbox"/> <input type="checkbox"/> N3a	<input type="checkbox"/> <input type="checkbox"/> N3b	<input type="checkbox"/> <input type="checkbox"/> N3c	<input type="checkbox"/> <input type="checkbox"/> NX		

M Stage M0 M1 MX

₉₉ Not assessed

F17. Additional information for invasive carcinoma

SECTION G: Prognostic Information: Assessment of Nodes**G1. Was sentinel node sampling performed?**

- ₁ No
₂ Yes

**G1a. Sentinel Node Site:**

- ₁ Axillary
₂ Internal Mammary
₃ Supraclavicular
₉₀ Unknown

₉₀ Indeterminate/Unknown

G2. Total number of sentinel nodes examined (removed):

G3. Total number of positive sentinel nodes:

G4. Size of largest metastasis:

_____ Mm

G5. Number of positive sentinel nodes examined by:

_____ Hemotoxylin & Eosin (H&E)

_____ Immunohistochemistry (IHC)

_____ Other, specify _____

G6. Was axillary dissection performed?

- ₁ No
₂ Yes

**G6a. Lymph Node Involvement:**

- ₁ Axillary
₂ Internal Mammary
₃ Supraclavicular
₃ Infraclavicular
₉₀ Unknown

₉₀ Indeterminate/Unknown

SECTION G: Prognostic Information: Assessment of Nodes (continued)**G7. Lymph Node Assessment**

<u>Lymph Node Type</u>	<i>For each type, No. of</i> <u>Positive Lymph Nodes</u>	<u>Size of Largest Lymph Node</u>	
<i>Axillary</i>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> < 0.2 mm by IHC only <input type="checkbox"/> 0.2 to 2 mm by H&E	<input type="checkbox"/> 2 mm to 2 cm <input type="checkbox"/> > 2 cm
<i>Internal mammary</i>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> < 0.2 mm by IHC only <input type="checkbox"/> 0.2 to 2 mm by H&E	<input type="checkbox"/> 2 mm to 2 cm <input type="checkbox"/> > 2 cm
<i>Supraclavicular</i>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> < 0.2 mm by IHC only <input type="checkbox"/> 0.2 to 2 mm by H&E	<input type="checkbox"/> 2 mm to 2 cm <input type="checkbox"/> > 2 cm
<i>Infraclavicular</i>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> < 0.2 mm by IHC only <input type="checkbox"/> 0.2 to 2 mm by H&E	<input type="checkbox"/> 2 mm to 2 cm <input type="checkbox"/> > 2 cm

G8. Additional information for lymph node involvement

SECTION H: Marker Status

Please duplicate section H for each tissue assayed.

H1. Please indicate laterality of the procedure:

- | | | | |
|---|--|--|--|
| <input type="checkbox"/> ₁ Left breast | <input type="checkbox"/> ₁ Upper Outer (UO) | <input type="checkbox"/> ₂ Right breast | <input type="checkbox"/> ₁ Upper Outer (UO) |
| | <input type="checkbox"/> ₂ Upper Inner (UI) | | <input type="checkbox"/> ₂ Upper Inner (UI) |
| | <input type="checkbox"/> ₃ Lower Outer (LO) | | <input type="checkbox"/> ₃ Lower Outer (LO) |
| | <input type="checkbox"/> ₄ Lower Inner (LI) | | <input type="checkbox"/> ₄ Lower Inner (LI) |
| | <input type="checkbox"/> ₅ Breast, NOS | | <input type="checkbox"/> ₅ Breast, NOS |
| | <input type="checkbox"/> ₆ Other, specify _____ | | <input type="checkbox"/> ₆ Other, specify _____ |
| | <input type="checkbox"/> ₉₀ Unknown | | <input type="checkbox"/> ₉₀ Unknown |

H2. Cores/Specimen collected and described:

H2a. Core/Specimen description:

H2b. Core/Specimen size:

H3. Estrogen receptor status:

Specify antibody clone and vendor for Estrogen test _____

Method used _____

____% of nuclei staining (Invasive tumor)
 ____% of nuclei staining (DCIS)

- ₁ Negative
₂ Positive
₉₀ Indeterminate/Unknown
₉₉ Test Not Performed

H4. Progesterone receptor status:

Specify antibody clone and vendor for Progesterone test _____

Method used _____

____% of nuclei staining (Invasive tumor)
 ____% of nuclei staining (DCIS)

- ₁ Negative
₂ Positive
₉₀ Indeterminate/Unknown
₉₉ Test Not Performed

H5. Her2/neu test(s) performed: (Check all that apply)

Specify antibody clone and vendor for HER2 test _____

- ₁ Immunohistochemistry (IHC)
₂ Fluorescent In-situ Hybridization (FISH)
₃ Enzyme-Linked Immunosorbent Assay (ELISA)
₉₉ Test not performed

SECTION H: Marker Status

Please duplicate section H for each tissue assayed.

H5a. Her2/neu status as determined by IHC:

- ₁ Negative (0,1+)
₂ Indeterminate (2+)
₃ Positive (3+)

H5b. Her2/neu status as determined by FISH:

- ₁ Positive for amplification (2-5 fold)
₂ Positive for high amplification (>5 fold)
₃ Negative for amplification
₉₀ Indeterminate/Unknown

H5c. Her2/neu status as determined by ELISA:

- ₁ Positive for amplification (2-5 fold)
₂ Positive for high amplification (>5 fold)
₃ Negative for amplification
₉₀ Indeterminate/Unknown

H6. KI-67 status:

- ₁ Low; <10%
₂ High; ≥ 20%
₃ Indeterminate; <20%, but >10%
₄ Actual number, if known _____
₅ Unknown/ Indeterminate
₉₉ Test not Performed

H7. Other Markers at diagnosis:

Marker	Performed	Not Performed	Result(s)
CA 27-29	<input type="checkbox"/> ₁	<input type="checkbox"/> ₉₉	
CA 15-3	<input type="checkbox"/> ₁	<input type="checkbox"/> ₉₉	
P53	<input type="checkbox"/> ₁	<input type="checkbox"/> ₉₉	
S phase	<input type="checkbox"/> ₁	<input type="checkbox"/> ₉₉	
CarcinoembryonicAntigen (CEA)	<input type="checkbox"/> ₁	<input type="checkbox"/> ₉₉	
DNA Ploidy	<input type="checkbox"/> ₁	<input type="checkbox"/> ₉₉	
Other, specify _____	<input type="checkbox"/> ₁		

H8. Additional information for marker status

SECTION I: Additional Comments or Information

Breast Cancer Early Discovery Study - Specimen Collection Form

THIS FORM MUST ACCOMPANY ALL PATIENT SPECIMENS
SUBMITTED TO THE CORE LABORATORY AND REPOSITORY

UPN: _____ Procedure: _____ Surgeon ID: _____ Procedure date: _____

Patient name: _____ Institution of Proc.: SMC PRV SCS ID: _____

Time tissue collected: _____ Time tissue process: _____ Radiograph? No Yes

Informed Consent Verified? No Yes Case status: Incident Recurrent Chemo for previous cancer? No Yes

Wire Loc? No Yes Blue Dye? No Yes Neo adj. chemo prior to surgery? No Yes

Specimen Information Place the duplicate barcode in the appropriate section (as applicable) and circle side from which each was removed.

Comments/Notes: _____			
<i>Primary</i>	Breast R L	Normal	Breast R L
OCT			Contralateral Breast R L
OCT			
OCT			
Frozen			
Total: _____		Total: _____	
		Total Frozen _____	

BCEDS – Breast Specimen Review Form

Patient ID: _____
 Tissue Type _____

Pathologist: _____
 Date of study pathologist review: ____/____/____

←————— **Diagnosis** —————→

Specimen ID	%Normal			Benign			Atypia			In situ			Invasive				
	E*	NE*	%	Dx1	%	Dx3	%	Dx2	%	Dx3	%	Dx1	%	Dx2	%	Dx3	%

*Normal: E=Epithelium, NE=Non-Epithelium; Dx = diagnosis; % = Viable Tumor Cells

Pathology Review Comments:

Pathology Diagnosis

- | | | |
|--|--|---|
| <p>Benign</p> <p><input type="checkbox"/>1 No specific pathologic change</p> <p><input type="checkbox"/>2 Ductal hyperplasia (w/o atypia), NOS</p> <p><input type="checkbox"/>3 Ductal hyperplasia (w/o atypia), specified</p> <p><input type="checkbox"/>4 Sclerosing adenosis</p> <p><input type="checkbox"/>5 Fibroadenoma</p> <p><input type="checkbox"/>6 Cellular fibroadenoma</p> <p><input type="checkbox"/>7 Intraductal papilloma</p> <p><input type="checkbox"/>8 Micropapilloma</p> <p><input type="checkbox"/>9 Fibrocystic changes, NOS</p> <p><input type="checkbox"/>10 Fibrocystic changes, specified</p> <p><input type="checkbox"/>11 Radial scar</p> <p><input type="checkbox"/>12 Columnar cell change (w/o atypia)</p> <p><input type="checkbox"/>13 Cyst</p> <p><input type="checkbox"/>14 Phylloides</p> <p><input type="checkbox"/>15 Other, specify _____</p> | <p>Atypia</p> <p><input type="checkbox"/>15 Ductal hyperplasia with atypia (ADH)</p> <p><input type="checkbox"/>16 Columnar cell change/ hyperplasia w/ atypia</p> <p><input type="checkbox"/>17 Intraductal papilloma w/ atypia</p> <p><input type="checkbox"/>18 Lobular hyperplasia w/ atypia (ALH)</p> <p><input type="checkbox"/>19 Other, specify _____</p> | <p>In-situ</p> <p><input type="checkbox"/>20 Comedo (Ductal)</p> <p><input type="checkbox"/>21 Solid (Ductal)</p> <p><input type="checkbox"/>22 Cribriform (Ductal)</p> <p><input type="checkbox"/>23 Micropapillary (Ductal)</p> <p><input type="checkbox"/>24 Apocrine (Ductal)</p> <p><input type="checkbox"/>25 Intracystic (Ductal)</p> <p><input type="checkbox"/>26 Papillary (Ductal)</p> <p><input type="checkbox"/>27 Clinging (Ductal)</p> <p><input type="checkbox"/>28 Lobular</p> <p><input type="checkbox"/>29 Other, specify _____</p> |
| <p>Invasive</p> <p><input type="checkbox"/>30 Ductal (Epithelial)</p> <p><input type="checkbox"/>31 Lobular (Epithelial)</p> <p><input type="checkbox"/>32 Mixed lobular/ductal (Epithelial)</p> <p><input type="checkbox"/>33 Medullary (Epithelial)</p> <p><input type="checkbox"/>34 Atypical Medullary (Epithelial)</p> <p><input type="checkbox"/>35 Tubular (Epithelial)</p> <p><input type="checkbox"/>36 Mixed tubular/lobular (Epithelial)</p> <p><input type="checkbox"/>37 Mucinous (Epithelial)</p> <p><input type="checkbox"/>38 Papillary (Epithelial)</p> <p><input type="checkbox"/>39 Adenoid cystic (Epithelial)</p> <p><input type="checkbox"/>40 Metaplastic (Epithelial)</p> <p><input type="checkbox"/>41 Squamous (Epithelial)</p> <p><input type="checkbox"/>42 Inflammatory (IBC, Epithelial)</p> <p><input type="checkbox"/>43 Phylloides (Stromal)</p> <p><input type="checkbox"/>44 Sarcoma specify type</p> <p style="text-align: center;">specify type _____</p> <p><input type="checkbox"/>45 Other, specify _____</p> | | |