

IRB #:

TITLE: Breast Cancer Reference Set Construction

Principal Investigator: Jeffrey R. Marks, Ph.D.
Duke University Medical Center
Box 3873 DUMC
Durham, NC 27710
Telephone: 919-684-6133
Fax: 919-668-4777
Email: marks003@mc.duke.edu

Participating Institutions: **Fox Chase Cancer Center**
Paul F. Engstrom, M.D., *Principal Investigator*
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111
Telephone: 215-728-2986
Fax: 215-728-5336
Email: paul.engstrom@fccc.edu

University of California, San Francisco
Laura Esserman, M.D., *Principal Investigator*
UCSF
Address
Telephone
Fax
e-mail address

Dana-Farber Cancer Institute
Karen Anderson, M.D., Ph.D., *Principal Investigator*
Dana-Farber Cancer Institute
44 Binney Street
Boston, MA 02115
Telephone
Fax
e-mail address

Protocol Version 1.1

Date:

March 10, 2009

1	OBJECTIVES	3
2	BACKGROUND	3
2.1	Feasibility and Time Frame	4
3	SUBJECT SELECTION	5
3.1	Eligibility Criteria	5
3.1.1	Cases (n=300 invasive cancer and 100 DCIS) and Benign Disease Controls (n=100 benign non-proliferative conditions and 100 benign proliferative conditions)	5
3.1.2	Normal Controls (n=100):	5
3.2	Exclusion Criteria	5
3.2.1	Cases and Benign Disease Controls.....	5
3.2.2	Normal Controls.....	5
3.3	Source of Subjects.....	6
3.3.1	Cases and Benign Disease Controls.....	6
3.3.2	Normal Controls.....	6
3.3.3	Selection for the Reference Set.....	6
3.4	Sample Size Justification	6
4	REGISTRATION PROCEDURES	7
4.1	General Guidelines.....	7
4.1.1	Identification of Subjects	7
4.1.2	Identification of Controls.....	7
4.2	Registration Process.....	8
5	SAMPLE COLLECTION AND PREPARATION/DATA COLLECTION	8
5.1	Sample Collection and Preparation.....	8
5.2	Data Collection	9
5.3	Duration of Follow Up.....	9
5.4	Study Discontinuation Criteria	9
6	ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS	9
6.1	Potential Risks	9
6.2	Adverse Event Reporting.....	10
7	DATA REPORTING/REGULATORY GUIDELINES	10
7.1	Data Reporting.....	10
7.1.1	Database Information:.....	10
7.1.2	Multi-center Guidelines	11
8	DATA ANALYSIS	11
9	REFERENCES	13
10	APPENDIX 1 – BLOOD HANDLING PROTOCOLS	14
11	APPENDIX 2 – CONSENT FOR RESEARCH	16

Breast Cancer Reference Set Construction

03/10/2009, Jeffrey R. Marks

1 Objectives

The primary objective of this study is to assemble a well-characterized set of blood specimens to test biomarkers that, in conjunction with mammography, can detect and discriminate breast cancer. These samples will be divided to provide “sets” of specimens that can be tested in a number of different laboratories. Since tests will be performed on the same sets of samples, the data will be directly comparable and decisions regarding which biomarker or set of biomarkers have value in breast cancer detection can be made. These sets will reside at a National Cancer Institute facility at Frederick, MD.

2 Background

The Early Detection Research Network (EDRN) is an NCI sponsored network of investigators dedicated to the discovery, testing, and validation of biomarkers for the detection of cancer. Breast cancer is one of the many cancers for which novel biomarkers are being sought in this context. Many markers that are or have been tested have been done on convenience sets available to the individual investigators. Results from these studies are not directly comparable and biases in patient selection, controls, and sample handling confound the ability to reproduce results. Therefore, investigators and program staff at the NCI have concluded that it is essential to create reference sets of samples that can be used to test markers. The sets, the governance thereof, and data on biomarkers using these samples will reside centrally and be available to both EDRN and non-EDRN scientists. It is anticipated that this process will aid and accelerate the testing and validation of useful cancer biomarkers.

Breast cancer detection has a number of special circumstances that need to be acknowledged in creating such a reference set. The most common forms of the disease are epithelial in nature and afflict women about 100 times more frequently than men. Incidence increases with age but peaks prior to the age of 80. Incidence has increased over the past 30 years however mortality due to the disease has recently trended lower. Much of the increased incidence is attributable to increasing numbers of women being diagnosed with early stage disease (stage I) or ductal carcinoma in situ (stage 0). This is almost certainly the result of increased use and quality of mammography and other imaging techniques.

Mammography is a useful screening tool for breast cancer. Application on a population basis has been shown in a number of studies to reduce breast cancer specific mortality, the most rigorous criterion for assessing utility for a disease screening method. Estimates for sensitivity approach 75-80% depending upon the country, the frequency of screening, and age of the population in question. Specificity, that is the number of women referred to invasive diagnostic procedures (biopsy or fine needle aspirate) based upon a mammographic finding, is relatively low but highly variable depending upon numerous factors, not the least of which are the low morbidity, ease, and high confidence of the invasive diagnostic procedures.

While mammography has clear-cut benefits and a large established clinical foundation, it remains costly and is applied with little regard to risk of disease. The recommended screening algorithm in the U.S. is based only upon gender and age. This raises the possibility that novel markers could provide additional information on individual risk of disease and guide the method or frequency of breast cancer screening.

Two separate but related applications of biomarkers for breast cancer detection will be investigated through this reference set: 1) Markers that can be used to select women for screening with mammography and other imaging procedures and 2) Markers that can discriminate benign from malignant breast conditions detected by mammography in order to reduce the number of false positive findings and subsequent biopsies. This two-fold application requires separate control sets as described below.

2.1 Feasibility and Time Frame

A broad range of investigators may eventually use the reference sets, however the proximal purpose is to make them available to scientists within and affiliated with the Early Detection Research Network (EDRN). Therefore, these samples will be accrued and deposited by EDRN investigators. A number of EDRN sites have access to large clinical populations of women undergoing diagnosis and treatment for breast cancer and have expressed their willingness to participate in the construction of these sets. All of these sites have specimens that are already banked. However, given the disparate nature of these banks, the reference sets will be constructed by prospective collection. Several sites will be participating and there is no shortage of incident cases. However, the collection phase of this protocol will remain open until accrual is complete. We anticipate that collection will take approximately 12 months.

3 Subject Selection

3.1 Eligibility Criteria

3.1.1 Cases (n=300 invasive cancer and 100 DCIS: Up to 100 LCIS and 100 Pagets may be included but are not the targeted population) and Benign Disease Controls (n=100 benign non-proliferative conditions and 100 benign proliferative conditions)

- a. Female
- b. At least 18 years of age
- c. Mammographic finding or palpable breast mass
- d. Undergoing initial diagnosis to determine if breast cancer is present

3.1.2 Normal Controls (n=100):

- a. Female
- b. At least 18 years of age
- c. Undergoing routine mammographic screening (with or without clinical breast exam)
- d. BIRADS score less than or equal to 2

3.2 Exclusion Criteria

3.2.1 Cases and Benign Disease Controls

- a. Already diagnosed by biopsy for current presentation of breast cancer or benign disease
- b. History of invasive breast or other cancers (except basal or squamous cell carcinoma of the skin)
- c. Recurrence of previous breast cancer
- d. Pregnant or nursing

The consenting process and blood draw will be carried out before primary pathology results are obtained. This may occur either before or after the diagnostic biopsy, but will be limited to the same day that the biopsy is performed or up to 2 weeks prior to biopsy. There are two reasons for this restriction: 1) It will ensure that the cancer (or benign) mass is present at the time of blood sampling and 2) It will reduce potential biases that might result from subjects knowing their diagnosis with certainty to be malignant or benign. No exclusion will be made based upon age, race, extent of disease, drug usage, family history, prior biopsies, prior benign diseases or prior DCIS.

3.2.2 Normal Controls

- a. Current evidence of breast abnormality (prior benign disease or DCIS acceptable)
- b. History of invasive breast or other cancers (except basal or squamous cell carcinoma of the skin)
- c. Pregnant or nursing
- d. BIRADS score greater than 2 or palpable mass

For the purpose of this study, we define “normal” as someone who has no evidence of a breast abnormality. In order to ensure this, only women who are undergoing mammographic screening and are assigned a BI-RADS score of 1 or 2 and if clinical breast exam performed have no palpable mass will be eligible.

3.3 Source of Subjects

3.3.1 Cases and Benign Disease Controls

Women undergoing diagnosis for breast cancer will be the source of subjects. This will typically encompass two venues in the modern medical center: 1) Diagnostic radiology where lesions detectable by imaging are sampled and 2) Surgical oncology where non-imaged masses are often found and sampled. Cancers found via these two avenues could conceivably have biologic properties and associated biomarkers that differ. Further, the purpose and application of biomarkers in these two settings could be fundamentally different. Therefore, these sets will be composed of subjects diagnosed in both ways. However, at this time, during prospective collection information regarding mode of detection will be recorded but the sets will not be specifically constructed around this parameter.

3.3.2 Normal Controls

The collection specifically targets women undergoing breast cancer diagnosis, not a normal or screening population. For markers that might be useful in discriminating risk of disease in women with no evidence of a breast abnormality, the control set of women with benign breast conditions are not the most appropriate. Therefore, in addition to the **100** women with benign non-proliferative breast conditions and **100** women with benign proliferative conditions ascertained by biopsy, the group will also obtain blood and questionnaire information on **100** women with no evidence of breast disease. The source of these subjects will be asymptomatic women undergoing routine screening mammography. Women are eligible by having a screening mammogram assigned a BIRADS score of 1 or 2 with no palpable mass.

3.3.3 Selection for the Reference Set

The reference set will be constructed with samples from **300** patients with invasive cancer, **100** with benign non-proliferative breast conditions, **100** with benign proliferative breast conditions, **100** cases of DCIS and **100** asymptomatic controls. These subjects will be identified retrospectively by the EDNR DMCC from those pre-enrolled. After subjects are selected, the DMCC will coordinate shipping of specimens for the reference set.

Each of the four study sites will contribute approximately **75 invasive cancers**. To the extent possible, each set of controls will be matched to cases within institution age and race/ethnicity.

3.4 Sample Size Justification

Markers will be developed for two potential clinical applications. First, we seek markers that will be measured in subjects with positive mammography or clinical exam who under current

practice are routinely sent for biopsy. The purpose will be to identify as marker negative, subjects who do not have invasive cancer and who therefore can avoid biopsy. Yet, we require that all subjects with invasive cancer be marker positive so that they undergo biopsy and have their cancers detected. Statistically we require that the marker has a very high sensitivity. The specificity need not be high in order to have benefit. For example, a specificity of 50% would reduce by ½ the number of unnecessary biopsies performed.

The second potential application concerns using a marker to select subjects as candidates for mammographic screening. We require that the marker be positive in almost all subjects with cancer who are currently positive on mammography. This will ensure that use of the marker does not result in a reduction in cancer detection. We will evaluate the proportion of normal subjects who test negative with the marker, i.e., the specificity. Again, a modest specificity could have large benefits, e.g., a specificity of 25% would reduce by 25% the number of women unnecessarily undergoing mammographic screening.

Sample size calculations were performed using methods described in Pepe (1) (p. 220–224). We chose 98% as the minimally acceptable sensitivity value. At the corresponding positivity threshold assume that a marker has specificity 50%. Suppose we must show statistically that the marker's specificity (at 98% sensitivity) is at least 25% ($\alpha=0.05$) and we seek to have 90% power to draw that conclusion. Using a 3:1 ratio of cases to controls the study requires 285 cases and 95 controls. Therefore, rounding up, we elect to build the reference set of specimens with 300 cases and 100 controls. The 100 controls are benign disease controls for the first clinical application and 100 normal controls for the second.

4 Registration Procedures

4.1 General Guidelines

4.1.1 Identification of Subjects

At each participating site before accrual begins, details of the study will be presented to the doctors and their clinical assistants by the site P.I. and the study coordinator. This presentation(s) will involve physicians who are most directly involved in the breast sampling procedures that result in pathologic diagnosis including radiologists, surgeons, and cytopathologists.

Subjects will be identified by either their physician or assistant as being eligible and capable of participating. If so, assent to be approached by the study coordinator will be obtained. The study coordinator will then describe the study, obtain written and verbal consent (sample consent form is located in *Appendix 2*), and pre-enroll the subject. Final enrollment occurs at DMCC and sites are notified of selected specimens.

4.1.2 Identification of Controls

At each participating site before accrual begins, details of the study will be presented to the doctors and their clinical assistants by the site P.I. and the study coordinator. This will involve the screening radiologists and their assistants.

Subjects will be identified by either their physician or assistant as being eligible and capable of participating. If so, assent to be approached by the study coordinator will be obtained. The study coordinator will then describe the study, obtain written and verbal consent, and pre-enroll the subject. Final selection of specimens to be included in the reference set will be determined by the DMCC.

4.2 Registration Process

The study coordinator will verify eligibility and pre-enroll the subject per institutional guidelines. Data pertaining to the participant and specimens may either be key-entered into VSIMS or into local database. Specimens are to be stored locally until the DMCC has notified you of the selected matched specimens. The selected specimens will be shipped to Harvard for aliquoting and then Harvard will ship the assembled specimen sets to NCI-Frederick.

5 Sample Collection and Preparation/Data Collection

5.1 Sample Collection and Preparation

The target amount to be collected from each subject will be 28mls of whole blood. This volume is based upon the high uptake rate of patients agreeing to donate 28mls or 1oz of blood. Blood will be collected in 2 x 7ml red top tubes and 2 x 7ml lavender top (EDTA) tubes. Processing and labeling of the blood will be done according to *Appendix 1* by the local institution. Lag time between collection and the start of processing will be within 5 hours and this time will be recorded for each sample. Three components will be stored from these tubes, serum, plasma, and buffy coat. If collected and handled properly, each of the four tubes should yield approximately 3mls of serum/plasma. Serum and plasma will be maintained as 1ml aliquots and frozen and stored at -80°C and buffy coat will be stored from each EDTA tube, at local institutional temperature guidelines.

Specimen Deposit: At the end of the collection phase, 4mls of serum and 4mls of plasma from each subject will be sent to the Dr. Steven Skates at Harvard for final division into 200 μl aliquots. This will provide approximately 20 aliquots of each serum and plasma sample for the repository. The aliquots, arranged in sets, will be shipped to NCI-Frederick for long-term storage and distribution. These samples will be maintained at this facility until exhausted.

Each institution will maintain, at a minimum, 2mls of serum, 2mls of plasma, and the white blood cell fraction from the EDTA tubes. These resources will not be part of the reference set but will provide backup, confirmation, and representation of these subjects within each individual institution's own bank. These samples will be maintained for a minimum of 10 years or until exhausted.

5.2 Data Collection

The questionnaire to be administered to each study subject is appended (*Appendix 3*). This instrument will require approximately 15 minutes and be administered by the study coordinator after blood is drawn. The questionnaire will have the patient name, medical record number, and the study ID number. The DMCC will only receive the unique Participant ID number associated with the participant. Questionnaire and data will be entered into a secure database (either VSIMS or a local database at institution) by a data technician/clinical research associate. Since final diagnoses and additional clinical information will not be known at this time, patient identifiers must be retained locally.

At weekly intervals, the data technician/research associate will update recently collected subjects for their pathology information. Data to be collected from online medical records will include radiology, pathology, and local and systemic treatment information. These data elements include: mode of detection (mammography or other), radiology information (BIRADS and density), extent of disease, histologic and molecular pathology on resected tissue, type of surgery, radiation and chemotherapeutic treatment, and disease outcome. This information will be collected on a data abstraction form (*Appendix 4*) and subsequently entered in a secure database (either VSIMS or local database)

5.3 Duration of Follow Up

In order to collect the type of information described above, it will be necessary to access patient records over time. Data from medical records or Cancer Center Tumor Registries will be updated on an annual basis. In addition to the information related to the primary cancer, annual updates will include disease status and additional treatment information. Updating will occur for a maximum of 20 years after initial enrollment.

5.4 Study Discontinuation Criteria

A subject will be removed from the study if she decides to withdraw. Follow up will continue, unless the subject notifies the investigator that she does not wish for follow up to continue. Blood samples and data which have already been collected will be used, unless the subject notifies the investigator in writing that she wishes for them not to be used. In this event, they will be discarded.

6 Adverse Events: List and Reporting Requirements

6.1 Potential Risks

Subjects will be evaluated for toxicity at the time of blood sample collection. There is a risk of pain or bruising at the site of the blood draw, and rare fainting or infection related to the blood draw. There are no serious adverse events expected on this study.

6.2 Adverse Event Reporting

This is a low risk, non-intervention, non-treatment protocol. Adverse events are unlikely in this study, however in the case of an adverse event, i.e., syncope or uncontrolled bleeding, the site Principal Investigator will notify the sponsor (EDRN) and IRB (following local IRB guidelines). Timely, accurate, and complete reporting of this safety information is crucial for the protection of subjects. All adverse events across centers will be reviewed by the study Principal Investigator.

All SAEs regardless of attribution are reported by phone to 206-667-3438 within 24 hours of becoming aware of the event. A written report using the EDRN – Adverse Event Form will follow within 48 hours.

Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the study Principal Investigator or their designee.

Each site is responsible to report all adverse and serious adverse events to their IRB of record following guidelines set by that IRB. The study Principal Investigator reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent to the study Principal Investigator or their designee at EDRN.

Adverse events, which are serious, but not life threatening, have a causal relationship to the research, and are unexpected, will be reported to all participating institutions for IRB submission within two weeks of becoming aware of the event. If the adverse event requires modification of the study protocol and informed consent, then these changes will be provided to all participating institutions for their IRB or record with the report of the adverse event. The study Principal Investigator or their designee will notify all participating sites if IRB submission is required.

If the results of a site or study Principal Investigator or their designee investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

7 Data Reporting/Regulatory Guidelines

7.1 Data Reporting

7.1.1 Database Information:

VSIMS is a web-based participant enrollment, data collection and specimen tracking application, as well as a resource for study-specific information and communication. The core system components include a Java application server and a web applications and database server, both with connections to backup equipment. Client system components are workstations, which connect to VSIMS via the Internet. The system will achieve connections between components using the COMPASS network, composed of the parent institution's network infrastructure (e.g. routers, hubs,

switches, cabling) and TCP/IP protocol software. The software that supports the system includes operating systems for servers and workstations, a database platform, Web platform, network software, backup software, and other utility software.

A user is only allowed to enter the VSIMS secure website if they supply the correct user name and password. A scheme called basic authentication provided by Microsoft Internet Information Server (IIS) is used here to identify VSIMS users. Basic authentication is the standard HTTP method of user authentication and is supported by most Web browsers. VSIMS also uses highest level (128-bit) of Secure Sockets Layer (SSL) protocol for encrypted transfer of data between VSIMS host server and users' computers.

For sites that enter their data into a local database, data export and conversion will occur locally, and the file will be sent to the DMCC in a secure fashion. The DMCC may request exports in regular intervals to monitor accrual.

7.1.2 Multi-center Guidelines

This study will be conducted at Duke University Medical Center, Fox Chase Cancer Center, University of California, San Francisco and Dana-Farber Cancer Institute. The site principal investigators will work together to provide monitoring to ensure that the study is conducted in a way that is in accordance with Good Clinical Practice guidelines and all applicable regulatory policies and regulations.

The EDRN-DMCC obtains photocopies of site IRB approval (containing FWA number), approved consent form and confirmation of Human Subjects Training. Access to VSIMS or receipt of data from a site is denied until these materials are received.

8 Data Analysis

ROC curves will be calculated to evaluate the performance of biomarkers. We will use as controls subjects without cancer who have undergone a diagnostic biopsy in order to assess the value of a marker in the diagnostic setting. We will estimate the false positive rate (FPR) associated with a marker when we set the threshold for positivity low enough that the sensitivity (true positive rate = TPR) is 98%. That is, $ROC^{-1}(0.98)$ will be estimated with confidence interval according to Pepe (1) (page 101, equation (5.3)). If the upper confidence interval is less than 75%, we will conclude that the marker can reduce by at least 25% the number of subjects unnecessarily undergoing biopsy while still identifying almost all subjects with cancer as requiring biopsy. Such a marker would be useful in the diagnostic setting.

Using logistic regression we will develop marker combinations. Their performances will also be assessed using ROC methods described above. However, cross-validation will be employed to adjust for optimism bias induced by developing the combination with the same data used to assess its performance.

For descriptive purposes we will calculate the proportion of subjects with DCIS that test positive and the proportion of subjects with benign proliferative disease that test positive using the threshold that yields 98% sensitivity for invasive cancer. Of particular interest will be the correlation between biomarker positivity and future progression to cancer, information that we will ascertain from long term follow up of these patients.

Markers that are effective in the diagnostic setting will be considered as candidate markers for primary screening. We will assess their performance in subjects with normal screening mammograms. Again we will define the marker as positive using the threshold that yields 98% sensitivity. (The strategy of pre-screening with the marker and using mammography on all women that screen positive will therefore detect 98% of the cancers currently detected with mammography alone). We will estimate the proportion of normal subjects that test negative with the marker, along with a confidence interval. If (the lower confidence limit for) the proportion exceeds 25% we will conclude that more than 25% of subjects can safely avoid mammography screening based on the biomarker test.

Combinations of markers will be constructed using logistic regression and evaluated as described above.

9 References

1. Pepe, M.S. The Statistical Evaluation of Medical Tests for Classification and Prediction, Oxford University Press Inc.: New York, 2003.

10 APPENDIX 1 – Blood Handling Protocols

Overview

- 1) Blood collection will be performed before cytoreductive surgery and in the absence of any systemic anesthesia
- 2) A minimum of **28mls** of whole blood will be collected, however individual sites are not prevented from obtaining more blood from each subject
- 3) Four x 7ml tubes will be obtained, 2 red top tubes for serum and 2 EDTA (lavender top) tubes for plasma and white blood cells
- 4) Blood will be spun within 5 hours of collection. Blood tubes will be spun at 3000 x g for 10' at 4°C and the serum or plasma removed by pipetting. Time to processing will be noted.
- 5) For the specimens going to Harvard, serum will be stored in four 1ml aliquots and the plasma in four 1ml aliquots. All samples will be stored at -80°C. White blood cell fraction will be stored in a single tube at local institutional temperature guidelines and kept locally along with any additional serum and plasma beyond the specimen volume sent to Harvard.

Shipping samples

At the conclusion of the collection phase of the protocol, specimens will be shipped via overnight FedEx carrier on dry ice to Harvard for central aliquoting and central dissemination. Sites will use an online specimen tracking system developed and maintained by the DMCC for all shipping and receiving of specimens. Specimens must be shipped only on Monday, Tuesday, or Wednesday. Each site must have an established contact person at Harvard to contact upon shipping. Specimens must be labeled with an EDRN provided specimen ID label prior to shipping to Harvard with an association in the VSIMS specimen tracking system to the unique participant ID and Parent Specimen ID. Once received, Harvard will accept delivery in VSIMS and store the specimens at –80°C until ready to aliquot. From this point forward, the MAPI system will be used at Harvard to create the 200µl aliquots. Linked data from the MAPI system will be sent to the DMCC upon shipping of specimens to NCI-Frederick.

- 1) Place 4 serum aliquot vials and 4 plasma aliquot vials (all aliquots should be 1 ml) in the cardboard storage boxes for shipping.
- 2) Put the filled cardboard boxes in a plastic ziplock bag along with an absorbent pad/material and seal.
- 3) Place bagged boxes (lid side up) in the bottom of the inner Styrofoam shipping box.
- 4) Fill the shipping box (around the storage boxes) with as much dry ice as possible to assure that the contents will stay frozen (even if delivery is delayed). Dry ice pellets work best for this.
- 5) Print the Blood Tracking form from the database; seal it in a plastic bag, and place on top of the dry ice before putting the insulated lid on box.
- 6) Seal the shipping box by taping the flaps of the cardboard outer box at the main seam across the top. Do not tape the seams along the top edges (required by shipping regulations to allow for the release of carbon dioxide gas).
- 7) Place a black and white label that reads “Dry Ice _____ kg” on top of each insulated shipping

- container. Complete the dry ice weight in the space “UN 1845, _____ kg.”
- 8) Place the required UN 3373/diagnostic specimens sticker on the shipping container (included).
 - 9) Complete the air bill and ship **overnight** (Specimens must be shipped only on Monday, Tuesday, or Wednesday) to the address listed below.
 - 10) Please send notification e-mail to (Steven Skates & Kathleen Grover). State you are sending the samples and list the carrier and the carrier tracking number in the e-mail.

Specimens being sent from contributing sites to Harvard:

Steve Skates
Brigham and Women’s Hospital
50 Staniford St, Suite 560
Boston, MA 02114

Specimens being shipped from Harvard to NCI-Frederick

Judith Frank
NCI Frederick
4600 Wedgewood Blvd, Suite H
Frederick, MD 21703

11 Appendix 2 – Consent for Research

IRB Protocol Number:

Creation of a Central Blood Reference Set for the Early Detection of Breast Cancer

You have been asked to join a research study on early detection of breast cancer. The purpose of this research study is to find substances in the blood that could detect cancer.

Taking part in the research study is your choice. If you decide not to take part in the study, or if you change your mind later and withdraw from the study, it will not involve any penalty or loss of benefits to which you are otherwise entitled. Important information about this research study is explained below, plus information about risks and benefits. You should ask your doctor and other staff members any questions you have about this research study.

Why is this research study being done?

This research study is being done because the earlier a cancer is detected, the more likely it is to be cured. A group of scientists is working together to find and test substances in the blood that could detect breast cancer early. We will compare the blood of people with breast cancer with the blood of people who do not have breast cancer. This study is sponsored by the National Cancer Institute.

How many people will take part in this study?

About 600 women will take part in this study at 4 medical centers across the country.

What is involved in the research study?

You will give 4 tubes of blood (28 mls or about one ounce). If you are having surgery, you will give blood before the surgery. This will be done by needle stick of a vein in your arm. This is the usual way to obtain blood.

At the time of your blood draw we will ask you to fill out a questionnaire. We will collect information from your medical records related to your disease if you have cancer. All information we collect about you and your medical condition will be kept confidential in a locked database.

Your blood will be separated into its parts (serum, plasma and white blood cells) and frozen at *Insert Institution Name*. When all 600 women are enrolled, a portion of your blood will be sent to Massachusetts General Hospital. It will be thawed and divided into small portions. It will then be sent to the National Cancer Institute at Frederick, Maryland where it will be stored.

You will have the following tests and procedures done if you take part in this research study:

These procedures are being done because you are in the research study. If you were not taking part in this research study, you may not need to have these procedures as part of your treatment.

- Blood draw (28 mls or about one ounce)
- Questionnaire (15-30 minutes)

Questionnaires

We are asking you to fill out a questionnaire for this research study. This questionnaire will tell us about your reproductive, medical, and family history. We are asking these questions to learn about other factors that could affect the results of our study. You will spend between 15 and 30 minutes filling out the questionnaire. We will ask you to fill it out only once during this research study.

You do not have to answer any questions that make you uneasy. Whether or not you answer any question will not affect your medical care. We will keep the paper copies of the questionnaire in a locked file to protect your privacy.

How long will you be on this research study?

You will probably be on this research study indefinitely.

What are the risks of the research study?

Some side effects may occur while you are on this research study. The side effects most likely to happen are listed below. You should discuss all possible side effects with your doctor. Sometimes other side effects occur that we do not expect.

You may have these side effects from having your blood taken: bruising and bleeding around the site where the blood was taken, discomfort or pain, fainting or infection (rare).

We will collect information from your medical records. This information will be coded with a unique number. Only research staff working on this study will have access to the code which links the unique number with your identity. We will do all we can to keep this information confidential, but there is a risk it will not remain confidential.

Are there benefits to taking part in the research study?

You will not benefit directly from taking part in this research study. We hope the information we get from this research study will help people with breast cancer or people suspected of having breast cancer in the future.

What other options are there?

Instead of taking part in this research study, you may be able to join a different research study. If you decide not to be in this research study, it will not affect your medical care in any way.

What about confidentiality?

We will do our best to keep your personal information private. We carefully guard our computer records, but we can never guarantee complete confidentiality. Your personal information may be released if required by law. The following groups may need to inspect and/or copy your records to see whether the research study was properly done (for quality assurance and data analysis): Representatives of the Food and Drug Administration (FDA), the research study's sponsor, the National Cancer Institute, ***Insert Institution Name***, other healthcare organizations. You will be given a separate form to review regarding the steps we will take to guard your privacy as part of your participation in the research study. By signing that additional authorization, you will be

providing your consent to use and disclosure described in that form connected with your participation in this research study.

Each person is assigned a unique participant ID. That participant ID is associated with a unique specimen ID. Only the site will know the identity of the person associated to the participant ID.

What are the costs?

You will not get paid for taking part in this research study. There will be no charge to you for costs related to this study.

Will you be compensated?

If you are harmed because of the research study, we will provide the medical care to treat that harm. You may have to pay for this treatment. **Insert site name** has not set aside funds to pay your salary if you cannot work or for any other damages if you are harmed because of the research study.

Questions

Who do you call if you have questions or problems with study treatment?

You can ask questions at any time about this research study and your treatment. You can ask for more information from your doctors and other staff who care for you. You can reach the study's principal investigator, **Insert PI Name**, at **Insert phone number**.

Who do you call if you have problems regarding your rights as a research subject?

If you have questions about the research study, or if you have concerns or complaints about the research study, become injured as a result of the research study, or if you have questions about your rights as a research subject, you may contact the Institutional Review Board, which supervises research projects at the **Insert Institution Name**. You may reach the Institutional Review Board office by calling **Insert IRB phone number** from 9:00 a.m. to 5:00 p.m., Monday through Friday, or by writing to the Institutional Review Board, **Insert IRB Address**.

Can you stop being on the research study? What are your rights?

Taking part in this research study is your choice. If you decide to take part in the research study, you can change your mind later and withdraw from the study.

Your choice to withdraw from the study will not change your regular medical care. It will not harm your relationship with your doctor. You can also choose to receive care from a different doctor. If you leave the research study, we will ask you permission to continue to watch your health by looking at your medical records. If you wish, the samples that are held in the bank for future research will be removed, and we will remove all your medical information from our research study database. If you want the samples to be removed from the bank and/or your medical information to be removed from our research database, we ask that you contact the principal investigator, **Insert PI Name**, in writing at **Insert Mailing Address**.

We may learn new things during the research study that you may need to know. We may also learn about things that might make you want to stop taking part in the research study. While you are on the research study, we will let you know of any important new information, good or bad. We will explain how this may concern you.

New findings

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Can you be removed from the research study?

Your doctors may remove you from the research study without your permission for any of the following reasons:

It would be dangerous for you to continue;

You do not follow the procedures as directed by the research study doctors; or

The sponsor decides to end the research study.

Where can you get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>

For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

Signature

By signing below, you tell us that you have gotten all of the information you need; that you have received clear answers to your questions, and that you agree to take part in the research study. You will receive a copy of this form. You may also request a copy of the research plan.

Signature of Participant

Date

Signature of Physician

Date

By signing this form the physician indicates that the research subject has been fully informed of all aspects of the research study and that the Consent form was signed voluntarily in his/her presence.

IRB Protocol Number:

Creation of a Central Blood Reference Set for the Early Detection of Breast Cancer

Future Research:

This part of the consent form is only for future laboratory research. Future research may be done to look at these samples. You are giving us permission to use your blood for future research studies. You may take part in the rest of the study even if you do not want your blood looked at for this reason.

In addition to the scientists within this group, your blood samples will be made available to other scientists studying breast cancer. Scientists who want to study these samples will apply to the scientists within this group for approval to use them. Approval will be based on scientific reason

You will not benefit directly from permitting us to use your samples in future research.

In the future, you may decide you do not want to participate in this research. We can remove your samples from the tissue bank.

Wherever possible, we will not use or disclose any information that could be used to identify you. We will try to keep your personal facts private. We will guard any central computer record. We will not release or publish anything that can identify you.

You will not receive any money for giving us permission to use your samples. You will not be paid if you take part in this part of the study. These tests will be done without any charge to you.

By signing below, you indicate that:

You have read this form

Received acceptable answers to any questions

You are giving us permission to use samples for future research studies

Willingly consent to participate.

You will get a copy of this form.

Signature of Participant

Date

Signature of Witness

Date

Authorization (Permission) to Use or Disclose (Release) Protected Health Information (PHI) for Research

IRB# and Protocol ID:

Study Title: Breast Cancer Reference Set Construction

Principal Investigator:

Coordinating Group (or Center): EDRN Data Management and Coordinating Center

Other Sponsor(s): National Cancer Institute

What is the purpose of this form?

This form is required by the Health Insurance Portability and Accountability Act of 1996. Specifically the privacy regulation (HIPAA) permits the research investigators listed above to use and disclose health information about you for the research study identified above which has been approved by the Insert Institution Name Institutional Review Board.

Insert Institution Name is an organization that does research to learn about the causes of cancer, and how to prevent and treat cancer. Researchers would like to use your protected health information for research. The elements of protected health information as defined by HIPAA are:

1. Data Elements for Protected Health Information (PHI)

Names

All geographic subdivisions smaller than a state (except for the first 3 digits of the zip code in some cases)

All elements of dates (except year) for dates directly related to an individual (e.g., birth date, admission date, discharge date, date of death) and all ages over age 89 and dates indicative of that age

Telephone numbers

Fax numbers

E-mail addresses

Social security numbers

Medical record numbers

Health plan beneficiary numbers

Account numbers

Certificate/license numbers

Vehicle identifiers and serial numbers, including license plate numbers

Device identifiers and serial numbers

Web Universal Resource Locators (URL)

Internet Protocol (IP) addresses

Biometric identifiers, including finger and voice prints

Full face photos and any comparable images

Any other unique identifying number, characteristic, or code

2. What protected health information do the researchers want to use?

The researchers may want to copy and use the portions of your health information that they will need for their research. If you enter a research study, health information that maybe used and/or released include the following:

Personal medical history;

Family medical history;

Tissue/blood/cells/DNA;

Content of audio/video recording of sessions;

Current and past cancer screening and lifestyle practices, medications, therapies, diagnostic tests, surgeries, and/or biopsies;

Information from a genetic test you may have had in the past (for example, BRCA1 and/or BRCA2 testing)

Any information collected in the Health History Questionnaire and/or other survey instruments completed during the course of the study.

You may request a blank copy of the data forms from the study doctor or his/her research staff to learn what information will be shared.

3. Why do the researchers want my protected health information?

Insert Institution Name will collect your protected health information and share it with the participating institutions if you enter a research study. The center will use your information in their cancer research study.

4. Who will be able to use my protected health information?

Insert Institution Name will use your health information for research. As part of this research, it may give your information to the following groups taking part in the research. The center may also permit these groups to come in to review your original records that are kept by Insert Institution Name so that they can monitor the research study.

National Cancer Institute

Funding Agency

Public health agencies and other government agencies (including non-U.S.) as authorized or required by law;

Other people or organizations assisting with research efforts of Insert Institution Name

5. How will information about me be kept private?

Insert Institution Name will keep all health information private to the extent possible. Only researchers working with Insert Institution Name or the sponsor will have access to your information. Insert Institution Name or the sponsor will not release personal health information about you to others except as authorized or required by law. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

6. What happens if I do not sign this permission form?

If you do not sign this permission form, you will not be able to take part in the research study for which you are being considered.

7. If I sign this form, will I automatically be entered into the research study?

No, you cannot be entered into any research study without further discussion and separate consent. After discussion, you may decide to take part in the research study. At that time, you will be asked to sign a specific research consent form.

Treatment by your physician will not be affected by whether you provide authorization for the requested use or disclosure except if your treatment is related to research.

8. What happens if I want to withdraw my permission?

You can change your mind at any time and withdraw your permission to allow your protected health information to be used in the research. If this happens, you must withdraw your permission in writing. Beginning on the date you withdraw your permission, no new protected health information will be used for research. However, researchers may continue to use the protected health information that was provided before you withdrew your permission. If you sign this form and enter the research study, but later change your mind and withdraw your permission, you will be removed from the research study at that time.

To withdraw your permission, please contact the person below. She will make sure your written request to withdraw your permission is processed correctly.

Contact Name:

Contact Address:

Contact Phone and FAX:

9. How long will this permission last?

If you agree by signing this form that researchers can use your protected health information, this permission has no expiration date. However, as stated above, you can change your mind and withdraw your permission at any time.

10. What are my rights regarding access to my personal health information?

You have the right to refuse to sign this permission form. You have the right to review and/or copy records of your protected health information kept by Insert Institution Name.

Signatures

I agree that my protected health information may be used for the research purposes described in this form.

Participant Signature: _____ Date: _____
or Legal Representative: _____ Date: _____
Printed Name of Legal Representative (if any): _____

Reference List

1 Pepe, M.S. The Statistical Evaluation of Medical Tests for Classification and Prediction, Oxford University Press Inc.: New York, 2003.