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14. ABSTRACT

The WRNMMC Clinical Breast Care Project/Winder Research Institute will continue to help lead the way in the 21st century in the crusade against breast disorders. The project will continue utilizing a multidisciplinary approach as the standard of care for treating breast diseases and breast cancer. This multidisciplinary model integrates prevention, screening, diagnosis, treatment and continuing care, but the project is further unique in the incorporation of advances in risk reduction, informatics, tissue banking and research. These efforts focus on decreasing the morbidity and mortality of breast cancer among American women.

15. SUBJECT TERMS

Biorepository, Biomedical Informatics, Focused Research, Breast Cancer Risk Reduction, Translational Clinical Care

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Breast Cancer Translational Research Center of Excellence

Final Report

COL Craig D. Shriver, M.D.; Principal Investigator and Director

Period covered: 24 August 2012 - 23 August 2017

1. INTRODUCTION

The Breast Cancer Translational Research Center of Excellence (BCTR-CoE) provides a multidisciplinary approach as the standard of care for treating breast diseases and breast cancer. This approach integrates prevention, screening, diagnosis, treatment and continuing care, incorporation of advances in risk reduction, biomedical informatics, tissue banking and translational research. The project is based on a discovery science paradigm, leveraging high-throughput molecular biology technology and our unique clinically well-characterized tissue repository with advances in biomedical informatics leading to hypothesis-generating discoveries that are then tested in hypothesis-driven experiments.

2. KEYWORDS: None

3. OVERALL PROJECT SUMMARY:

Objective/Hypothesis: Utilize and extend our unique DoD biorepository of well characterized biospecimens from a broad subset of patients with breast cancer and other breast diseases to broaden our knowledge of the etiology and pathology of breast disease specifically focused on breast cancers affecting the readiness of active duty women. Leverage the technological and information technology advances in genomic, proteomic, and total metabolomics research to further our understanding of breast cancer through discoveries in molecular biology, pathway analysis and systems biology that can be readily translated into the clinic.

Background: Breast cancer is the most common non skin-related malignancy among women in the western world. It accounts for one-third of all cancers diagnosed. Age is the single most important risk factor for the development of breast cancer, as incidence and mortality both increase with age. However, a significant number of breast cancers are diagnosed among young women and this shift towards younger women developing breast cancer has increased in the past five years. Each year, over 10,000 new breast cancer cases are detected in women under the age of 40. Over 90% of these occur among women aged 30-39 years and 8 women per 10,000 in this age group die from breast cancer every year. Breast cancer is the single leading cause of death in women aged 40-49 years. Despite the low absolute risk of breast cancer in women under 40 years of age, the incidence is increasing in this age group. The incidence in younger women is probably underestimated based on the current understanding of the biology of breast cancer. The focus of the Breast Cancer Translational Research Center of Excellence (BCTR-CoE) is to work towards decreasing the morbidity and mortality of breast cancer among American women with a specific focus on the problem as it pertains to the active duty military population, an increasing number and proportion of which are female and are in this under-40 age group of increasing breast cancer development, risk, and poorer outcomes. As all jobs and

positions in the military are now available to women including combat positions, the increasing incidence of breast cancer in younger (military-age) women and the increased lethality of that subtype of breast cancer, coupled with the military's critical reliance on a Total Force of all personnel inclusive of a high and increasing percentage female, demands a continued effort of the DoD through the BCTR-CoE to focus on surveillance, screening, early detection, curative treatments, and post-treatment Return To Duty Survivorship programs. The BCTR-COE has had a **16** year history of doing just that, and we are robustly moving into the future by targeting our valuable resources to the active duty military cancer problem, aligning ourselves with other DoD and federal agencies in order to increase efficiencies and allow best use of government funds, and ensuring we are in complete alignment with the DoD QUAD AIM with the central pillar of our efforts focused on READINESS of the Total Force.

Military Relevance: Breast cancer is the most common non-skin cancer in women. It is the single greatest cause of cancer deaths among women under 40, and is a significant cause of mortality for women in the United States Armed Forces. Breast cancer mortality among women <50 years accounts for >40% of years of life lost due to this disease. The economic, social and emotional costs to families are far greater when a young woman dies than when an older woman dies of breast cancer. The more aggressive nature of the disease in young patients along with the attendant costs underscores the importance of early detection of breast cancer in young women. Breast cancer is a curable disease if it is detected early; as such early detection is related to survivorship, cost of treatment and quality of life for the affected woman.

The majority (>90%) of women in active military service are < 40 years of age. The Department of Defense (DOD) with its high percentage (and increasing percentage, as all roles in the military are now open to all genders, including combat roles) of young women and its commitment to health care is particularly concerned about breast cancer. When discovered at a later stage, treatment of breast cancer is expensive, aggressive and results in considerable disruption to the woman's ability to contribute to the military and society. Cost and disruption to life are considerably less when the carcinoma is discovered at an earlier stage and therefore treatable with less invasive methods and curable in up to 90% of cases for Stage I disease. Furthermore, the DOD has a high percentage of African-American (~30%) and Hispanic (~10%) women. Death rates from breast cancer tend to be particularly high in these ethnic groups owing in part to later stage of detection and to the more aggressive nature of breast cancer in these groups.

The active duty military force is approximately 20% female. Most of these service members are in the age range (30-40 years) where routine screening for breast cancer consists only of clinical breast examination. Both mammography and clinical breast examination have a very poor accuracy in the young active duty force in determining which breast abnormalities require treatment, and which are benign and can be left alone. The immense scale and impact of this problem for the military can be assessed by the fact that there were over 2,000 cases of breast cancer diagnosed in active duty service members over the last ten years (source: ACTURS DoD Tumor Registry data).

Furthermore, there were over 8,000 unnecessary breast biopsies done on active duty women during this time because it takes 4 breast biopsies of normal non-cancerous lesions to find each individual breast cancer. Hence, women often need to take lengthy amounts of time off from duty in order to undergo multiple tests leading up to the biopsy as well as time off from duty because of the biopsy itself. This translates into approximately 10,000 weeks, or 30 person-years, of time lost in the

evaluation of normal, benign breast lesions in active duty service members. This would be unacceptable for any other healthcare issue, and should be so for this one. Unfortunately, at the present time there is no completely accurate screening tool currently available to diagnose breast cancer in the early, curable stages for women under the age of 40, who make up the vast majority of women in military uniform.

As indicated, approximately 20% of the active duty military force is female, most under the age of 50. Breast cancer strikes one in eight women in her lifetime, and there is a documented change in breast cancer incidence in recent years, such that breast cancer is being detected and diagnosed more often in younger women (under age 50), and the same is true in our military members. In the same way that diagnostic and therapeutic efforts through the military and US Army are carried out in infectious disease care and research, eg. Malaria, Typhoid, etc., so too must the military continue to address the effects of the scourge of breast cancer and breast diseases on the 20% of total active duty force who are women.

Moreover, CBCP/BCTR-COE, developed and to this day maintains the only specialty breast cancer evaluation and treatment center in the US Army, which is at the CBCP Comprehensive Breast Center at Walter Reed National Military Medical Center.

Additionally, our Breast Center is the only Army facility that financially supports direct genetic testing of active duty (all Services) women who are identified in our Center as being in a high risk category of carrying a BRCA genetic mutation, which when present can signify an up to 90% increased risk of breast cancer development, and for which we then deploy individualized cancer preventive therapies.

The BCTR-COE (CBCP) Breast Center is the Army-recognized and Military-recognized specialty referral center for tri-service active duty personnel from around the globe with medical disorders related to all breast diseases and breast cancer. CBCP Breast Center routinely cares for women on active duty Army from places such as the Middle East, Southwest Asia, OEF, Korea, Europe, and the Far East. CBCP at WRNMMC annually cares for over 7,500 patients.

Public Purpose: The BCTR-CoE is the continuation of the Clinical Breast Care Project (CBCP) that has been ongoing for 16 years. Its uniqueness and relevance has been attested to by numerous outside world-class cancer experts, from the innumerable public scientific and invited lecture presentations made by CBCP PI and investigators over the years, as well as by the extensive peer-reviewed publication record of CBCP researchers. The BCTR-COE has the world's largest biorepository of highly-characterized and pristinely-collected specimens from breast patients made up of human breast tissues, lymph nodes, sentinel nodes, sera, bone marrow aspirates, cancers, benign tumors, and pre-malignant disease, which amounts in-total presently to **72,688 as of 23 August 2017**. This unique DoD resource, stored, maintained, tracked, and kept under strict QA in the CAP accredited CBCP-repository at the Windber Research Institute since 2001. **As of 23 August 2017 the project has used 25,744 samples** in support of both internal genomic and proteomic researchers, as well as targeted collaborations with extramural collaborators from academia, governmental organizations, and corporate entities.

This biorepository is also unique in that its specimens are tightly coupled to highly-accurate clinical, demographic, and pathologic data collected from its originating patients through robust IRB-approved and fully HIPAA (Health Insurance Portability and Accountability Act)- compliant protocols that exceed all existing regulatory requirements for patient consent, privacy, and oversight.

The BCTR-COE has one of the few fully integrated genomic and proteomic molecular biology research programs in the nation devoted exclusively to research in breast diseases. We have an established track record of publication and scientific communication in this field.

The BCTR-COE has deployed a unique biomedical informatics data warehouse system that integrates clinical, pathologic, and molecular data on breast research subjects, allowing for a novel in-silico biology discovery platform.

The BCTR-COE is a true translational research-clinical care environment, where there actually exists an organizationally-driven and structured collaborative effort between basic scientists, clinical scientists, clinicians, nurses, patients, and multiple other personnel.

Pillar Specific Goals, Objectives for CBCP through this award (2012-2017)

I. Breast Cancer Risk Reduction:

Objectives:

- To collect data on all female patients 18 and older who present to the CBCP Breast Center of Excellence at Murtha Cancer Center at Walter Reed National Military Medical Center - Bethesda and are found to be at an increased or elevated risk for developing breast cancer.
- To utilize this database to analyze the diagnosis, treatment, and treatment outcomes for patients found to be at an increased risk for developing breast cancer. Analysis includes but is not limited to: risk factors for developing breast cancer, effectiveness of various modalities of risk-reduction treatment (medical, surgical), and actual risk of developing cancer.

The Risk Reduction Clinic at WRNMMC is a multi-disciplinary program designed to identify, counsel and manage women at high risk for breast cancer. Patients receive an in-depth personal and family health history by a world renowned medical oncologist.

Current research shows there are risk factors that may influence the development of breast cancer. Identifying people with these risk factors and implementing closer surveillance and risk reduction techniques may detect cancer earlier. Earlier detection of breast cancer leads to better prognosis and outcomes. Calculations of risk are based on computer models extensively validated as accurate in identifying women at high risk.

II. Biorepository:

Objectives:

- Continue to collect and store a broad spectrum of biospecimens from every patient undergoing a breast biopsy and/or breast surgery at WRNMMC, Windber Medical Center (WMC), Anne Arundel Medical Center (AAMC), and our affiliated hospitals that consent to participate in BCTR-COE IRB-approved protocols.
- Continue to collect and store biospecimens (blood) from women who are free of breast disease who consent to participate in BCTR-COE IRB-approved protocols to act as controls.
- Utilize the power of this extensive biorepository as a major resource for breast disease research.
- Leverage the BCTR-COE biorepository to maximize the utilization of the repository, with BCTR-COE leadership approval, for the overall benefit of breast cancer patients and research, as able and appropriate.
- Participate in national/international projects that can benefit from resources of the BCTR-COE biorepository.

Although there have been remarkable improvements in breast cancer diagnosis and management, most of the complex molecular mechanisms associated with the onset, progression and/or severity of breast cancer are still not well understood. As part of the BCTR-COE we carry out molecular, biochemical and histological analysis of breast tissue and/or blood and blood components from breast cancer patients to provide insights into the molecular mechanisms that may be relevant in the development of breast cancer and breast diseases. To achieve this aim, a large supply and a wide variety of good quality tissue samples are needed. Unfortunately, good quality donor breast tissue is extremely scarce and when available is often not backed by a comprehensive medical history and/or is not a good representation of the target population or study area. The non-availability of a steady and consistent supply of good quality tissue limits the systematic analysis of tissues and negatively impacts the generation of biologically useful information in research laboratories and by extension negatively impacts new findings that benefit clinical practice. The objective of this project is therefore the acquisition and banking of breast tissue, lymph nodes, serum/plasma and other blood derivatives from informed and consenting donors.

III. Focused Research:

Objective:

The ultimate goal of all BCTR-CoE research projects is to generate new knowledge that will benefit breast cancer patient treatment. The large volume of molecular data from BCTR-COE patients, integrated with the clinicopathologic data including the highly valuable treatment and outcome information, provides a gold data mining opportunity for BCTR-CoE scientists to generate new hypotheses for study and validate new experimental findings. This opportunity is even more enriched by the availability of large-scale high-quality datasets such as those from TCGA across multiple cancer types. Such raw data, combined with public annotation databases on genes, proteins, pathways, and human diseases, will enable derivation of new knowledge for breast cancer patient treatment.

There are two themes for BCTR-CoE research. Theme 1 focuses on breast cancer mechanistic studies of clinically important questions, and Theme 2 focuses on therapy-relevant molecular studies of breast cancers. For Theme 1 studies, one important topic is integrative profiling of breast cancers. The current 4 major breast cancer subtypes—termed "intrinsic subtypes"—were based on gene expression profiling. IHC-based subtyping using ER, PR, Ki67 and HER2 are available and are of clinical significance, although such subtyping is sometimes referred to as surrogate for intrinsic subtyping. Information on a broader panel of proteins and their post-translational modifications as well as their subcellular location information is needed for a more comprehensive understanding of breast cancer stratification which is important for cancer treatment. Thus such studies are important not only for Theme 1 but also for Theme 2, for example, the identification of protein markers for endocrine resistance.

For Theme 1 studies, the BCTR-COE provides a good research environment on young breast cancer patients and African American patients. Young age at breast cancer diagnosis and being African American are considered risk factors for poor outcomes of breast cancer patients. BCTR-COE has enrolled a high percentage of AA patients, and there is also a good size of young breast cancer patients enrolled due to the demographics of the active-duty military population. Using these resources BCTR-COE scientists have conducted molecular studies, and have proposed additional molecular, epidemiologic, and comparative survival analysis using both BCTR-COE data and the data in the public domain.

The topic of tumor heterogeneity is not only important to the understanding of breast cancer development (Theme 1), but also of therapeutic significance (Theme 2). Tumor heterogeneity refers to the cellular heterogeneity of tumor development environment, where there are cancer cells, stromal cells, lymphocytes, etc., and the MCC has chosen "Inflammation, Infection, Immunity, and Stroma (I3S) as one of the focuses for research. Tumor heterogeneity also refers to the fact that one physical tumor could contain multiple lineages of tumors that are not necessarily of the same molecular subtype. When only one subtype was diagnosed and treated, the other subtypes could be left untreated which could lead to detrimental outcome of the patient.

Additional topics are proposed to be studied on mechanistic understanding of breast cancer development. These include genetic dispositions, exposure to environmental risks, access to healthcare and treatment disparities, and impact of certain life style factors as well as comorbidities.

For Theme 2 studies, profiling of human biospecimens alone is important but insufficient; biospecimens are no longer alive after excision from the human body, and in order to study the impact of drugs or the response to drugs of a mutated gene, a live model system is needed. BC-COE scientists has developed tissue culture systems for both 2D and 3D model systems of breast cancer cell lines, with a focus on the triple-negative subtype that are currently difficult to treat. Findings from such studies are validated or sometimes guided by bioinformatics analysis of the data on human tissues. In addition, collaboration with university faculty members have been developed to use animal models to validate findings made from cell lines.

IV. Biomedical Informatics:

Objective:

As one of the five pillars of the CBCP, Biomedical Informatics (BMIX) has developed a comprehensive informatics system supporting the activities in all of the other 4 pillars. Biomedical Informatics also provides support to other research projects and leads its own research, by working with scientists both within and outside of the WRI. In the recent years, the BCTR-CoE has been conducting or participating in several large-scale molecular studies, including the TCGA-BC, Massive Parallel Molecular Processing in collaboration with the Pacific North Western National Lab, a Komen Promise Grant for therapy relevant molecular stratification of breast cancers in collaboration with Thomas Jefferson, etc. New initiatives are in development. The BCTR-CoE is now also addressing the collection of treatment and outcome data for invasive cancer patients enrolled in the study. These projects, combined with the research conducted by scientists at the WRI, has generated a large amount of molecular data as well as new types of clinical data. It is thus critical to expand our current informatics infrastructure to manage all these data, and more importantly, it is critical we expand our bioinformatics research capability to conduct integrative analysis to analyze these data, mine for new hypothesis for validation both computationally and experimentally, so as to make the best use of the data towards making important findings in understanding cancer development mechanisms, identifying cancer treatment drug targets, and develop physician decision support system to aid in cancer treatment.

Biomedical Informatics is now broadly defined as a multi-disciplinary subject for the management and utilization of biomedical information encompassing clinical informatics, public health informatics, and bioinformatics. This definition is increasingly important as new concepts and technologies enter into medical practice and related basic research, and require new types of information management and data analysis that relies on sophisticated statistical and computational technologies. Figure DD.0 shows the major components in this d efinition of BMIX.

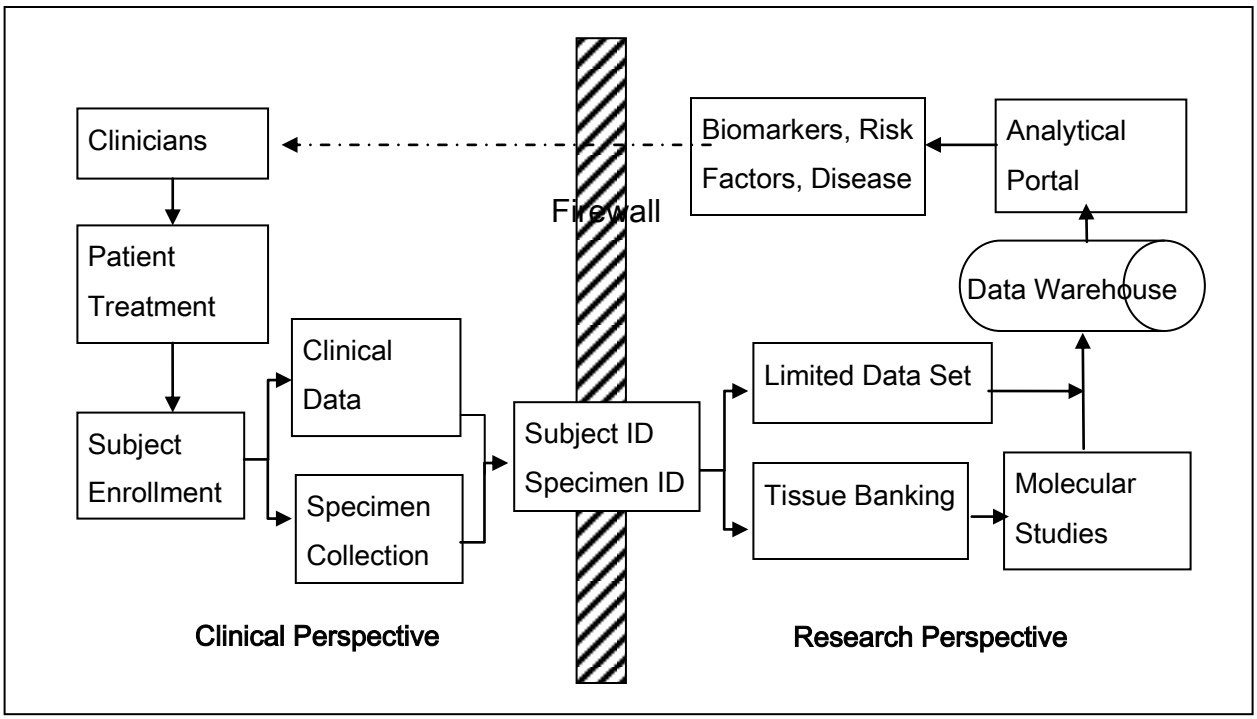

Figure DD.0. Major components of biomedical informatics.

Clinically, patients receive treatment, subjects are enrolled in the study, and clinical data as well as specimens are collected. To protect the privacy of human subjects, de-identified subject IDs and specimen IDs are created and properly mapped before being transferred to the research side with the corresponding clinical data and the specimens. On the research side, clinical data are properly stored, tissues properly banked and genomic and proteomic studies conducted. All data are then warehoused, analyzed, and mined for biomarkers, risk factors, and disease models. Newly obtained knowledge is fed back to the clinic to aid in clinical decision-making.

From the data flow point of view, these BMIX components include 1) supporting data collection and generation across clinical, genomic, and proteomic platforms, 2) data tracking, 3) data centralization, 4) data analysis and mining, and 5) knowledge generation and presentation to research and clinical applications. We have been working towards developing a complete BMIX infrastructure for the BCTR-COE. The system we are developing was designed to be flexible to enable expansion to support translational research in other disease areas. In the following we will present the background, the current status, and the plan for each of these 5 components of BMIX.

V. Translational Clinical Care:

Objectives:

- Decrease the negative psychological impact on the patient of having an evaluation or treatment intervention for breast disease by utilizing objective measurement instruments to longitudinally assess the patient's psychological response to evaluation and intervention, and base modifications of these procedures on those results.

- Create and maintain an environment (medical, physical, psychological) conductive to the multiple needs of the patient undergoing breast disease evaluation / treatment.
- Recruit patients into the various BCTR protocols to obtain the clinical data and biospecimens needed to meet the BCTR's translational research goals.

This pillar of the BCTR is the foundation upon which all the success of and project rests. Without patients enrolled in our biospecimen repository protocols, there would be no translational research center of excellence. These patients come from the clinical care environment. Since its inception in 2001, the CBCP has had as a priority, the development and staffing of the core clinical centers at Walter Reed National Military Medical Center, the Joyce Murtha Breast Care Center in Windber, PA and at our newest site, the Pat and Lesly Sajack Breast Center at Anne Arundel Medical Center in Annapolis, Maryland. Under the direction of Lorraine Tafra, MD more than 500 newly diagnosed cases of breast cancer are seen at AAMC each year.

At each center the staff is dually trained as clinical/research providers, to seamlessly integrate the need for a strong research focus in the clinical center with the requirement to provide state-of-the-art clinical care to the patients. The reputation of CBCP is that of an exceptional translational research project with very possibly the world's most pristine collection of breast tissue. This has resulted in a number of well-respected medical centers expressing interest in joining us as research partners. The care of our patients is provided by Physicians, Advance Practice Nurses (Nurse Practitioners) and certified Nurse Navigators with all personnel having as their prime job description, the research aspects of the BCTR.

Walter Reed National Military Medical Center in Bethesda, MD has a state of the art comprehensive breast care center with women's imaging co-located with the breast care center. The Breast Center has a procedure room, recovery room enabling surgery within the center as well as a designated Aurora Breast MRI machine. We evaluate on average 7,500 patients per year and diagnose approximately 250 new breast cancers per year. **Of note, the Breast Care and Translational Research Center of Excellence received a 3 year full accreditation by the NAPBC (National Accreditation Program for Breast Centers) and are accredited through September 2018.**

4. KEY RESEARCH ACCOMPLISHMENTS:

Breast Cancer Translational Research Center of Excellence (BCTR-COE)
Statement of Work

Task 1: Identify and counsel 100 patients annually at high risk for development of breast cancer, and employ risk reduction strategies.

CBCP evaluated a total of 1684 high risk patients over the 5 year period; 1400 patients were seen in the clinic and 284 telephone consults were conducted at Walter Reed National Military Medical Center in Bethesda, MD from 24 August 2012 – 23 August 2017.

Task 2: Accrue over 500 patients annually to the "core" BCTR-COE protocols through consenting patients in the main BCTR-COE clinical sites.

Total Patients Consented from 24 August 2012 – 23 August 2017.
WRNMMC: 1,019
Windber: 853
AAMC: 931

Task 3: Acquire through consented protocol acquisitions, over 5,000 specimens annually (neoplastic and non-neoplastic breast tissues and tumors, lymph nodes, metastatic deposits, blood and its components, bone marrow) on patients with all types of breast diseases and cancer.

Total Samples Collected from 24 August 2012 – 23 August 2017.
Total Blood: 18,585
Total Breast: 4,294
Total LN: 344
Total Other: 557

Specimen types and processing formats are summarized below:

CBCP Tissue Types	*Preservation*
Breast Tumor	*OCT, Flash Frozen*
Benign Breast Tissue	*OCT, Flash Frozen*
Lymph Node	*OCT, Flash Frozen*

Blood Collection Tubes	*Components Stored*
Green Top Tubes (Sodium Heparin)	*plasma, blood cells*
Red Top Tubes	*serum, clot*
Paxgene Blood RNA Tubes	*whole blood for RNA extraction*

Task 4/5: Bank these biospecimens in the BCTR-COE Biorepository as the substrate for all molecular analyses carried out in BCTR-COE labs, as outlined in the BCTR-COE Core Protocols. Utilize this repository as the basis for intramural and extramural collaborations for secondary usage research.

Since the inception of the Clinical Breast Care Project the Biorepository Pillar has been critical to the success of the project, it is important to look at the success of the biorepository and to understand the firm foundation that it has laid for building the Center of Excellence.

The charts below show the cumulative patient accrual into the CBCP protocols and total number of specimens stored in our biorepository since 2002. These patients, who have been recruited and consented into the CBCP protocols at WRAMC, WRNMMC, AAMC, WMC and other participating CBCP clinical intake sites are the foundations of the translational research that has occurred within the

CBCP. **From these patients we have collected and stored in our biorepository over 72,688 biospecimens (Figure BB-1) donated by 8,443 fully consented subjects to our IRB approved tissue and blood protocols. (Figure BB-2).**

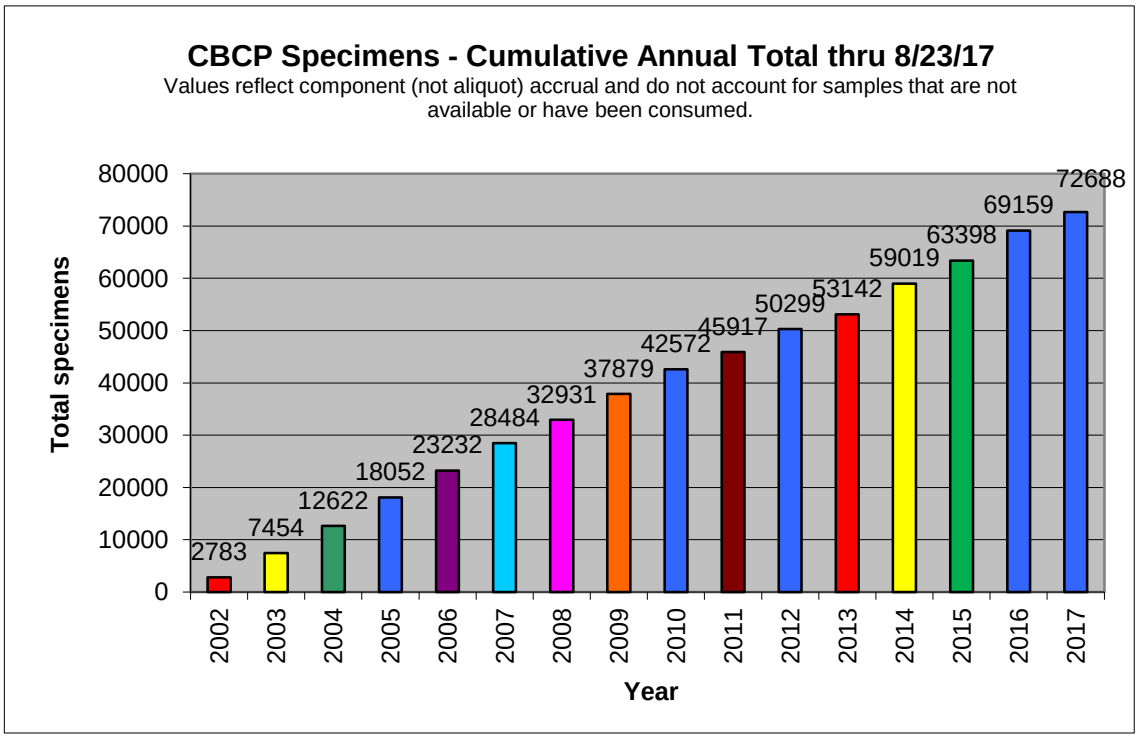

Figure BB-1 Total biospecimens collected and banked by the biorepository.

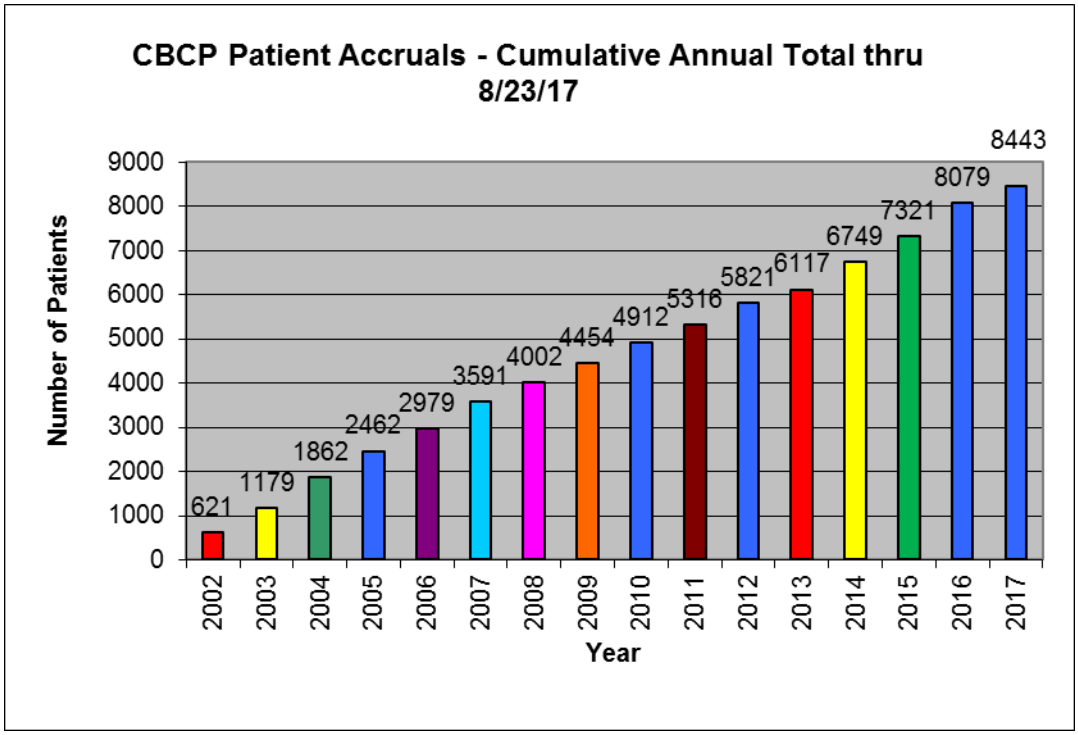

Figure BB-2. Cumulative patient accruals into CBCP protocols since 2002.

Task 6: Perform whole genome DNA sequencing on DNA from 40 or more cases of breast cancer over the life of the project.

We have completed whole genome sequencing of 31 cases in a young women study at The American Genome Center at USU, reporting mutation patterns in young women (Wilkerson, AACR 2017). In collaboration with TAGC we also completed 8 cases in a tumor purity study on RNA vs. DNA mutation, reporting that tumors with a lower purity have a higher RNA/DNA mutation ratio (Te, AACR 2017). In addition, 100 cases were analyzed in a separate proteogenomic study where we reported proteogenomic properties of tumors after laser microdissection (Sridihara, AACR 2017; Raj Kumar, AACR 2017). Multiple manuscripts are in preparation.

Task 7: Develop and support a robust laboratory information management system to ensure proper tracking of data acquisition and a clinically relevant and laboratory research-linked prospective, longitudinal computerized data warehouse to support translational research and ultimately support physician decision making.

In the period between 2012-2017 we implemented the Data Tracking System for CBCP (DTS-CBCP) – our replacement for the CLWS. It completely covered clinical and tissue bank operations. The DTS-CBCP system includes 11 modules (Pathology, Security, Enrollment, Clinical and Outcome, Treatment, Prognostic Studies, Sample: Registration, Sample: Shipment, Sample: Verification, and Sample: Export to FreezerWorks modules). It was implemented using state of the art architecture and technology and used the latest tools for implementation. Following CAP guidelines, a number of documents have been implemented including a variety of SOPs, Data Dictionary, Use Case documents, and release notes. As a continuation of development, we are planning to implement a variety of reports and additional QA rules, extension for supporting histopathology and sample preparation for different experiments.

Task 8: Develop an analytical system for integrative data analysis and mining, and develop a breast knowledgebase to support clinical and research activities in BC-COE.

In the period between 2012-2017 we developed DW4TR to extract data from CLWS and put into the Data Warehouse using InforSense tools. We also performed the data migration between CLWS and DTS-CBCP. After the DTS-CBCP was implemented, we developed a method for extracting information and putting it into the improved Data Warehouse. On top of it, we developed a set of tools for data analysis, mining, and reporting. Some reports are automatically generated and sent to the users. We also created and implemented a process for submitting data for publication where the author should provide result files before clearance is granted. In addition to that we compiled, cataloged, and archived all tissue microarray results performed in WRI. We investigated a number of freely available knowledge systems and did not find one that will satisfy our needs. We will continue working on improving our Data Warehouse by developing new tools and more robust ways for data mining and analysis.

Task 9: Conduct quantitative analysis of therapy relevant proteins by immunohistochemistry within subclasses of breast cancer to provide better patient selection into clinical trials for targeted and combination therapies.

A proof of principle of the analysis for 27 markers have been performed for over 200 cases, connecting the information on ER, PR, and HER2 to other markers for increased understanding of molecular connectivity in breast cancer tumors. Using this dataset we analyzed markers CD163 and phosphohistoneH3, and reported that they were associated with patient survival and patient or tumor characteristics (SABCS 2015).Additional markers and sets of markers have been analyzed, with observations confirming reported results. For some markers, such as the HER family receptors, more cases would be needed to derive a robust result. A program has been developed to enable semi-automatic analysis of any markers when more results (more cases, or more markers) are available. In addition, we conducted a preliminary Bayesian analysis of the whole dataset, and found leads for new hypotheses while confirming known relationships between the markers.

Task 10: Study molecular differences between breast tumors from African American and Caucasian women as the identification of such differences will allow for the development of more effective therapies that will improve outcomes in African American women with breast cancer.

In the period between 2012-2017, we have published 4 manuscripts evaluating molecular differences in breast tumors between African American and European American women. We found that gene expression patterns differ between populations, especially genes such as CRYBB2P1, PSPHL and SOS1 (LA Field, B Love, B Deyarmin, JA Hooke, CD Shriver, RE Ellsworth. Identification of differentially expressed genes in breast tumors from African American compared to Caucasian women. Cancer 118:1334-1344, 2012), however these changes were also detected in normal breast tissue from women without breast disease. Functional evaluation of differentially expressed genes further demonstrated that these differentially expressed genes represent the effects of population stratification and are not causative (S Rummel, C Penatzer, CD Shriver, RE Ellsworth. PSPHL and breast cancer in African American women: causative gene or population stratification? BMC Genetics 15:38, 2014). Together, these data suggest that reduction of survival disparities may be best accomplished by a) identifying factors, genetic and environmental, associated with increased risk of TNBC in young African American women and b) improving therapeutics for patients with TNBC.

Task 11: Using state-of-the-art 3D cell culture techniques and modern approaches to the study of cancer cell biology, study the mechanisms of cell invasion, migration and ultimately metastasis in breast cancer cell lines. Ongoing, several abstracts and publications have been presented on this topic.

AIM#1 CSPG4-NEDD) interaction promotes triple-negative breast cancer progression and metastasis

There are lines of evidence demonstrating NEDD9 plays a key role in facilitating breast cancer progression and metastasis by regulating proliferation, migration, and invasion into tissues. We hypothesized that NEDD9 would associate with cell adhesion receptors and transducer signals important for promoting malignant phenotypes of triple-negative breast cancer cells**.** In the period of 2012 to 2017, we published 2 papers describing novel mechanisms of malignant phenotypes of breast cancer cells. We tested our hypothesis by co-immunoprecipitation assays and demonstrated that NEDD9 associated with a cell surface adhesion receptor, CSPG4 (chondroitin sulfate proteoglycan 4) in triple-negative breast cancer cells, which promote breast cancer cell migration (Iida, J. and Dorchak, J. et al. PLos One 7(9), e44418, 2012). In order to further characterize NEDD9 in promoting malignant phenotypes of breast cancer cells, we established a model system in which NEDD9 is over expressed in parental cell line, HCC38. Analyses of genes expressed by NEDD9 suggest that enzymes such as CHST11, CHST15, and CSGALNACT1 are upregulated on both transcription and translation levels, implicating CSE (chondroitin sulfate E) biosynthesis is enhanced in NEDD9 expressing cells. Biochemical approaches identified CD44 and Serglycin that are modified by CSE subunit. We, for the first time, that CSE enhance stem cell phenotype of triple-negative breast cancer cells (IIDA, J., DORCHAK, J., et al., Exp Cell Res, 330**,** 358-70, 2015). We are continuing the studies further focusing on characterizing novel cytoplasmic and mitochondria signaling mechanisms through NEDD9 for promoting malignant phenotypes of breast cancer cells. These results are currently prepared for two manuscripts. These results suggest that CSPG4-NEDD9 complex plays a key role in enhancing malignant and stem cell phenotypes of triple-negative breast cancer cells, thus serving as a therapeutic target for patients diagnosed with this subtype of breast cancer cells.

Poster Presentations

DORCHAK, J., IIDA, J., CLANCY, R., LUO, C., CHEN, Y., HU, H., MURAL, R. J. & SHRIVER, C. D. 2012. FH535 inhibited migration and growth of breast cancer cells. 35th San Antonio Breast Cancer Symposium. San Antonio, TX,

IIDA, J., DORCHAK, J., CLANCY, R., LUO, C., CHEN, Y., HU, H., MURAL, R. J. & SHRIVER, C. D. 2012. CSPG4-NEDD9 interaction promotes migration, invasion, and growth of breast cancer cells. American Society for Cell Biology Annual Meeting. San Francisco, CA,

IIDA, J., DORCHAK, J., CLANCY, R., MURAL, R. J. & SHRIVER, C. D. 2013. Role for NEDD9 to promote malignant phenotypes of triple-negative breast cancer cells. Gordon Research Conference on Mammary Gland Biology. Stoweflake Resort and Conference: Stove, VT,

IIDA, J., DORCHAK, J., CLANCY, R., SLAVIK, J., CUTLER, M. & SHRIVER, C. D. 2015. Tumor-associated glycans as key molecules to promote triple-negative breast cancer cells. 38th San Antonio Breast Cancer Symposium. San Antonio, TX,

IIDA, J., DORCHAK, J., CLANCY, R., SLAVIK, J., CUTLER, M. & SHRIVER, C. D. 2016. Role for chondroitin sulfate for promoting triple-negative breast cancer cells. Proteoglycan Gordon Research Conference. Andover, NH,

IIDA, J., DORCHAK, J., SLAVIK, J., CLANCY, R., CUTLER, M. & SHRIVER, C. D. 2016. NEDD9 promotes breast cancer metastasis by regulating mitochondrial functions. 39th San Antonio Breast Cancer Symposium. San Antonio, TX,

Invited Speaker
Proteoglycan Gordon Research Conference at Andover, NH. Chondroitin sulfate-E as a key glycan to promote triple-negative breast cancer growth

Aim 2. Development of DNA aptamers against CD44 that inhibit breast cancer invasion and metastasis.
Our hypothesis is that CD44 promotes malignant phenotypes of breast cancer through the interaction with cell surface receptor kinase (s). In order to test this hypothesis, we developed DNA aptamer that specifically recognizes exon V10 of CD44 by in vitro aptamer screening system, SELEX (Systematic Evolution of Ligands by Exponential Enrichment). The selected aptamers were screened for inhibiting breast cancer migration. Biochemical analyses of the inhibitory aptamers suggest that CD44 forms a complex with EphA2 on triple-negative breast cancer cell surface. Thus, our results support a novel mechanism of cancer cell migration involving CD44-EphA2 molecular complex formed on cell surface and provide significant insights for developing target-specific therapy for breast cancers and possibly other cancer types expressing CD44 exon v10(IIDA, J., CLANCY, R., et al, 2014 PLoS One, e88712 2014).
We are currently further characterizing CD44-EphA2 molecular complex for promoting stem cell phenotypes of breast cancer cells. Our recent studies suggest that CD44 or EphA2 alone did not stimulate mammosphere formation, while double transfecting these genes significantly facilitate the process in the presence of hyaluronan (Iida, J., Clancy, R. Purazo, M, Cutler, ML, and Shriver, CD. manuscript in preparation). Since we identified 4 residues in the cytoplasmidc domain of EphA2 (^{594}Y, ^{588}Y, ^{772}Y, and ^{897}S), our current focuses are 1) identification of key phosphorylation site(s) of EphA2 are phosphorylated an evaluating these phosphorylation in regulating mammosphere formation if breast canccer cells. These results suggest that CD44 –EphA2 plays a role in regulating breast cancer stem cell phenotypes, thus attenuating EphA2 kinase function is a promising approach for detecting and killing breast cancer stem cells, which may provide significant insights to develop novel anti-breast cancer stem cell therapies.

Aim 3.Identification of drug-targets for triple-negative breast cancer.
We developed systematic approaches to identify the targets by encompassing Biology, Bioinformatics, Animal models between WRI and USUHS. We are currently characterizing SOX10, which are highly expressed in triple-negative breast cancer tissues, for their biological functions in facilitating tumor growth, migration, and growth. Based on the preliminary results supported by this grant, we successfully obtained additional grant from USMCI-CCC grant in collaboration with Professor Mary Lou Cutler at USUHS.

We hypothesized that SOX10 promotes malignant phenotypes breast cancer cells by interacting with partner proteins in cytoplasm. In order to test this hypothesis, we performed co-immunoprecipitation

assays from triple-negative breast cancer cell lysates and the precipitates were subjected to mass spectrometry. We found zyxin as a candidate partner proteins from the analyses and demonstrated that SOX10 forms a complex with zyxin in various breast cancer cells by co-immunoprecipitation assays. Further analysis demonstrated that Serine residues at 24 and 45 of SOX10 are phosphorylated. We, then, mutated these residues to Alanine and determined that 45S is a key residue for interacting with zyxin. In order to test our hypothesis, we performed microarray studies by asking question whether SOX10-zyxin and SOX10 alone differentially regulate gene expressions in triple-negative breast cancer cells. We identified several metastasis-promoting genes are upregulated by SOX10-zyxin complex but not by SOX10 alone, These results provide a novel gene expression regulatory mechanisms by a transcription factor-cytoskeletal protein complex that promotes progression and metastasis of breast cancer cells. Furthermore, our model would provide significant information for understanding microenvironment-specific gene expression regulation during physiological and pathological processes. These results are currently prepared for as three separate manuscripts.

As an alternative approaches to identify drug targets in breast cancer cells, we took an approach of chemical biology for structure-activity relationship (SAR) studies. We used a transition metal, ruthenium (Ru), as a model metal for synthesizing several molecules with different structures. We identified one Ru-compound that significantly inhibited multiple human cancer cells such as breast cancer, osteosarcoma, and lymphoma. Importantly, the identified compound synergistically inhibited a malignant triple-negative breast cancer cell line, MDA-MB-231, with cyclophosphamide. These results suggest that Ru compounds are promising anti-cancer reagents that would inhibit various cancer cell types. Furthermore, identifying the molecular target of the Ru-compound would provide important information for developing novel therapeutic strategies.

Publications

IIDA, J., BELL-LONCELLA, E. T., PURAZO, M. L., LU, Y., DORCHAK, J., CLANCY, R., SLAVIK, J., CUTLER, M. L. & SHRIVER, C. D. 2016a. Inhibition of cancer cell growth by ruthenium complexes. J Transl Med, 14, 48.

Poster Presentations

BELL-LONCELLA, E. T., PURAZO, M. L., LU, Y., IIDA, J. & SHRIVER, C. D. 2014. Structure-activity relationship of ruthenium (Ru) complexes to inhibit breast cancer growth and metastasis. 45th Central Regional American Society Meeting of American Chemical Society. Pittsburgh, PA

IIDA, J., PURAZO, M. L., LU, Y., BELL-LONCELLA, E. T. & SHRIVER, C. D. 2014b. Structure-activity relationship of ruthenium (Ru) complexes to inhibit breast cancer growth and metastasis. 37th San Antonio Breast Cancer Symposium. San Antonio, TX,

PURAZO, M. L., LU, Y., DORCHAK, J. & AL., E. 2014a. Use of triple-negative breast cancer cell lines to screen half-sandwich ruthenium (ii)-arene anticancer complexes. American Chemical Society Regional Meeting. Pittsburgh, PA,

Task 12: Use our unique collection of breast cancer biospecimens to characterize microRNA (miRNA) expression in breast cancer progression and metastasis.

This project had been placed on hold.

Task 13: Identify protein signatures associated with the development and progression of pre-malignant breast disease to improve our understanding of the biologic processes involved in early breast disease development and progression and to drive the development of personalized therapeutics for breast disease.

This project was submitted as a proposal for NIH funding. The grant was not funded and the project never commenced.

Task 14: Identify genetic changes in low- and high-grade breast tumors to improve our understanding of the evolutionary process of breast cancer and to identify a protein signature that can discriminate low- from high-grade breast tumors, allowing for more accurate diagnosis and risk assessment.

Data was generated using mRNA and miRNA arrays and in situ proteomics. 1583 genes and 81 miRNAs were differentially expressed between high- and low-grade tumors. mRNA was able to correctly classify 93% of samples, miRNA was able to classify 89%. Twelve protein features were differentially expressed between low and high-grade tumors, two of which, calgizzarin and calgranulin A, were also differentially expressed at the mRNA level.

Task 15: Use our unique collection of breast cancer biospecimens to characterize molecular signatures that can differentiate primary breast tumors with and without metastatic potential, as well as between primary tumors and subsequent metastases.

We determined copy number changes in 122 breast tumors with known clinical outcome and found that changes at chromosomes 7q31, 8p22, 13q14, 17p13.3, 17p13.1 and 22q12.3 were associated with mortality and 16q22-q24 with good outcome. Copy number changes at 13q14 were associated with long-term (>5-year) mortality (LM Voeghtly, K Mamula, JL Campbell, CD Shriver, RE Ellsworth. Molecular alterations associated with early and late breast cancer mortality. PLoS One 7:e46814, 2012). Gene expression analysis in primary breast tumors was not able to identify a profile that could differentiate metastatic from non-metastatic tumors (CD Shriver, MT Hueman, RE Ellsworth. Molecular signatures of lymph node status by breast cancer intrinsic subtype. J Exp Clin Cancer Res, 33: 782, 2014). We also explored molecular changes in the metastatic microenvironment (e.g. lymph node tissues) and found an immunotolerant phenotype in colonized lymph nodes (AL Valente, JL Kane, DL Ellsworth, CD Shriver, RE Ellsworth. Molecular response of the axillary lymph node microenvironment to metastatic colonization. Clin Exp Metastasis 31:565-572, 2014); these changes are restricted to those nodes within the axillary basin that harbor disseminated tumor cells (HL Blackburn, DL Ellsworth, CD Shriver, RE Ellsworth. Breast cancer metastasis to the axillary lymph nodes: are changes to the lymph node "soil" localized or systemic? Breast Cancer: Basic Clin Res Epub ahead of print).

Task 16: Objective 1 Evaluate differences in the molecular profiles of patients with increased HER2 expression

Fluorescence in situ hybridization (FISH) using the PathVysion kit was performed on invasive breast tumors from patients enrolled in the Clinical Breast Care Project (CBCP) to determine HER2 and CEP17 copy numbers. Those patients with increased HER2 copy number (≥4 copies/cell) were selected for inclusion in this study; those with a HER2/CEP17 ratio <2.2 were considered to have chromosome 17 polysomy while those with a ratio >2.2 were considered to be HER2 amplified. Clinical characteristics of the polysomic (N=42) and amplified (N=71) cases were compared. Tumor grade, size and stage did not differ between polysomic and amplified cases. Polysomic cases were

more likely than amplified cases to have ER+ tumors, but this difference did not reach statistical significance. Patients with HER2 amplified tumors were more likely to be diagnosed before age 50 (P=0.017) and with lymph node metastases (P=0.008) than patients with chromosome 17 polysomy.

Frozen OCT-embedded breast tumor specimens were available for 14 polysomic and 18 amplified cases. The tumors were laser microdissected to obtain pure tumor cells and RNA isolated and used to generate gene expression microarray profiles. In preliminary data analysis, 67 genes were identified as differentially expressed (P<0.01; fold change >2) between the polysomic and amplified groups. Many of these are involved in cellular processes that could impact breast tumorigenesis, including cell cycle control, cell adhesion and migration, cell differentiation, cytoskeleton organization, signal transduction, protein synthesis and degradation, and ion transport. The top four most significant genes with higher expression in the polysomic cases, TUBG1, CPD, BLMH, and JUP, are all located on chromosome 17q. The results of this work were presented at two conferences as poster presentations (see below).

Due to the limited number of HER2 amplified and polysomic cases available in OCT, we decided to use archived FFPE breast tumor specimens for additional studies. First, we needed to develop and optimize protocols for isolating and utilizing RNA from FFPE specimens, particularly for gene expression analysis by qRT-PCR. RNA was isolated from laser microdissected FFPE breast tumor specimens using the RecoverAll kit. In order to preserve material and the relatively low yield of RNA from FFPE specimens, we utilized the TaqMan PreAmp Master Mix to pre-amplify target genes of interest prior to qRT-PCR. For our initial tests, we determined HER2 expression in pre-amplified FFPE samples by qRT-PCR and compared these results to those obtained by immunohistochemistry (IHC). These results agreed very well. Our next step is to compare the expression of a few test genes in breast tumors with specimens available in both OCT and FFPE and determine the concordance of expression between the two types of storage media. If these results are agreeable, we will then use these protocols to validate the gene expression differences identified from microarray analysis of frozen specimens using an independent set of archived FFPE specimens as well as for pathway-focused gene expression analysis of FFPE specimens. These protocols using RNA from FFPE specimens should also prove useful to other projects in the CBCP.

Poster Presentations

Lori A. Field*, Brenda Deyarmin, Rachel E. Ellsworth, Craig D. Shriver. Comparison of breast tumors with HER2 amplification and polysomy 17. San Antonio Breast Cancer Symposium, San Antonio, TX, 2012.*

Lori A. Field*, Brenda Deyarmin, Rachel E. Ellsworth, Craig D. Shriver. Comparison of breast tumors with increased HER2 copy number with and without polysomy 17. Society of Surgical Oncology Cancer Symposium, National Harbor, MD, 2013.*

Task 17: Study the role of matrix metalloproteinases in breast cancer with the goal of developing diagnostic and prognostic marker of breast cancer based on expression of MMPs and polymorphisms in MMPs.

Matrix metalloproteinases (MMPs) are involved in extracellular matrix modification and associated with invasive and metastatic behavior of human malignant tumors. Specifically, MMP2 and MMP9 are

implicated in both early and late processes of tumor development and the MMP-1 polymorphism (MMP-1 2G) may be linked to early onset and aggression in cancer. MMPs occur as inactive precursors, active enzymes or enzyme inhibitor complexes in biological samples. However, their role in disease and significance of their concentration and activity in plasma or serum of breast cancer patients continues to be investigated. It is possible that changes in plasma or serum levels of MMPs can be exploited for early detection or classification of patients into different risk or disease categories. Matrix metalloproteinase concentration and activity was analyzed in a variety of breast cancer patients-carcinoma, benign disease and patients at high risk for developing breast cancer. In these studies, we measured concentration and activity of MMP2/9 in sera and plasma and our results suggest that preoperative plasma concentration and activity of MMP2 and MMP9 may permit sub-classification of female patients with breast disorders and also provide evidence supporting the potential role of serum MMP2/9 as biomarkers for breast disease classification.

We also studied the impact of a guanine insertion polymorphism in matrix metalloproteinase-1 promoter (MMP-1 2G) to determine its role on MMP-1 expression in breast cancer severity. Our studies showed no significant difference in genotype distribution among different disease groups but MMP-1 expression was significantly higher in atypical ductal hyperplasia patients compared to benign breast disease and in invasive breast cancer compared to in situ breast cancer. MMP-1 2G insertion polymorphism in the invasive group of breast cancer patients was observed to correlate significantly with the expression of MMP-1 and the breast cancer prognostic markers HER2 and P53.

Task 18: Identify molecular alterations in the breast tumor microenvironment that contribute to tumorigenesis and which may lead to improved methods of breast cancer prevention and treatment.
Adipose adjacent to and distant from invasive breast tumors (n=20), or adjacent to non-malignant diagnoses (n=20) was laser microdissected from post-menopausal women, gene expression data generated and data analyzed. Pathway analysis revealed significant differences in immune response between non-malignant, distant and tumor adjacent adipose, with the highest response in tumor-adjacent and lowest in non-malignant adipose. These data suggest that molecular profiles of adipose differ depending on presence of or proximity to tumor cells. Heightened immunotolerance in adipose from invasive breasts provides a microenvironment favorable to tumorigenesis. In addition, tumor-adjacent adipose demonstrates expression of genes associated with tumor growth and progression. Thus, adipose is not an inert component of the breast microenvironment but plays an active role in tumorigenesis.

Task 19: Use our unique collection of breast cancer biospecimens to study angiogenesis and lymphogenesis in different grades of DCIS and IDC.
This project had been placed on hold.

Task 20: Incorporate the rapidly growing public genomic and proteomic datasets related to breast cancer into our data warehouse to be able to mine the combined data sets for the generation of new hypotheses regarding breast cancer development, progression and treatment.
We focused on integrating TCGA-BC data. This project was composed of 5 subaims. We generated a tissue-experiment inventory for TCGA-BC BC-CoE cases (Subaim 1). In integrating gene expression microarray data, we originally planned to do it for both Level 1 and 3 data, but found out that integrating Level 3 data and with file links to Level 1 data is sufficient, and that's what we did (Subaim 2). In developing applications to use the integrated gene expression data, we found out that the most

needed application was to provide a query interface and that developing more complicated applications would not be cost-efficient, so we developed the query tool (Subaim 3). We also integrate Level 3 DNA Sequencing data, and make results available to scientists, using similar approaches (Subaim 4). As to say Subaim 5, integrating SNP data, we found out that this type of data was not immediately needed so we shifted our focus to supporting other studies.

In working on data integration our bioinformatics team also worked as part of the TCGA-BC Analaysis Working Group in analyzing TCGA-BC data, and a dozen CBCP researchers were part of the TCGA Network co-authoring the TCGA-BC marker paper published Nature (TCGA Network, 2012, Nature 2012;490(7418):61-70). We also contributed to the lobular breast cancer study as part of the TCGA Network (Ciriello et al, Cell; 2015; 163(2):506-19).

Task 21: Comparing biomarker expression in core biopsy and surgically resected tumors.
Female patients enrolled in the Clinical Breast Care Project (CBCP) from a civilian site were selected for this study, where expression of ER, PR, HER2, and Ki67 were assayed by IHC in a reference lab on CBs; the same 4 assays were performed on SRTs by a CBCP central lab. On IHC assays, Ki67 expression is strikingly higher in CBs than in SRTs, and ER expression is also higher in CBs than in SRTs. This directly resulted in more LB than LA subtypes based on CBs. SRT-based LB1 cases concentrate more on higher grades compared to CB-based cases, which is more consistent with the observation that LB subtypes have worse outcomes. A limitation of this study is that technical differences between the labs may contribute to the observed differences between CBs and SRTs. Further studies need to be performed to determine whether SRT should also be assayed in addition to CB for treatment regimen decision-making. These results were presented at *SABCS 2013.*

Task 22: HER2+ and HER2- luminal B subtypes of invasive breast cancers.
A total of 215 female IBC cases enrolled in CBCP from 2000 to 2010 were included in this study. All IHC and pathology slides were reviewed by a single pathologist, we used cell proliferation marker Ki67 to help classify luminal IBCs into LA, LB1 (HER2-), and LB2 (HER2+). Overall survival analysis result for all cases was consistent with the literature, Ki67+ cases tended towards worse outcomes, and no outcome difference was identified between LB1 and LB2. Histologic grade distributions in different subtypes were consistent with the literature; we further found no difference between LB1 and LB2 subtypes. *The results were reported at the SABCS 2013.*

Task 23: Maintaining efficient Quality Management Systems (QMS) to provide quality tissue for research. Performing Biospecimen Research activities so that data obtained will be utilized to design data driven protocols and procedures. These activities will help the biobank maintain the integrity of its biospecimen and thus provide a biorepository environment that meets the industry's standards.

College of American Pathology (CAP) Accreditation
The biobank received CAP accreditation in May, 2015 after a successful inspection on April 7th, 2015. CAP Self-Assessment- In order to remain CAP accredited CAP Self-Assessment is required 60 days to the anniversary of the biobank's accreditation. The first self-assessment was completed on 6/17/2016. All required paperwork and forms for the 2017 CAP self-assessment have been completed and includes- a self-inspection, copies of staff competencies, and the Quality Management Annual Assessment Summary where we describe the Quality Management initiatives undertaken since the last self-assessment and corrective action initiated if and when required.

Quality Management Systems
Quality Assurance- In our continued efforts to improve quality, consistency and reliability in our operations, we have performed 40 Quality Assurance Studies between 11/1/12 and 2/28/17. These audits cover areas which include tissue quality, inventory, blood/collection/processing freeze time, liquid nitrogen storage, and environmental monitoring.
Standard Operating Procedures (SOP) - To date we have 107 active SOPs and over 87 logs and forms for documentation. 51 New SOPs were approved during the period 11/1/12 – 2/28/17. 34 SOPs were Revised during the period 11/1/12 – 2/28/17.

Proficiency Testing (PT)-Our initial PT Testing with Integrated Biobank of Luxembourg (IBBL) occurred in 2004. We have continued to participate yearly in PT testing in the following areas;
DNA Quantification and Purity
RNA Quantification and Purity
RNA Integrity
DNA Extraction Efficiency from Whole Blood
RNA Extraction Efficiency from Whole Blood
Total RNA Extraction Efficiency from Frozen Tissue
DNA Extraction Efficiency from FFPE Cells
DNA Extraction Efficiency from Frozen Tissue
Tissue Histology

Competency Assessments- Competency and troubleshooting skills were assessed internally for biobank staff throughout the years. We have Dr. Jeff Hooke, CBCP Pathologist, evaluating histology staff for competency in microtomy and slide staining.

Biospecimen Research
We continue to design and carry out relevant experiments in the area of biospecimen science research to support our SOPs. A summary of the research activities that have been initiated to date are;

- RNA Quality-Effect of room temperature storage on tissue integrity
- DNA quality from tissue biopsies: Effect of different processing methods
- RNA quality from laser microdissected tissue- Effect of different slide treatments.
- Exploring Nondestructive methods for tissue Quality Assessment: Assessing proteome markers for tissue quality.
- RNA from tissue imprints- potential as a routine collection/source of tissue RNA.
- RNA from blood imprints-potential as a routine collection/source of blood RNA

The results of our experiments on DNA Quality from different processing methods has been applied to our DNA isolation protocol where we have included homogenization as an optional step since in most cases it produces greater DNA yield.

These projects are at different stages either the experiment are ongoing or near completion /competed. Some have manuscripts drafts at different stages of preparation. The unfortunate situation is that we

usually have to halt these activities when we are inundated with sample processing for researchers and for the different programs such as APOLLO. This is a major reason for the slow pace of our research activities. We will continue to catch up with these activities and bring them to completion. The last 2 activities listed above did not show promising results and have since been suspended.

Education and Training- We continue to explore avenues for improving our knowledge and keeping abreast with new developments in the industry. This is achieved through online webinars/seminars. Additionally, all staff members take the NIH Web-based training course "Protecting Human Research Participants." Renewal is required every three years. Staff involved in shipping are required to receive the SafTPak Transport of Dangerous Good Training. All New and Revised SOPs are also read and signed off by appropriate staff members. We participated in a total of 64 educational activities during the period of 11/1/12 through 2/28/17.

In house training activities- All staff are mandated to participate in the institute's yearly Safety Training program which includes laboratory and fire safety. Security staff who monitor the freezer rooms over the weekends and after office hours receive training on general safety and biobank procedures relevant *to* their duties.

Task 24: Evaluation of molecular and epidemiological data associated with outcome disparities in African American women with breast cancer

Evaluation of outcomes within defined intrinsic subtypes (LA Sturtz, J Melley, CD Shriver, RE Ellsworth. Evaluation of epidemiological and molecular differences in African American and Caucasian women with triple negative breast cancer. BMC Cancer 14:62, 2014; NS Costantino, B Freeman, CD Shriver, RE Ellsworth. Outcome disparities in African American compared to European American women with ER+HER2- tumors treated within an equal-access health care system. Ethn Dis 26:407-416, 2016) revealed that survival disparities do not exist between populations.

We also worked as part of The Cancer Genome Atlas-Breast Cancer Analysis Working Group for a focused study on this racial disparity. Using 930 breast cancer patients including 154 blacks of African ancestry and 776 whites of European ancestry, we analyzed multiple platforms of molecular data and survival using breast cancer-free interval as the end point. While a racial disparity was observed between the two races, on the molecular level, after adjusting for intrinsic subtype frequency differences, we found a modest number of genomic differences between blacks and whites in the TCGA dataset. Moreover, >40% of breast cancer subtype frequency differences could be explained by genetic variants. The paper has been accepted by a leading journal currently in embargo until May 4, 2017 (Huo et al 2017).

Task 25: Evaluation of molecular and epidemiological data associated with outcome disparities in Young Women with breast cancer.

No significant gene expression differences were detected in young women compared to older age groups. Evaluation of germline mutations revealed that 23% of young women with invasive breast cancer harbor pathogenic mutations in breast cancer genes, with an additional 3% of women having mutations in colon cancer genes. This work is in preparation. We also evaluated epidemiological data to determine non-genetic factors that contribute to tumor etiology in young women and found that

Hispanic ancestry was associated with decreased risk of breast cancer while later age at FFTP, earlier and longer use of oral contraceptives and decreased physical activity were associated with increased risk (NS Costantino, TM Cox, CD Shriver, RE Ellsworth. Lifestyle and reproductive factors associated with breast cancer risk in young women. EC Gynaecology 4.2:36045m 2017)

Task 26: Identification of blood-based signatures of breast disease.
Gene expression data fiom blood samples in cases and controls were generated. No significant differences were detected between women with and without breast cancer or between invasive patients with and without metastases. Blood is a complex tissue and this complexity may obscure signals. Our hope to evaluate serum samples from women with and without metastatic breast cancer using immuoassays did not commence as protocol approval to send samples to Myriad RBM was not granted.

Task 27: Effect of a diagnosis of invasive breast cancer on lifestyle choices.
To determine whether a diagnosis of breast cancer was a sufficient motivator for behavioral changes in fat intake, alcohol and tobacco use, exercise, BSE, HRT use and BMI were analyzed from patients diagnosed with invasive breast cancer and those with benign breast disease. Only use of HRT use (decreased) and BSE (increased) differed after diagnosis in the invasive patients. As both HRT and BSE are addressed by the clinical staff of the CBCP while diet and physical activity are not addressed, this suggests that without the proper education or resources, adoption of healthier lifestyle choices is unlikely in breast cancer survivors. These results were presented at the San Antonio Breast Cancer Symposium 2015 (N Costantino, AL Toro, CD Shriver, DL Ellsworth, RE Ellsworth. Can a diagnosis of invasive breast cancer effectively motivate patients to follow healthy lifestyles? San Antonio Breast Cancer Symposium 2015.

Task 28: Abundance and distribution of polychlorinated biphenyls (PCBs) in breast tissue.
The objective of this project was to assess the abundance and distribution of PCB congeners in human breast tissue through a comprehensive survey of mastectomy specimens from the Clinical Breast Care Project. Breast tissues have been collected from 302 quadrants from 62 patients with pathological diagnoses ranging from disease free prophylactic mastectomy samples to metastatic breast cancer. Analysis of 98 PCB congeners in these tissues has been conducted by pressurized liquid extraction followed by high resolution capillary gas chromatography in collaboration with Paul J. Kostyniak, Toxicology Research Center, State University of New York at Buffalo. Although PCB levels were associated with age, no link between any of the congeners were associated with breast cancer risk, pathology or location in the breast (RE Ellsworth, K Mamula, B Deyarmin, PJ Kostyniak, D Gillard, CD Shriver, DL Ellsworth. Abundance and distribution of polychlorinated biphenyls (PCBs) in breast tissue. Environ Res 138: 291-297, 2015).

Task 29: Genomic heterogeneity in primary breast carcinomas and among sentinel lymph node metastases: Implications for clinical management of breast cancer patients.
Previous work in our lab demonstrated heterogeneity between primary tumors and metastatic lymph node tumors, suggesting that metastasis is influenced by the timing of dissemination. We furthered this work by microdissecting primary tumors into discrete regions and evaluating copy number alterations in multiple metastatic lymph nodes. We found that the metastatic process is influenced by both temporal and spatial factors and that molecular divergence within the lymph node tumors is

associated with poor survival (RE Ellsworth, AL Toro, HL Blackburn, A Decewicz, B Deyarmin, KA Mamula, NS Costantino, JA Hooke, CD Shriver, DL Ellsworth. Molecular heterogeneity in primary breast carcinomas and axillary lymph node metastases assessed by genomic fingerprinting analysis. Cancer Growth Metastasis 8:15-24, 2015). We also published an invited review paper describing the effects of molecular heterogeneity in breast cancer evolution (RE Ellsworth, HL Blackburn, CD Shriver, P Soon-Shiong, DL Ellsworth. Molecular heterogeneity in breast cancer: state of the science and implications for patient care. Semin Cell Dev Biol Epub ahead of print 2016).

5. CONCLUSIONS:

In summary, we were successful in all components of the outcome metrics and expectations during this grant cycle of BCTRCoE funding. As a result, we contributed in unparalleled and significant ways to the national conversation on breast cancer while also demonstrating remarkable value to the Department of Defense and service members with breast cancer or at high risk for same.

Specifically:
The goal of identifying and counseling 100 patients annually at high risk for development of breast cancer while employing risk reduction strategies was achieved – *evaluated 1,684 high risk patients over the 5 year period.*

BCTR-CoE successfully accrued and consented patients to our protocols, which continued to increase the specimen total in our biprepository. As of 23 August 2017 BCTR-CoE had banked more than 72,688 biospecimens in the BCTR-COE Biorepository, which are used as the basis for intramural and extramural collaborations for secondary usage research.

During the year BCTR performed focused research on the biospecimens and clinical data collected under the BCTR-COE Core protocols, which resulted in **120** publications, abstracts and presentations by CBCP staff at peer-reviewed national meetings. National meetings included the Military Health System Research Symposium, San Antonio Breast Cancer Symposium, Society of Surgical Oncology Annual Cancer Symposium and the American Association for Cancer Research, Annual Meeting. *See publications, abstracts and presentations on page 29.*

The BCTR-CoE held its combined annual retreat with the Murth Cancer Center at the Uniformed Services University of the Health Sciences. There were multiple presentations at the retreat covering the 5 pillars of the CBCP, as well as a wide range of other cancers (GYN and Prostate related) - *see attached annual retreat agendas (Attachment 8).*

BCTR-CoE underwent a thorough National Accreditation Programs of Breast Centers (NAPBC) inspection on 9/10/2015 and received an outstanding summary from the Surveyor where she described our Center as being excellent, we are exceeding all standards and there are "no discrepancies" with our program. Our breast center received a full 3 year accreditation and is now accredited through September 2018. - *see attached annual retreat agendas (Attachment 9).*

A comparative survival analysis of patients with invasive breast cancer treated by a U.S. military treatment facility was conducted comparing BCTR-CoE's outcomes with with national database

results (SEER) in 2015. The summary of findings revealed that breast cancer patients from the Clinical Breast Care Project/BCTR-CoE at the Walter Reed National Military Medical Center showed a statistically significant advantage in disease-specific survival, overall survival, and 5-year survival rates over matched patients from the Surveillance, Epidemiology, and End Results program. Tumor characteristics explained only one-fourth to one-third of the 5-year survival rate differences at the whole cohort level.

The BCTR-CoE Biorepository underwent a thorough inspection on 4/7/2015 and successfully received its College of American Pathologists (CAP) Accreditation. - *see attached annual retreat agendas (Attachment 10).*

The WRNMMC-Bethesda hosted a Naming Ceremony for the Cancer Center on Dec 3, 2012, on the third floor of the America Building starting at 1300 hrs. The Secretary of Defense was the keynote speaker durin this ceremony to officially name the Cancer Center after the late Congressman John P. Murtha; and to note the Cancer Center's recent achievement of being officially recognized by DoD as a Cancer Center of Excellence.

The John P. Murtha Cancer Center hosts its Annual Cancer Awareness Day every June in the lobby of the America Building at WRNNMC. CBCP has a strong presence with presentations and display tables for patients/staff annually to support the cancer awareness day

6. PUBLICATIONS, ABSTRACTS AND PRESENTATIONS:

PERIOD COVERED: 24 AUG 2012 – 23 AUG 2017 (newest to oldest)

CBCP Publications 24 AUG 2016 – 23 AUG 2017

Liu J, Kovatich AJ, Hooke JA, Campbell-Fantacone JL, Kvecher L, Sturtz LA, Shriver CD, and Hu H. Race is not a contributing factor to breast cancer-free interval outcome for patients treated at the Walter Reed National Military Medical Center. 2016 Military Health System Research Symposium, 2016 Aug 15-18, Kissimmee, FL.

Ellsworth RE, Blackburn HL, Shriver CD, Soon-Shiong P, Ellsworth DL. Molecular heterogeneity in breast cancer: state of the science and implications for patient care. Semin Cell Dev Biol. 2016 Aug 26. pii: S1084-9521(16)30266-X.

Constantino N, Freeman B, Shriver CD, Ellsworth RE. Outcome disparities in African American compared to European American women with ER+HER2- tumors treated within an equal-access health care system. Ethnicity and Disease, 2016 Jul 21; 26(3):407-16.

Sabino J, Lucas DJ, Shriver CD, Vertrees AE, Valerio IL, Singh DP. NSQIP analysis: increased immediate reconstruction in the treatment of breast cancer. Am Surg. 2016 Jun;82(6):540-5.

Brown D, Shao S, Jatoi I, Shriver CD, Zhu K. Trends in use of contralateral prophylactic mastectomy by racial/ethnic group and ER/PR status among patients with breast cancer: A SEER population-based study. Cancer Epidemiol. 2016 Jun; 42:24-31.

Peck AR, Girondo MA, Liu C, Kovatich AJ, Hooke JA, Shriver CD, Hu H, Mitchell EP, Freydin B, Hyslop T, Chervoneva I, and Rui H. Validation of tumor protein marker quantification by two independent automated immunofluorescence image analysis platforms. Mod Pathol. 2016 Jun 17.

Schwartzberg BS, Abdelatif O, Lewin J, Bernard J, Bu-Ali H, Cawthorn S, Chen-Seeto M, Feldman SM, Govindarajulu S, Jones L, Juette A, Kavia S, Maganini R, Pain S, Shere M, Shriver CD, Smith S, Valencia A, Whitacre EB, and Whitney R. Multicenter, phase II open-label trial of percutaneous laser ablation (PLA) for 61 patients (PTS) with early-stage (ES) primary breast cancer: radiographic (MRI) and pathological correlation." J Clin Oncol 34, 2016 (suppl; abstr e12525). Published in conjunction with the American Society of Clinical Oncology (ASCO) Annual Meeting, 3-7 Jun 2016, Chicago, IL.

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Rummel, SK, Ellsworth RE. The role of histoblood ABO group in cancer. Future Science OA. 2016 Mar 15. FSO107.

Iida J, Bell-Loncella ET, Purazo ML, Lu Y, Dorchak J, Clancy R, Slavik J, Cutler ML, Shriver CD. Inhibition of cancer cell growth by ruthenium complexes. J Transl Med. 2016 Feb 12;14(1):48. doi: 10.1186/s12967-016-0797-9.

CBCP Publications 24 AUG 2015 – 23 AUG 2016

Constantino N, Freeman B, Shriver CD, Ellsworth RE. Outcome disparities in African American compared to European American women with ER+HER2- tumors treated within an equal-access health care system. Ethnicity and Disease, 2016 Jul 21; 26(3):407-16.

Rummel SK, Shriver CD, and Ellsworth RE. Contribution of germline mutations in cancer predisposition genes to tumor etiology in women diagnosed with invasive breast cancer before 40 years. WRNMMC publication clearance approved, 24 Jun 2016.

Huo D, Hu H, Rhie SK, Gamazon EG, Cherniack AD, Liu J, Yoshimatsu TF, Pitt JJ, Hoadley KA, Ru Y, Lichtenberg T, Sturtz L, Laird PW, Shriver CD, Perou CM and Olopade OI. Comprehensive Comparison of Breast Cancer Molecular Portraits between Black and White Patients in The Cancer Genome Atlas. WRNMMC publication clearance approved, 20 Jun 2016.

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Iida J, Bell-Loncella ET, Purazo ML, Lu Y, Dorchak J, Clancy R, Slavik J, Cutler ML, Shriver CD. Inhibition of cancer cell growth by ruthenium complexes. J Transl Med. 2016 Feb 12;14(1):48. doi: 10.1186/s12967-016-0797-9.

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Cammarata FJ, Kvecher L, Rui H, Kovatich AJ, Campbell LF, Hooke JA, Joseph NP, Shriver CD, Mural RJ, Hu H. "A data repository system for translational research."

American Medical Informatics Association (AMIA) Annual Symposium, Nov 15-19, 2014, Washington, DC.

Joseph N, Kvecher L, Deyarmin B, Sturz L, Cammarata F, Larson C, Shriver CD, Mural RJ, Hu H. "Tissue-experiment inventory: a system to enable cataloguing of experimental results in association with tissue and participant information." American Medical Informatics Association (AMIA) Annual Symposium, Nov 15-19, 2014, Washington, DC.

Henning J, Oakes N, Valente AL, Deyarmin B, Meyer J, Hueman MT, Shriver CD, Ellsworth RE. "Evaluation of the role of EBV in breast cancer." Annual CTRC-AARC San Antonio Breast Cancer Symposium, Dec 9-13, 2014, San Antonio, TX.

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Ru Y, Lin J, Campbell JL, Zhu K, Kovatich AJ, Hooke JA, Kvecher L, Deyarmin B, Kovatich AW, Cammarata F, Rui H, Mural RJ, Shriver CD, Hu H. "Survival comparative analysis of patients with invasive breast cancer treated by a military medical center and matched patients of the U.S. general population." Annual CTRC-AARC San Antonio Breast Cancer Symposium, Dec 9-13, 2014, San Antonio, TX.

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Field L, Deyarmin B, van Laar R, Shriver CD, Ellsworth RE. "Identification of gene expression profiles associated with different types of breast adipose and their relationship to tumorigenesis" AACR Advances in Breast Cancer Research Conference, 3-6 October 2013, San Diego, CA

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Greer LT, Rosman M, Mylander WC, Hooke J, Kovatich A, Sawyer K, Buras R, Shriver CD, Tafra L. "Does breast tumor heterogeneity necessitate further immunohistochemical staining on surgical specimens?" Association of Women Surgeons (AWS), September 2012, Chicago, IL, in conjunction with the American College of Surgeons 98th Annual Clinical Congress.

Iida J, Dorchak J, Lehman JR, Clancy R, Luo C, Chen Y, Somiari S, Ellsworth RE, Hu H, Mural RJ, Shriver CD. "FH535 inhibited migration and growth of breast cancer cells" PLOS ONE, 11 Sept 2012

Greer LT, Rosman M, Mylander W, Wareham J, Campbell JL, Hooke J, Kovatich A, Shriver CD, Tafra L. "Should immunohistochemical (IHC) markers be performed on axillary lymph node metastases in view of the lack of concordance between the primary tumor and axillary lymph node metastases?" American College of Surgeons 98th Annual Clinical Congress, 30 Sep-4 Oct 2012, Chicago, IL

Voeghtly LM, Mamula K, Campbell JL, Shriver CD, Ellsworth RE. "Molecular alterations associated with early and late breast cancer mortality" PLOS ONE, 4 Oct 2012

Shriver CD and Mural RJ. "Prestigious Journal to Publish Collaborative Breast Cancer Research" HJF newsletter 'SCOOP', Oct 2012

Ellsworth RE and Shriver CD. "Demographic differences in African American compared to Caucasian women with luminal A breast cancer" AACR, San Diego, CA, 27-30 Oct 2012
Rummel SE, Shriver CD, Ellsworth RE. " Evaluation of BRCA1 mutations in patients with family history of breast cancer" ASHG, 6-10 Nov 2012, San Francisco, CA

Valente AL, Rummel S, Shriver CD, Ellsworth RE "CDH1 mutations in patients with lobular carcinoma of the breast" ASHG, 6-10 Nov 2012, San Francisco, CA

Iida J, Dorchak J, Clancy R, Luo C, Chen Y, Hu H, Mural RJ, Shriver CD. "CSPG4-NEDD9 interaction promotes migration, invasion, and growth of breast cancer cells" ASCB, San Francisco,

CA, 15-19 Dec 2012

Barrow TM, Barault L, Ellsworth RE, Harris HR, Valente AL, Shriver CD, Michels KB. "Aberrant methylation of imprinted genes is associated with triple-negative hormone receptor status in invasive breast cancer" Max Planck Freiburg Epigenetics Meeting, 5-8 Dec 2012, Freiburg, Germany

Valente AL, Kane JL, Ellsworth DL, Shriver CD, Ellsworth RE. "Molecular response of the axillary lymph node microenvironment to metastatic colonization" AACR, 4-8 Dec 2012, San Antonio, TX

Ellsworth RE, Valente AL, Shriver CD. "The effect of HER2 expression on luminal A breast tumors" SABCS, 4-8 Dec 2012, San Antonio, TX

Field L, Deyarmin B, van Laar R, Hooke J, Shriver C, Ellsworth R. "Molecular characteristics of breast tumor-associated adipose" SABCS, San Antonio, TX 4-8 Dec 2012

Kovatich AJ, Luo C, Chen Y, Hooke JA, Kvecher L, Rui H, Shriver CD, Mural RJ, Hu H. "Molecular subtypes of invasive breast cancers show differential expression of the proliferation marker Aurora Kinase A (AURKA)" SABCS, San Antonio, TX 4-8 Dec 2012

Chen Y, Bekhash A, Kovatich AJ, Hooke JA, Kvecher L, Mitchell EP, Rui H, Mural RJ, Shriver CD, Hu H. "Fibroadenomatoid changes are more prevalent in middle-aged women and have a positive association with invasive breast cancer" SABCS, San Antonio, TX 4-8 Dec 2012

Luo C, Iida J, Chen Y, Dorchak J, Kovatich AJ, Mural RJ, Hu H, Shriver CD. "Higher gene expression of CSPG4 in the basal-like subtype of invasive breast cancer and its negative association with lymph node metastasis" SABCS, San Antonio, TX 4-8 Dec 2012
Luo C, Chen Y, Kovatich AJ, Hooke JA, Kvecher L, Shriver CD, Mural RJ, Hu H. "p53 gene and protein expression patterns in human invasive breast cancers are correlated with its mutation status" SABCS, San Antonio, TX 4-8 Dec 2012

Dorchak J, Iida J, Clancy R, Luo C, Chen Y, Hu H, Mural RJ, Shriver CD. "FH535 inhibited migration and growth of breast cancer cells" SABCS, San Antonio, TX 4-8 Dec 2012

Luo C, Chen Y, Shriver CD, Hu H, Mural RJ. "Breast cancer subtype distribution among HapMap classified ethnic groups" SABCS, San Antonio, TX 4-8 Dec 2012

Rummel S, Varner E, Shriver CD, Ellsworth RE. "Evaluation of BRCA1 mutations in an unselected patient population with triple negative breast cancer" Breast Cancer Research and Treatment, Jan 2013
Barault L, Ellsworth RE, Harris HR, Valente AL, Shriver CD, Michels KB. "Leukocyte DNA as surrogate for the evaluation of imprinted loci methylation in mammary tissue DNA" PLOS ONE, 7 Feb 2013

Barror TM, Barault L, Ellsworth RE, Harris HR, Valente AL, Shriver CD, Michels KB. "Aberrant methylation of imprinted genes is associated with negative hormone receptor status in invasive breast cancer" Dana Farber Harvard Cancer Center, Breast and Gynecological Cancers symposium, 22 March 2013, Boston, MA

Rummel S, Penatzer C, Shriver CD, Ellsworth RE. "PSPHL and breast cancer in African American women: causative gene or population stratification?" AACR, Washington, DC, 6-10 April 2013

Barrow TM, Ellsworth RE, Harris H, Barault L, Velente A, Shriver CD, Michels KB. "Loss of imprinting in PEG3, MEST and ARHI/DIRAS3 in invasive breast cancer" AACR, 6-10 April 2013, Washington, DC

Greenspan R, O'Donnell A, Meyer J, Kane J, Mamula K, Deyarmin B, Larson C, Rigby S., Greenawalt A, Vatanian N, Mural R, Shriver C, Somiari S. "Tissue imprints and scrapings: assessing their potential as routine biobanking specimens for molecular research" Biopreservation and Biobanking Journal, submitted to publication in April 2013

Barrow, TM, Barault L, Ellsworth RE, Harris HR, Valente AL, Shriver CD, Michels KB. "Aberrant methylation of imprinted genes is associated with negative hormone receptor status in invasive breast cancer" Gordon Research Conferences: Cancer Genetics and Epigenetics, 21-26 April 2013, Lucca (Barga), Italy

Sato T, Tran TH, Peck AR, Girondo MA, Liu C, Goodman CR, Neilson LM, Freydin B, Chervoneva I, Hyslop T, Kovatich AJ, Hooke JA, Shriver CD, Fuchs SY, Rui H. "Prolactin suppresses a progestin-induced CK5-positive cell population in luminal breast cancer by a mechanism that involves inhibition of progestin-driven BCL6 expression" Oncogene Journal, 27 May 2013

Ellsworth RE, Penatzer C, Shriver CD. "Demographic and pathological differences between women treated in rural compared to urban-military breast cancer centers" ASCO, 31 May-4 June 2013

The Cancer Genome Atlas-Breast Cancer project team recently published a milestone research article in Nature (on-line Sep. 23, 2012; in print, Oct. 4, 2012

7. INVENTIONS, PATENTS AND LICENSES: None

8. REPORTABLE OUTCOMES

FINAL Report Numbers

Total Patients Consented from 24 August 2012 – 23 August 2017.

WRNMMC: 1,019
Windber: 853
AAMC: 931

Total Samples Collected from 24 August 2012 – 23 August 2017.

Total Blood: 18,585
Total Breast: 4,294
Total LN: 344
Total Other: 557

During the 5 year period (2012-2017) BCTR-COE performed focused research on the biospecimens and clinical data collected under the BCTR-COE Core protocols, which resulted in **120** publications, abstracts and presentations by CBCP staff at peer-reviewed national meetings.

9. OTHER ACHIEVEMENTS: NONE

10. REFERENCES: NONE

11. APPENDICES:

- ATTACHMENT 1: CBCP Personnel 2012-2017
- ATTACHMENT 2: WRI Personnel (CBCP Lab) 2012-2017
- ATTACHMENT 3: Blood Library Protocol (3 May 2017)
- ATTACHMENT 4: Blood ICD (Informed Consent Document) (3 May 2017)
- ATTACHMENT 5: Tissue Protocol (3 May 2017)
- ATTACHMENT 6: Tissue ICD (Informed Consent Document) (3 May 2017)
- ATTACHMENT 7: Case Report Form (CRF)
- ATTACHMENT 8: Annual Retreat Agendas 2015, 2016 and 2017
- ATTACHMENT 9: National Accreditation Programs of Breast Centers (NAPBC) Certificate
- ATTACHMENT 10: College of American Pathologists (CAP) Accreditation Certificate

ATTACHMENT 1:
CBCP Personnel 2012-2017

CBCP Personnel 2017

Full Name	Title
Basham, Janice B	Licensed Practical Nurse
Boone, Jaime J.	Executive Director
Campbell, Jamie Leigh	Path. Assist./Sr Res Assoc
Ellsworth, Rachel E.	Cancer Geneticist
Hilton, Karrie R.	Research Nurse Manager
Holden, Allan	Sr.Data Management Specialist
Hooke, Jeffrey A	Head of Pathology
Joseph, Julie	Research Assistant II
Kovatich, Albert	Scientist
Leto, Jamie Lynn	Histology Technician
McDonough, Christin Elizabeth	Research Assistant
Mullican, Lynn Marie	Clinical Data Abstractor
Patterson, Carol M	Research Assist - Med Tech
Pereira, Dianne	Executive Asst. to Director
Sakura, Sara Denman	Sr Res Protocol Coord Lead
Seaborn, Nile Melvin	Data Manager
Trupp, Rebecca Saron	Nurse Navigator
Wareham, Janet Andrea Yoder	Pathologists Assistant
Williamson, Eric	Breast Center Administrator
Zingmark, Rebecca N.	Histotechnologist/Res. Assist.
Dugger, Erica	Program Management Assistant
Tran, Crysta Ngoc	Pathologist Assistant

CBCP Personnel - 2016

Full Name	Title
Shriver, Craig D.	Principal Investigator
Basham,Janice B	Licensed Practical Nurse
Bates,Mechelle Ariana	Administrative Coordinator
Boone,Jaime J.	Executive Director
Brockett,Stella Marie	Certificed Cancer Registrar
Campbell,Jamie Leigh	Pathologist Assist./Site Coord
Ellsworth,Rachel E.	Cancer Geneticist
Fasaye,Grace-Ann O	Senior Genetic Counselor
Freeman,Benjamin Thomas	Research Assistant
Hilton,Karrie R.	Research Nurse Manager
Holden,Allan	Sr.Data Management Specialist
Hooke,Jeffrey A	Head of Pathology
Joseph,Julie	Research Assistant II
Kovatich,Albert	Scientist
Leto, Jamie Lynn	Histology Tech
Medley,Vilisha	Certified Cancer Registrar
Miskovsky,Vicki Jones	Admin Reviewer CCC Protocols
Mullican,Lynn Marie	Clinical Data Abstractor
Patterson,Carol M	Medical Assistant
Pereira,Dianne	Office Manager/Admin. Assist.
Sakura,Sara Denman	Research Protocol Coordinator
Trupp,Rebecca Saron	Nurse Navigator
Wareham,Janet Andrea Yoder	Pathologists Assistant
Williamson,Eric	Breast Center Administrator
Zhu,Kangmin	Assoc Dir for Epidemiology
Zingmark,Rebecca N.	Histotechnologist/Res. Assist.
Weiss,Raymond B	Physician
Bronfman,Eileen T	Advisor

CBCP Personnel - 2015

Last, First	Business Title
Shriver, Craig D.	Principal Investigator
Basham,Janice B	Licensed Practical Nurse
Boone,Jaime J.	Senior Program Manager
Campbell,Jamie Leigh	Pathologist Assist./Site Coord
Ellsworth,Rachel E.	Cancer Geneticist
Freeman, Benjamin	Research Assistant
Hilton,Karrie R.	Assistant Head Nurse
Holden,Allan	Sr.Data Management Specialist
Hooke,Jeffrey A	Head of Pathology
Joseph,Julie	Research Assistant II
Kovatich,Albert	Scientist
Miskovsky,Vicki Jones	Admin Reviewer CCC Protocols
Patterson,Carol M	Medical Assistant
Pereira,Dianne	Office Manager/Admin. Assist.
Sakura,Sara Denman	Research Protocol Coordinator
Trupp,Rebecca Saron	Nurse Navigator
Wareham,Janet Andrea Yoder	Pathologists Assistant
Williamson,Eric	Breast Center Administrator
Zhu,Kangmin	Assoc Dir for Epidemiology
Zingmark,Rebecca N.	Histotechnologist
Bronfman,Eileen T	Administrative Director
Weiss,Raymond B	Physician
Rigatti,Michael Kevin	Research Assistant
Vilakazi,Patricia N.	Biomedical Informatics Coord.
Davis,Herma Elaine	Sr. Data Manager

CBCP Personnel - 2014

Name	Role on Project
Shriver, Craig D.	Principal Investigator
Basham,Janice B	Licensed Practical Nurse
Boone,Jaime J.	Senior Program Manager
Bronfman,Eileen T	Administrative Director
Campbell,Jamie Leigh	Pathologist Assist./Site Coord
Ellsworth,Rachel E.	Cancer Geneticist
Hilton,Karrie R.	Assistant Head Nurse
Holden,Allan	Sr.Data Management Specialist
Hooke,Jeffrey A	Head of Pathology
Joseph,Julie	Research Assistant II
Kovatich,Albert	Scientist
Miskovsky,Vicki Jones	Admin Reviewer CCC Protocols
Patterson,Carol M	Medical Assistant
Pereira,Dianne	Office Manager/Admin. Assist.
Rigatti,Michael Kevin	Research Assistant
Sakura,Sara Denman	Research Protocol Coordinator
Smith,Stephanie R	Research Nurse
Vilakazi,Patricia N.	Biomedical Informatics Coord.
Wareham,Janet Andrea	Pathologists Assistant
Williamson,Eric	Breast Center Administrator
Zhu,Kangmin	Assoc Dir for Epidemiology
Zingmark,Rebecca N.	Histotechnologist
Cordes,Rosemarie	Research Nurse
Weiss,Raymond B	Physician

CBCP Personnel - 2013

Last Name	First Name	Role on Project
Shriver	**Craig**	**Principal Investigator**
Basham	Janice	Licensed Practical Nurse
Boone	Jaime	Program Manager/Budget Analyst
Bronfman	Eileen	Administrative Director
Campbell	Jamie Leigh	Pathology Assistant
Chestang	Allan	Data Manager
Cordes	Rosemarie	Research Nurse
Cronin	Kerri	Administrative Assistant
Eckhauser	Peggy Lee	Research Nurse
Ellsworth	Rachael	Director of Translational Genomics
Hilton	Karrie	Research Nurse
Hooke	Jeffrey	Head of Pathology
Kelly	Kay	Research Protocol Coordinator
Kovatich	Albert	Scientist
Means	Marilyn	Lab Tech
Miskovsky	Vicki Jones	Admin Reviewer CCC Protocols
Nielsen	Deborah	Research Nurse
Patterson	Carol	Medical Assistant
Simmons	Stephanie	Research Nurse
Tracey	Dianne	Administrative Assistant/Office Mngr.
Vilakazi	Patricia	Research Nurse
Wareham	Janet	Pathologist Assistant
Weiss	Raymond	Physician
Williamson	Eric	Clinic Administrator
Yambaka	Baredu	Receptionist/Research Assistant
Zhu	Kangmin	Epidemiologist
Zingmark	Rebecca	Histology Tech

CBCP Personnel 2012

Last Name	First Name	Role
Shriver	**Craig**	**Principal Investigator**
Basham	Janice	Licensed Practical Nurse
Boone	Jaime	Program Manager/Budget Analyst
Bronfman	Eileen	Administrative Director
Chestang	Allan	Data Manager
Cronin	Kerri	Administrative Assistant
Eckhauser	Peggy Lee	Research Nurse
Ellsworth	Rachael	Director of Translational Genomics
Enwold	Lindsey	Epidemiologist
Campbell	Jamie Leigh	Pathology Assistant
Hilton	Karrie	Research Nurse
Hooke	Jeffrey	Head of Pathology
Kelly	Kay	Research Protocol Coordinator
Means	Marilyn	Lab Tech
Neilson	Deborah	Research Nurse
Patterson	Carol	Medical Assistant
Tracey	Dianne	Administrative Assistant/Office Mngr.
Simmons	Stephanie	Research Nurse
Vilakazi	Patricia	Research Nurse
Willlamson	Eric	Clinic Administrator
Yambaka	Baredu	Receptionist/Research Assistant
Zingmark	Rebecca	Histology Tech
Zhu	Kangmin	Epidemiologist
Weiss	Raymond	Physican
Wareham	Janet	Pathologist Assistant
Pangaro	Katherine	Clinical Oncology ResearchNurse
Miskovsky	Vicki Jones	Admin Reviewer CCC Protocols

ATTACHMENT 2:
WRI Personnel (CBCP Lab)
2012-2017

WRI Personnel - 2017

Employees	Titles
Blackburn, Heather	Research Assoc. II
Cammarata, Frank	IT Developer
Clancy, Rebecca	Research Assoc. II
Costantino, Nick	Sr. Statistical Analyst
Deyarmin, Brenda	Research Assoc. III
Dorchak, Jesse	Research Assoc. II
Ellsworth, Darrell	Chief Clinical Applications Officer
Elston, Ed	IT Manager
Furmanchik, Lydia	Finance Asst.
Greenawalt, Amber	Research Assoc. II
Hu, Hai	VP for Research
Iida, George	Director, Cell Biology
Kane, Jen	Research Assoc. III
Kohr, Joni	Admin Assist. II
Kutzner, Ryan	Research Assoc. I
Kvecher, Leonid	Director, Biomed Inf. Infrastructure
Larson, Caroline	Manager, Biobank
Lovejoy, Leann	Research Assoc. II
Lubert, Sue	Lab Manager
Miller, Katie	Research Assoc. I
Mostoller, Brad	Sr. IT Developer
Murtha, Kim	IT Developer II
Raj Kumar, Praveen	Bioinformatics Scientist
Rigby, Sean	Research Assoc. I
Rummel, Seth	Research Assoc. II
Slavik, Julianna	Research Assoc. II
Somiari, Stella	Senior Director, Biobank
Sturtz, Lori	Scientist
Trostle, Lynn	Grant Program Coordinator
Yarina, William	Research Assoc. II

WRI Personnel - 2016

Employees	Titles
Blackburn, Heather	Research Assoc. II
Cammarata, Frank	IT Developer
Clancy, Rebecca	Research Assoc. II
Costantino, Nick	Sr. Statistical Analyst
Craig, James	Scientist
Deyarmin, Brenda	Research Assoc. III
Dorchak, Jesse	Research Assoc. II
Ellsworth, Darrell	Chief Clinical Applications Officer
Elston, Ed	IT Manager
Furmanchik, Lydia	Finance Asst.
Greenawalt, Amber	Research Assoc. II
Hu, Hai	VP for Research
Iida, George	Director, Cell Biology
Joseph, Norman	Database Developer
Kane, Jen	Research Assoc. III
Kentes, Michael	Database Developer
Kohr, Joni	Admin Assist. II
Kutzner, Ryan	Research Assoc. I
Kvecher, Leonid	Director, Biomed Inf. Infrastructure
Larson, Caroline	Manager, Biobank
Latoche, Joseph	Research Assoc. II
Liu, Jianfang	Statistical Analyst
Lovejoy, Leann	Research Assoc. II
Lubert, Sue	Lab Manager
Marinkovich, Kristina	Clinical Admin. Coord.
Melley, Jen	Research Assoc. II
Meyer, Jeff	Research Assoc. II
Miller, Katie	Research Assoc. I
Mostoller, Brad	Sr. IT Developer
Murtha, Kim	IT Developer II
Purazo, Marc	Research Assoc. I
Raj Kumar, Praveen	Bioinformatics Scientist
Rigby, Sean	Research Assoc. I
Rummel, Seth	Research Assoc. II
Shaffer, Apryl	Data Entry Tech.
Slavik, Julianna	Research Assoc. II
Somiari, Stella	Senior Director, Biobank
Sridhara, Viswanadhai	Scientist
Sturtz, Lori	Scientist
Trostle, Lynn	Grant Program Coordinator
Yarina, William	Research Assoc. II

WRI Personnel - 2015

Employees	Titles
Blackburn, Heather	Research Assoc. II
Brown, Scott	Research Assoc. I
Cammarata, Frank	IT Developer
Clancy, Rebecca	Research Assoc. II
Costantino, Nick	Sr. Statistical Analyst
Craig, James	Scientist
Deyarmin, Brenda	Research Assoc. III
Dorchak, Jesse	Research Assoc. II
Ellsworth, Darrell	Chief Clinical Applications Officer
Elston, Ed	IT Manager
Furmanchik, Lydia	Finance Asst.
Greenawalt, Amber	Research Assoc. II
Harrington, Colin	Intern
Hu, Hai	VP for Research
Iida, George	Director, Cell Biology
Joseph, Norman	Database Developer
Kane, Jen	Research Assoc. III
Kohr, Joni	Admin Assist. II
Kutzner, Ryan	Research Assoc. I
Kvecher, Leonid	Director, Biomed Inf. Infrastructure
Larson, Caroline	Manager, Biobank
Liu, Jianfang	Statistical Analyst
Lubert, Sue	Lab Manager
Mamula, Kim	Statistician
Melley, Jen	Research Assoc. II
Meyer, Jeff	Research Assoc. II
Mostoller, Brad	Sr. IT Developer
Purazo, Marc	Research Assoc. I
Rigby, Sean	Research Assoc. I
Ru, Yuanbin	Scientist
Rummel, Seth	Research Assoc, II
Schroeder, Bradley	Research Assoc. I
Shaffer, Apryl	Data Entry Tech.
Slavik, Julianna	Research Assoc. II
Somiari, Stella	Senior Director
Sturtz, Lori	Scientist
Toro, Allyson	Research Assoc. III
Trostle, Lynn	Grant Program Coordinator
Weise, Jonathan	IT Support
Yarina, William	Research Assoc. II

WRI Personnel – 2014

Full name	**Role on project**
Brown, Scott	Research Associate I
Cammarata, Frank	IT Developer
Clancy, Rebecca	Research Associate II
Deyarmin, Brenda	Research Associate III
Dorchak, Jesse	Research Associate I
Elston, Ed	IT Manager
Furmanchik, Lydia	Finance Assistant
Greenawalt, Amber	Research Associate II
Hu, Hai	Deputy CSO/Sr. Dir.
Iida, George	Director
Joseph, Norman	Database Developer
Kane, Jennifer	Research Associate II
Kohr, Joni	Admin. Assistant II
Kvecher, Leonid	Data Manager
Larson, Caroline	Resource Manager
Li, Renhua	Scientist
Liu, Jianfang	Statistacal Analyst
Lubert, Sue	Lab Manager
Mamula, Kim	St. Statistical Analyst
Melley, Jennifer	Research Associate II
Meyer, Jeff	Research Associate II
Mural, Richard	CSO
Rigby, Sean	Research Assistant
Ru, Yuanbin	Scientist
Rummel, Seth	Research Associate II
Schroeder, Brad	Research Associate I
Shaffer, Apryl	Data Entry Technician
Slavik, Juliana	Research Asociate II
Somiari, Stella	Senior Director
Sturtz, Lori	Scientist
Trostle, Lynn	Grant Program Coord.
Valente, Allison	Research Associate III
Weise, Jonathan	IT Support Specialist
Yarina, William	Research Associate II

WRI Personnel – 2013

Full name	Role on project
Blackburn, Heather	Research Associate III
Blankenship, Sara	Research Associate II
Bomba, Hunter	Intern
Brown, Scott	Research Associate I
Chen, Yaqin	Statistical Analyst
Cammaratta, Frank	IT Developer
Clancy, Rebecca	Research Associate I
Deyarmin, Brenda	Research Associate III
Dorchak, Jesse	Research Associate I
Ellsworth, Darrell	Senior Director
Elston, Ed	IT Manager
Furmanchik, Lydia	Finance Assistant
Gdula, Dan	Intern
Good, Evan	Intern
Greenawalt, Amber	Research Associate I
Hu, Hai	Deputy CSO/Director Biomed. Inf.
Iida, George	Director
Joseph, Norman	Research Associate II
Kane, Jennifer	Research Associate II
Kohr, Joni	Administrative Assistant
Kvecher, Leonid	Data Manager
Larson, Caroline	Resource Manager
Latoche, Joseph	Research Associate II
Li, Renhua	Scientist
Lubert, Sue	Lab Manager
Mamula, Kim	St. Statistical Analyst
Melley, Jen	Research Associate II
Meyer, Jeff	Research Associate II
Mural, Richard	Chief Scientific Officer
O'Donnell, Amy	Research Associate II
Rigby, Sean	Research Assistant
Ru, Yuanbin	Scientist
Rummel, Seth	Research Associate II
Shaffer, Apryl	Data Entry Tech
Slavik, Julianna	Research Associate II
Somiari, Stella	Senior Director
Sturtz, Lori	Scientist
Trostle, Lynn	Grant Program Coordinator
Valente, Allyson	Research Associate III

Weise, Jonathan	IT Support Specialist
Wu, Weiqiang	Research Associate III
Yarina, William	Research Associate II

WRI Personnel - 2012

Full Name	Department Name	Title	FTE
Chen, Yaqin	BCTR	Statistical Analyst	
Clancy, Rebecca	BCTR	Research Associate I	
Croft, Daniel T.	CADRE	Research Associate III	
Cruse, Steven M.	Administration	Housekeeper	
Deyarmin, Brenda	BCTR	Research Associate III	
Deyarmin, Dennis R.	Administration	Housekeeper	
Ditton, Dana L.	CADRE	Research Assistant	
Dorchak, Jesse A.	BCTR	Research Associate I	
Ellsworth, Darrell	CADRE	Senior Director	
Elston, Edward J.	Administration	It Manager	
Ferrau, Annalisa	halt	Administrative Assista	
Furmanchik, Lydia	WRI Administration	Finance Assistant	
Greenawalt, Amber M.	BCTR	Research Associate I	
Holliday, Charvonne	Bullying Institute	Public Health Associat	
Hu, Hai	BCTR	Deputy Chief Scientific	
Ilda, George	BCTR	Director	
Kane, Jennifer	BCTR	Research Associate II	
Kohr, Joni	BCTR	Administrative Assista	
Kurtz, Thomas M.	WRI Administration	President	
Kvecher, Leonid	BCTR	Data Manager	
Larson, Caroline M.	BCTR	Resource Manager	
Lubert, Susan M.	BCTR	Lab Manager	
Mamula, Kimberly A.	CADRE	Sr. Statistical Analyst	
Masiello, Matthew	Dr. Masiello	Chief Medical Officer	
Melley, Jennifer	BCTR	Research Associate II	
Meyer, Jeffrey B.	BCTR	Research Associate II	
Mural, Richard J.	WRI Administration	Chief Scientific Officer	
O'Donnell, Amy	BCTR	Research Associate II	
Patney, Heather	CADRE	Research Associate II	
Penatzer, Cayla E.	CBCP	Intern/student/paid	
Rigby, Sean	BCTR	Research Assistant	
Rummel, Seth	BCTR	Research Associate II	
Seltz, Brianne J.	CADRE	Intern/student/paid	
Shaffer, Apryl	BCTR	Data Entry Technician	
Shawley, Cynthia M.	WRI Administration	Executive Assistant	
Slavik, Julianna E.	CADRE	Research Associate II	
Somlari, Stella	BCTR	Senior Director	
Sturtz, Lori	BCTR	Scientist	
Trostle, Lynn	WRI Administration	Grant Program Coordi	
Valente, Allyson	BCTR	Research Associate III	
Voeghtly, Eric	Administration	Manager	
Wang, Hua	BCTR	It Developer	
Weise, Jonathan P.	Administration	It Support Specialist	
Wu, Weiqiang	BCTR	Research Associate III	

ATTACHMENT 3:
Blood Library Protocol
(3 May 2017)

EIRB Protocol Template (Version 1.1)

1.0 General Information

* Please enter the full title of your study:

Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development

* Please enter the Protocol Number you would like to use to reference the protocol:

20705

* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study

Primary Dept?	Department Name
◉	P and R - Walter Reed National Military Medical Center (WRNMMC)

3.0 Assign project personnel access to the project

3.1 * Please add a Principal Investigator for the study:

CRAIG DAVID SHRIVER, MD

Select if applicable

☐ Student ☐ Department Chair ☐ Resident ☐ Fellow

If the Principal Investigator is a Student, Resident, or Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Jeffrey A Hooke

Associate Investigator

JOEL T MONCUR

Associate Investigator

Denise Marchand Thigpen

Associate Investigator

B) Research Support Staff

KAY FRANCES KELLEY

Research Coordinator

Sara Denman Sakura

Research Coordinator

3.3 Please add a Protocol Contact:

CRAIG DAVID SHRIVER, MD

Sara Denman Sakura

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Philip Perdue

Department Chair

Robert Stewart

Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 Is this a research study?

(•) Yes ( ) No

4.2 What type of research is this?

- [x] Biomedical Research
- [ ] Clinical trial (FDA regulated)
- [ ] Behavioral Research
- [ ] Educational Research
- [ ] Psychosocial Research
- [ ] Oral History
- [ ] Other

4.4 Is this human subjects research (Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects) and DoDI 3216.02)?

(•) Yes ( ) No

4.5 Do you believe this human subjects research is exempt from IRB review?

( ) Yes (•) No

5.0 Personnel Details

5.1 Will you have a Research Monitor for this study?

( ) Yes
( ) No
(•) N/A

Research Monitor Role:

If applicable, you may nominate an individual to serve as the Research Monitor:

	Selected Users
No Users have been selected.	

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source		Funding Type	Amount		
:	Congressionally Directed Medical Research Program (CDMRP)	Clinical Breast Care Project			

Total amount of funding:

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

8.0 Study Locations

8.1 Has another IRB reviewed this study?

○ Yes ◉ No

8.2 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

○ Yes ◉ No

9.0 Study Details

9.1 Abstract/ Summary:

Summarize the proposed study in 500 words or less, to include the purpose, the subject population, the study's design type, and procedures

Purpose

Although there have been remarkable improvements in breast cancer diagnosis and management, most of the complex molecular mechanisms associated with the onset, progression and/or severity of breast cancer are still not well understood. The Clinical Breast Care Project (CBCP) is a congressionally mandated and funded military-civilian collaboration between Windber Medical Center (WRI) Windber, PA, Walter Reed National Military Medical Center (WRNMMC) Bethesda, MD, and the Uniformed Services University of the Health Sciences in Bethesda, MD. As part of the CBCP we propose to carry out molecular, biochemical and histologic analysis blood serum and plasma to provide more insights on the molecular mechanisms that may be relevant in breast cancer development and breast diseases.

Research Design

The proposed study is designed as a minimal risk, prospective study aimed at characterizing the gene and protein expression in blood. A blood sample will be collected from all participants at enrollment and later as follow for patients in the three categories listed in section 2.3 below.

Methodology/Technical Approach

The population for this study includes military health care beneficiaries over the age of 18 years presenting with the diagnosis of breast cancer or at high risk for developing breast cancer. All participants will be patients presenting to the CBCP Breast Centers at WRNMMC who consent to join in the study. These will include (1) patients attending the Breast Center risk reduction clinic; (2) patients diagnosed with breast cancer; and (3) patients diagnosed with any other breast disorder or presenting for regular breast screening. The far majority of patients will be female, however, 1 percent of all breast cancers occur in males and these male patients with breast cancer would be eligible for this study as well.

As stated in the informed consent form for this protocol, study procedures will apply for the subject's current and all subsequent clinical appointments related to their breast disease unless they withdraw from the study.

9.2 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Breast cancer, biobank, molecular, proteomics, genomics

9.3 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Breast cancer is one of the most common cancers among women. Like many other cancers, it is complex and involves multiple biological changes, which could be somatic or heritable. These changes characterize the transition of a cell from normal to neoplastic and its final progression into an invasive cancer[1,2]. Broad generalizations can be made about risk, natural history and clinical pattern, but it is not at present possible to accurately predict the future of an individual classified as being "at high-risk" for the development of breast cancer. This label of "high-risk" is applied generally to women who, upon undergoing screening via the computerized Gail Model (which is a validated NCI tool using a series of patient questions / answers resulting in an individualized computerized risk assessment), have any risk outcome that results in a >1.67% risk of breast cancer development over the next 5 years. Current diagnostic procedures are invasive involving biopsies with a high rate of negative results. To make significant future improvements on early breast cancer diagnosis and management, a more effective and minimally invasive method will be required that will be sensitive, predictive and allow accurate diagnosis at the earliest stage of disease onset. Neoplastic cells can be detected in bodily fluids that drain or bathe affected organs[3]. The use of peripheral blood as a sample source for clinical research purposes is very attractive since it requires a less invasive procedure for sample collection (i.e. a simple blood stick). Clearly the use of circulating soluble markers that can be easily quantified through sensitive procedures such as the polymerase chain reaction (PCR) would be considerably more accurate than subjective approaches such as immunohistochemical staining which also require more invasive procedures for sample (tissue) collection. The spectrum of genetic and physiological events associated with primary tumors can be potential targets for molecular detection in the blood of patients and circulating soluble molecules in blood have been used as biological markers in cancer providing diagnostic and prognostic value[4,5]. High levels of circulating DNA have been observed in patients with metastatic disease and even patients with early stage cancer may harbor these free circulating DNA[3].

In order to diagnose breast cancer at the earliest possible stage and provide appropriate therapy after such detection, we need to understand the global profile of the genes and proteins in the blood. So far approximately 68 genes have been associated with breast cancer. They fall into several groups including DNA repair, cell cycle regulation, tumor suppression, internal/external signaling and transcription/growth factor regulation. However their exact expression pattern, which may impact upon disease onset and

progression, are not yet fully understood. The techniques of Microarray Analysis and Single nucleotide polymorphism (SNPs) screening are high throughout gene expression analysis strategies that have been used successfully to characterize gene expression in many medical conditions. Microarray analysis allows the identification of gene expression differences through the simultaneous monitoring of thousands of genes in parallel using complementary DNA (cDNA) which are preloaded onto a small (size of a dime) chip. On the other hand, using the SNPs technique, single base variations in DNA can be identified. These new high-throughput technologies provide the tools for the identification of potential markers for disease detection and monitoring, and insights can be gained into individual differences observed in relation to disease susceptibility, onset of disease and/or response to therapy.

Significant improvement in breast cancer mortality rates will be achieved when we can either prevent the disease, or correctly diagnose it at an early stage and provide treatment that will halt metastasis. Until we find a means of preventing cancer, we can reduce mortality rates through early and accurate diagnosis followed by proper management. Developing a diagnosis/prognostic strategy that will be sensitive and which will require only samples collected through a minimally invasive procedure such as a blood stick, would significantly impact breast cancer management.

The current standard of care for treating breast diseases and breast cancer is based on a multidisciplinary model that integrates prevention, screening, diagnosis, treatment, and continuing care. The CBCP is modeled after this multidisciplinary approach. However, the CBCP is unique in its field. It incorporates advances in breast cancer risk reduction, informatics, tissue banking, and research. The present protocol represents one aspect of this integrated approach. It will interdigitate and synergize with the clinical, informatics, and research components of the CBCP, to achieve the overall objective of improving breast care and reducing the morbidity and mortality associated with breast disease.

In 2002, a panel of microsatellite markers was developed to assess allelic imbalance (AI) at the 26 most commonly altered regions in breast cancer. This panel was used to investigate how tumors develop and progress. For example, this panel was applied to 42 columnar cell lesions (CCL) and 31 atypical ductal hyperplasias (ADH), both non-neoplastic diseases of the breast. Of note, we assessed genetic changes only in pure CCL and ADH without concomitant DCIS or invasive breast cancer (IBC). This approach was quite different than the then current body of literature that had evaluated synchronous non-neoplastic lesions and, based on shared genetic changes between the neoplastic and non-neoplastic diseases, suggested that CCL and ADH were non-obligatory precursors to DCIS/IBC. Our study was one of the first to look at pure CCL and ADH, and unlike the other studies, we found very few genetic changes, suggesting that these lesions are genetically naïve and that earlier models of progression based on synchronous lesions may not accurately reflect tumor progression[6].

In contrast, the 100 pure DCIS lesions we assayed shared many of the same alterations found in IBC, suggesting that DCIS lesions are genetically advanced[7]. We also found that low-grade DCIS and IBC are genetically distinct from high-grade DCIS and IBC, based largely on high rates of loss of chromosome 16q in low-grade disease and high rates of alterations at 9p21, 11q23, 13q14, 17p13.1 and 17p12[8, 9] . These data suggest that high-grade disease does not progress from low-grade disease but rather that low- and high-grade disease are distinct diseases.

CBCP has been investigating molecular changes in the tumor microenvironment. Tumor epithelial and corresponding adjacent stroma <850 m from the tumor were laser microdissected from 30 formalin-fixed, paraffin-embedded tumor specimens and evaluated using the allelic imbalance panel. Discordant patterns of LOH/AI between epithelial and stromal components were detected such that hierarchical clustering samples from the same patient rarely clustered together[10]. In a second study evaluating LOH/AI data generated from archival breast quadrants from 21 patients who underwent mastectomy, levels of LOH/AI were significantly higher (P<0.05) in the tumor-adjacent (15.4%) compared to distant (3.7%) tissues, suggesting that chromosomal alterations in stroma close to the tumor may promote tumorigenesis[11]. These data lead to the invitation to write review papers for *Lancet Oncology*

and *Expert Reviews in Molecular Diagnosis*[12, 13] .

We have also had an interest in health care disparities between Caucasian (CW) and African American women (AAW) with breast cancer. Enrollment of patients within the DOD health-care system affords us the opportunity to evaluate clinical, epidemiological and molecular differences in patients treated within an equal-access health-care system, thus minimizing the impact of disparate access to quality-health care seen in the general population. Recruitment of African Americans into the Clinical Breast Care Project (CBCP) has been effective: in 2007, 25% of the patients enrolled were self-described AAW[14]. No differences in education levels, breast health practices (e.g., self-breast exam, routine screening mammograms) or reproductive histories were seen between AAW and CW with invasive breast cancer, however, AAW were more likely to use oral contraceptives, less likely to use HRT or to breastfeed and were more likely to be obese and have extremely high fat-intake. Breast tumors from AAW were also more likely to be diagnosed at a younger age, and are larger, more frequently ER negative and/or triple negative, and of higher grade. Evaluation of gene expression patterns between AAW and CW matched by age, grade and ER status revealed differentially expression of 23 genes, suggesting that tumors from AAW and CW are molecularly different and these differences may contribute to the less favorable outcome in AAW[15].

We have also performed a number of studies to determine the molecular mechanisms of metastasis. Using our AI panel, we evaluated patterns of chromosomal changes in primary breast tumors and matched metastatic lymph node tumors and found disparate patterns of alterations between the two tumor types, suggesting that metastatic cells diverge early in tumorigenesis[16]. A follow-up study evaluated genetic changes between primary tumors (n=26) and multiple lymph node tumors (n=146) to determine how metastasis spreads. Divergent patterns of chromosomal alterations were seen between lymph nodes and the primary tumor, but also between metastatic lymph node tumors from the same patients. This genetic heterogeneity may impact response to adjuvant therapy, recurrence, and survival, and thus may be important to improving clinical management of breast cancer patients[17]. Gene expression analysis was also performed on primary breast tumors and matched metastatic lymph node tumors to improve our understanding of the metastatic process. Fifty-one genes were differentially expression ($P < 1x10^{-5}$, >2-fold differences). Genes expressed at higher levels in the primary tumors were involved in degradation of the extracellular matrix, enabling cells with metastatic potential to disseminate, while genes expressed at higher levels in metastases were involved in transcription, signal transduction and immune response, providing cells with proliferation and survival advantages. These data improve our understanding of the biological processes involved in successful metastasis and provide new targets to arrest tumor cell dissemination and metastatic colonization[13]. Evaluation of primary tumors from patients with metastases and those without has also been performed; however, in this study we were unable to identify a molecular signature that could effectively classify the two tumor types[18]. The inability to derive molecular profiles of metastasis in primary tumors may reflect tumor heterogeneity, paucity of cells within the primary tumor with metastatic potential, influence of the microenvironment, or inherited host susceptibility to metastasis[19].

Biomedical Informatics (BMIX) has been focused on: 1) development and implementation of an infrastructure system that supports the acquisition, storage, and maintenance of the clinical and molecular data generated in the study, and 2) application of existing algorithms and methods, and development of new ones as needed, for biomedical informatics research as well as for supporting other scientific research in the study. Our work has resulted in an advanced and recognized infrastructure system that supports translational research[20, 21], a number of peer-reviewed publications and conference presentations, and competitive extramural funding. The following is a high-level summary of the activities and achievements in BMIX.

Quality Control (QC) and Quality Assurance (QA). To obtain high-quality data we have developed a set of QA programs, and many of the QC/QA procedures have been embedded into our SOPs. For example, the clinical QA program consists of: 1) a visual inspection of missing values and obvious inconsistencies, 2) double data-entry to reduce data entry errors, 3) a computer program named QAMetrics that deploys established QA rules to check for data integrity across the whole questionnaire, and 4) a web-based QA Issue Tracking system to enable efficient communications between WRI and the clinical sites for resolving QA problems of the clinical data [22-25] . In addition, we have developed a microarray QA program to identify outlier arrays from a population of similar arrays [26, 27] . Additional QA programs have been developed or are in development to ensure the quality of the data generated at WRI. These

QA programs are evolving as data collection and generation technologies develop.

The Laboratory Information Management System (LIMS). A LIMS is needed to track and manage the sheer volume of data involved in translational research. Our clinical and tissue banking activities are tracked by the Clinical Laboratory Workflow System that we co-developed with Cimarron Software that was deployed in 2004 [28] . To support the evolving needs of breast cancer studies, we are now in the process of developing a replacement system of the CLWS using up-to-date IT technologies. Through the years of practice, we concluded that for tracking the laboratory experimental activities, a light-weight LIMS is most appropriate, recording experimental results and essential information that is needed for experimental results interpretation. We plan to develop such a light-weight system after the replacement system for the CLWS is developed.

The Data Warehouse for Translational Research (DW4TR). We have developed the DW4TR to integrate internally collected and generated clinicopathological data and molecular data from all the platforms. The development is done with our IT development partner, InforSense Ltd (currently part of IDBS). We have developed an innovative patient-centric, modularly-structured data model for clinicopathologic data, which contains disease-independent and disease-specific submodules to enable easy expansion to support the study of new diseases. A specimen-centric data model has been developed for molecular data. We have also developed a temporal data model to resolve the problem of the temporal information alignment between the data and specimens that were collected at multiple points of the time. The DW4TR has two major intuitive interfaces, one is the Aggregated Biomedical-information Browser and the other is the Individual Subject Information Viewer. The DW4TR has successfully supported the Clinical Breast Care Project with a total of 799 data elements, and has been expanded to support additional translational research programs [29-32] .

Other Applications: We have developed a Biomedical Informatics Portal, using the InforSense analytical workflow platform, to host additional applications deployed or developed by us to facilitate integrative biomedical research. For example, we have developed a specimen selection tool for scientists to use to select specimens in our tissue bank using the temporal and other information in the DW4TR [33] . The user can specify the inclusion/exclusion criteria. We have also developed a Data Correction Utility to enable correction of data errors in the DW4TR.

Research : Our research focuses on clinicopathologic risk factors of breast cancers, biomarker identification, and mechanistic understanding of primary and metastatic breast cancer, and we do so mostly by applying existing data mining methods [34, 35] . We also have developed new algorithms and visualization tools for clinicopathologic risk factor analysis, and reported interesting new breast disease co-occurrence patterns among other findings [36-42] . We found ethnicity-specific benign breast disease co-occurrence with breast cancer [43, 44] , reported different characteristics of invasive breast cancer between Caucasian and African American women [45] , and identified subtype-specific clinicopathologic properties of breast cancers [46, 47] . We worked closely with laboratory scientists in identifying biomarkers of breast cancer and breast cancer metastasis, and used bioinformatics tools to seek mechanistic understanding of breast cancer development and metastasis [48-50] , and we collaborated with external scientists as well in study human diseases [51, 52] . In performing a peripheral blood gene expression analysis, we have identified differential enrichment of signaling pathways between breast cancer patients and normal subjects [53] . In another project using breast cancer tissues we have identified significant difference between lymph node positive and lymph node negative cases in a carefully stratified population. We also performed a transcription factor-centric

computational analysis of genes differentially expressed in healthy breast tissues from African American and Caucasian women [54] . We used the semantic similarity measures to characterize human metabolic and regulatory pathways, which will help us to understand human disease development mechanisms. [55, 56]

Human Subjects Justification

The purpose of using human subjects for this study is to prospectively collect human blood specimens in order to study breast cancer and disease. This minimal risk study is likely to yield important information about the risk factors, diagnosis, prognosis and treatment of breast disease. Please also see Section 3.1 (Medical Application).

9.4 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

As part of the CBCP, we propose to carry out molecular, biochemical and histologic analysis of human blood and serum to provide more insight into the molecular mechanisms that may be relevant in breast cancer development and breast diseases. To achieve this aim, a large supply and a wide variety of good quality blood specimens are needed. Unfortunately, good quality donor blood specimens are scarce and, when available, are often not backed by a comprehensive medical history and/or not a good representation of the target population or study area. The non-availability of a steady and consistent supply of blood specimens negatively impacts the generation of biologically useful information in the laboratories and in clinical practice. The objectives of this protocol are therefore:

1. Acquisition and banking of blood and serum from informed and consenting donors.
2. To characterize gene and protein expression profiles and single nucleotide polymorphisms associated with breast disease and breast cancer development.
3. Establishment of standardized procedures for blood collection, processing and storage through biospecimen science research activities.This research data will feed evidence based standard operating procedures of the biobank and will allow the maintenance of the biospecimen integrity throughout the biospecimens' life-cycle.
4. Identify factors within patient serum and/or blood-derived cellular components that correlate with patient risk factors or clinical status as defined in the corresponding clinical patient database.

9.5 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data/specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

This will be a prospective study aimed at characterizing the gene and protein expression in blood. A blood sample will be collected from all participants at enrollment and subsequently may be collected for at any future clinical appointments at the Breast Center. A CBCP study clinician will draw up to 20 mls (about 4 teaspoons) of blood from study participants at each sample collection. These samples will be processed and shipped as described below.

After study enrollment, all blood draws for study participants will take place only at the time of standard, clinically recommended follow-up appointments. Study participants will come to the Breast Center only for physician directed and clinically indicated visits. At these times, the study team may take the opportunity to obtain blood samples for patients enrolled in this protocol. Additionally, at the time of the initial visit, patients will complete the CBCP Case Report Form (CRF) and some general diagnostic information will be obtained, assisted by one of the breast clinic nurses. If a CRF is not fully completed during patient appointments, a Breast Center clinician may consult the patient's medical records to obtain information to complete the CRF or may phone the patient, with their verbal permission, to obtain this information..

Study Procedures:

A. Subjects: All participants will be patients attending clinical appointments at the WRNMMC Breast Care Center who have consented to join in the study. They will include:

i) patients seen in the Risk Reduction clinics;
ii) patients diagnosed with breast cancer;
iii) patients diagnosed with any other type of breast disorder.

The far majority of patients will be female, however, 1% of all breast cancers occur in males and these male patients with breast cancer (ii above) would be eligible as well.

B. Inclusion and exclusion criteria:

Inclusion criteria:

1) adult over the age of 18 years;
2) mentally competent and willing to provide informed consent;
3) military beneficiaries;
4) presenting to the Breast Center or the Women's Imaging Center of the WRNMMC with evidence of possible breast disease;
5) high risk beneficiaries

Exclusion criteria:

(1) Minors under the age of 18
(2) Non-beneficiaries of the military health care system.
(3) Adult subjects with severe mental illness or other conditions that significantly impair memory, such as Alzheimer's disease
(5) Patients with pre-existing coagulopathies.
(6) Patients with any other conditions for which invasive biopsy or surgery is medically contraindicated.

During their clinic visit patients will be offered the opportunity to participate in our studies. If they choose to participate, before signing an informed consent, they will have the study explained to them by a CBCP research team member (e.g. purpose of study, where samples will be stored, the GINA law, how to withdraw from the study) and provided time to discuss any concerns and/or ask questions regarding the study and their participation. They will be offered the opportunity to consent for future research to be performed on their samples. A signed copy of the ICD/HIPAA will be provided to the subject prior to departing.

Each consented study participant will be assigned a unique, 9-digit coded identifier (CBCP number) and all associated serum, and/or blood samples to be archived will be assigned an 8-digit barcode. Both the CBCP numbers and the corresponding sample barcodes will be registered into the clinical database. Under separate approved protocols (WRNMMC IRB#20704 and WRNMMC IRB#20705) a clinical database continues to be maintained which describes the characteristics of CBCP blood and tissue donors. Linkage between the patient and research samples will be kept in a password protected-limited access database and in individual patient records held in gang-locked cabinets.

Laboratory research utilizing the blood samples and data collected for this protocol will be carried out at the CBCP's research facility, Windber Research Institute, located in Windber, PA. Along with the global genome and proteome expression profiling studies, other CBCP sponsored studies and collaborations with outside organizations utilizing CBCP tissue and bloodbased specimens will be defined, reviewed and approved per the scientific (clinical and basic science) leadership of the CBCP. These additional studies will be supported by separate research protocols and collaborative agreements in compliance with WRNMMC IRB regulations and guidelines.

Specimen repository storage: All specimens will be held in CBCP freezers for an indefinite period of time into the future. Exceptions to this will occur when specimens are exhausted (consumed) due to their use in the approved research within CBCP labs and elsewhere, or when previously consented patients withdraw their consent and use of their specimens, at which time that patient's specimens will be withdrawn from the

repository and destroyed. The CBCP PI is responsible for maintaining the integrity of the Tissue Bank, Serum/Blood Bank Repository, and all databases. In the event that the named PI leaves WRNMMC, another WRNMMC investigator will be named through in-place processes), and that new CBCP PI will take full responsibility for the banked samples and data. If under any circumstance a new CBCP PI is not named, then the WRNMMC Institutional Review Board (IRB) will be notified, and the IRB will determine the disposition of this tissue and blood library.

Methodology:

1. Blood collection and processing: Patients will have up to 20 cc of venous blood collected by a phlebotomist or nurse. Before blood is drawn, a nurse will explain the study, consent the patient and also assist the patient in completing the CBCP Case Report Form. All consenting patients will be assigned a unique 9-digit identifier (CBCP number) and all associated serum, and/or blood samples to be archived will be assigned an 8-digit barcode. Both the CBCP numbers and the corresponding sample barcodes will be registered into the clinical database. The clinical database which describes the characteristics of the blood donors will be maintained. Linkage between the patient and research samples will be kept in a password protected-limited access database and in individual patient records held in gang-locked cabinets.

A portion of the blood will be placed in PAX-gene blood tubes (Quigen, Inc), which stabilizes the RNA for up to seven days. Plasma and serum will be processed within 2 hours by spinning blood down and aliqoting into separate tubes, after which they will be stored at -80 degrees in the CBCP freezer. The CBCP specimens will be transferred to the CBCP Genomics / Proteomics Center at the Windber Research Institute on a weekly scheduled basis, where the following procedures will be carried out:

a. RNA, DNA and Protein from blood isolation from blood: RNA will be purified from blood collected by PAXgene RNA tubes using the RNA Test Kit (PAXgene™, Quiagen Inc., CA). RNA will then be employed for other downstream analysis after determining concentration with a DNA/RNA calculator. DNA will be isolated from blood using the QIAamp DNA blood kit. This involves lysing the blood in appropriate buffer and loading this on a spin column. DNA gets bound to the silica gel-based membrane and pure DNA eluted in water or low-salt buffer. Protein will be isolated from plasma or serum samples using an extraction buffer (50mM Tris HCL, pH 7.5 and 0.1% Nonidet P-40) as described below. Approximately two volumes of buffer per volume of the sample are centrifuged at 14,000rpm/15minutes at room temperature. The supernatant is transferred to a fresh tube and about twice its volume of isopropanol added. The mixture is allowed to stand at room temperature for 15-20 minutes before centrifugation as described above. The supernatant is discarded and precipitate reconstituted in the Tris buffer. Total protein concentration will be determined by the Bradford protein assay procedure.

b. Primary uses of the blood and serum specimens:

The known primary uses under this protocol for the acquired serum and blood fall into five major subsections listed below. Additional topics of investigation for internal (CBCP) and external (CBCP collaborations with outside institutions) will be identified and approved by CBCP leadership and supported as required by separate research protocols and collaborative agreements in compliance with WRNMMC IRB guidelines. The five major subsections are:

i. Serum/Blood repository Banking – this includes sample definition and receiving, flash freezing/labeling/storage, OCT embedding /labeling (putting identifier codes on each sample for subsequent tracking)/storage, and Inventory/tracking. The inventory and tracking of all samples will be done electronically with barcodes and sample tracking software – initially the software will be Freezerworks™ to be followed by our own developed software module by Cimmaron Inc. that will be integrated with our laboratory analysis software GenoMax™.

ii. Gene Expression Profiling – RNA will be extracted from blood using various kits appropriate to the storage conditions of the samples (PAXGene blood samples, etc). RNA will be used for Northern Analysis, RT-PCR, and mRNA expression analysis using Affymetrix arrays and in future RNA Seq analysis.

iii. Sequencing –Traditional and next generation sequencing approaches are performed on genomic DNA

from diseased tissues, historically normal tissues, and blood.

iv. Genotyping – Blood will undergo DNA quantification followed by PCR set-up, thermal cycling, SNP (single nucleotide polymorphism) reaction clean-up, capillary electrophoresis set-up, genotype calling, and genotype QC. Genotyping is also performed using Affymetrix arrays.

v. Protein Expression Analysis – Current mass spectrometry analysis, will be conducted for protein identification and quantification.

At the end of each of the above five laboratory workflows, the data will be QA'd, analyzed using powerful genomics/proteomics software tools, and placed into the CBCP database / data warehouse. QA of the data involves using software tools that interrogate the fields of the data that come out of the workflow stations, to ensure the data has consistency and is within expected or known ranges; any data found to be outside of expected ranges is not necessarily flawed, but is them identified for closer analysis by researchers.

Data will be stored in the CBCP server(s) and/or data warehouse (being developed with NCR Inc.), on CBCP sites at WRNMMC or WRI, and eventually at the CBCP Data Warehouse in Fort Detrick, MD (as part of our MANVT initiative, funded separately). The MANVT initiative is a Medical Are Network Virtual Technologies program. Its ultimate goal is to allow for the near-real time interaction between all of the CBCP sites (WRNMMC,Windber clinical and WRI) with regards to movement of high volumes of research data across a virtual fiberoptic network linking the sites, as well as allow for creation of a data warehouse (situated at least in part at Fort Detrick, MD or to have a significant redundancy backup there).

2. Data collection: All individuals signed up for the study will be categorized into groups and further clinical classification and staging of patients with tumors will be based on the tumor-nodes-metastasis (TNM) classification and the Union Internationale Contre Cancer (UICC) staging system for breast cancer incorporating the TNM classification. Blood samples will be obtained from all participants at consent and at all other recommended visits as indicated in above. There will be no patient identifiers sent to the laboratory with the blood samples but all participants will be coded for easy tracking of results and other clinical data. All results will be saved on the CBCP database.

At the time of the initial visit, a member of the research team will assist the study participant in completing a Case Report Form (CRF) including demographic, medical history, diagnostic and other information (see Appendix 1). Study participants will confirm and update their CRF information on an annual basis at clinically directed follow-up visits. The CRF and CRF administration procedures are described in greater detail in Section 5.5.5 of this protocol.

3. Sample size/Data Analysis: Sample size will grow according to the frequency of patients attending the breast care center. Primary analysis will be comparison of gene expression patterns, protein expression profiles, and single base variations in DNA across the different patient categories. Laboratory analysis data will be correlated with clinical data on the individual patients to determine relationship of gene expression patterns and variation within DNA sequences with disease onset and progression. Specific secondary testing and analysis of samples will be submitted as a separate protocol.

Other institutions are intended to join in this protocol. These other sites will be both military and civilian. As with multi-center protocols, a Principal Investigator will be responsible at each separate institution for overseeing the protocol, conforming the protocol and consent form to their own institutional IRB requirements, and for achieving their own institution's IRB approval prior to proceeding.

4. CBCP Resource Utilization Oversight

The molecular and biologic investigations for this study will be carried out at the CBCP's research facility, the Windber Research Institute, located in Windber, PA. The CBCP Scientific and Data Review Committee provides internal review and oversight for all CBCP research protocols and projects, as well as CBCP budgetary oversight, review and approval. This committee includes members form WRNMMC, Windber

Research Institute and the Henry Jackson Foundation. Along with the global and proteome expression profiling studies, other CBCP sponsored studies and collaborations with outside organizations utilizing CBCP tissue and blood/serum specimens will be defined, reviewed and approved per the scientific (clinical and basic science) leadership of the CBCP. These additional studies will be supported by separate research protocols and collaborative agreements in compliance with WRNMMC IRB regulations and guidelines. All requests to utilize CBCP tissue and blood specimens and/or data, either for internal CBCP protocols or collaborations with outside organizations, require the completion of the WRI-CBCP Project/Sample Approval Form. This form must be reviewed, approved and signed by the CBCP PI and CBCP Scientific and Data Review committee before new CBCP research studies can begin.

Other institutions are intended to join this protocol. These other sites will be both military and civilian. As with multi-center protocols, a Principal Investigator will be responsible at each separate institution for overseeing the protocol, conforming the protocol and consent form to their own institutional IRB requirements, and for achieving their own institution's IRB approval prior to proceeding.

9.6 Target Population:

Describe the population to whom the study findings will be generalized

Please see Section 9.5

9.7 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

One of the major challenges facing researchers and clinicians today is to understand the mechanisms associated with the evolution of benign breast disease and/or transition of breast disorders to breast cancer. The creation of a comprehensive tissue/blood bank is essential to the application of modern molecular and genetic analysis of breast diseases. Amongst other goals, this entire (overall CBCP) project will:

1. Establish a repository of high quality breast tissue and related (lymph nodal, blood) specimens for research on breast cancer and associated breast diseases, and
2. Permit the establishment of a single relational database with accurate and comprehensive biologically and clinically relevant information on breast diseases.

Since the standard of care for treating breast diseases and breast cancer is based on a multidisciplinary model that integrates prevention, screening, diagnosis, treatment and management, this CBCP project will provide the necessary framework for such an integrated approach, which will positively impact the future management of breast cancer.

This proposed study will identify differences in gene markers and protein expression patterns observed amongst a variety of patients attending the CBCP breast clinic at WRNMMC, and WMC. The patients will be grouped either as (1) high-risk for breast cancer development; (2) those diagnosed with breast cancer; or (3) other breast diseases (e.g. benign, or non/pre-invasive). Information obtained from the blood analysis will be linked with other clinical data to establish possible relationships between gene expression patterns and specific genetic alteration with disease onset and progression. The medical implication of this study is the identification of molecular markers that may enable early breast cancer detection, monitoring and prognosis/prediction through a less subjective and less intrusive procedure.

10.0 Study Procedures and Data management

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

The facilities to be used in this research study include the following:

1. Walter Reed National Military Medical Center (WRNMMC):

a. The Comprehensive Breast Center (CBCP), located in Building 19, 3rd floor, which contains a breast biopsy procedure room / recovery area, a fully-functional pathology laboratory, the tissue bank area with freezer, the separate patient blood-drawing room, blood centrifuge equipment and blood storage facilities, and the clinical and counseling areas.

b. The Women's Imaging Center, located in Building 19, 3rd floor, where non-surgical breast biopsies will take place.

c. CBCP address and phone number:
Clinical Breast Care Project

Walter Reed National Military Medical Center
America Building 19, Room 3233
4954 North Palmer Road
Bethesda, MD 20889-5630
Phone: (301) 400-2766

2. Windber Research Institute (WRI):

a. The Windber Research Institute (WRI), located in Windber, PA.

b. This facility is a 6,000 square foot, highly integrated laboratory that is adequately equipped for tissue processing and archiving, functional genomics, proteomics, high-throughput gene and protein expression profiling, microarray construction, DNA sequencing, single nucleotide polymorphism analysis, micro satellite analysis, mass spectral analysis, laser capture microdissection, bioimaging and microscopy. The CBCP tissue/blood/serum bank storage capability on-site at WRI is in isothermic liquid nitrogen freezers with a storage capacity of up to 80,0000 specimens.

c. WRI address and phone number:

Winder Research Institute
620 Seventh Street
Windber, PA 15963-1300
Phone: (814) 361-6950

Anticipated start date: 2002
Anticipated completion: Indefinite

1.
Subjects: All participants will be patients attending clinical appointments at the WRNMMC Breast Care Center who have consented to join in the study. They will include:

i) patients seen in the Risk Reduction clinics;

ii) patients diagnosed with breast cancer;

iii) patients diagnosed with any other type of breast disorder.

The far majority of patients will be female, however, 1% of all breast cancers occur in males and these male patients with breast cancer (ii above) would be eligible as well.

1.
Inclusion and exclusion criteria:

Inclusion criteria:

1) adult over the age of 18 years;

2) mentally competent and willing to provide informed consent;

3) military beneficiaries;

4) presenting to the Breast Center or the Women's Imaging Center of the WRNMMC with evidence of possible breast disease;

5) high risk beneficiaries

Exclusion criteria :

1.
Minors under the age of 18

2.
Non-beneficiaries of the military health care system.

3.

Adult subjects with severe mental illness or other conditions that significantly impair memory, such as Alzheimer's disease

(5) Patients with pre-existing coagulopathies.

(6) Patients with any other conditions for which invasive biopsy or surgery is medically contraindicated.

During their clinic visit patients will be offered the opportunity to participate in our studies. If they choose to participate, before signing an informed consent, they will have the study explained to them by a CBCP research team member (e.g. purpose of study, where samples will be stored, the GINA law, how to withdraw from the study) and provided time to discuss any concerns and/or ask questions regarding the study and their participation. They will be offered the opportunity to consent for future research to be performed on their samples. A signed copy of the ICD/HIPAA will be provided to the subject prior to departing.

Each consented study participant will be assigned a unique, 9-digit coded identifier (CBCP number) and all associated serum, and/or blood samples to be archived will be assigned an 8-digit barcode. Both the CBCP numbers and the corresponding sample barcodes will be registered into the clinical database. Under separate approved protocols (WRNMMC IRB#20704 and WRNMMC IRB#20705) a clinical database continues to be maintained which describes the characteristics of CBCP blood and tissue donors. Linkage between the patient and research samples will be kept in a password protected-limited access database and in individual patient records held in gang-locked cabinets.

Laboratory research utilizing the blood samples and data collected for this protocol will be carried out at the CBCP's research facility, Windber Research Institute, located in Windber, PA. Along with the global genome and proteome expression profiling studies, other CBCP sponsored studies and collaborations with outside organizations utilizing CBCP tissue and bloodbased specimens will be defined, reviewed and approved per the scientific (clinical and basic science) leadership of the CBCP. These additional studies will be supported by separate research protocols and collaborative agreements in compliance with WRNMMC IRB regulations and guidelines.

Specimen repository storage: All specimens will be held in CBCP freezers for an indefinite period of time into the future. Exceptions to this will occur when specimens are exhausted (consumed) due to their use in the approved research within CBCP labs and elsewhere, or when previously consented patients withdraw their consent and use of their specimens, at which time that patient's specimens will be withdrawn from the repository and destroyed. The CBCP PI is responsible for maintaining the integrity of the Tissue Bank, Serum/Blood Bank Repository, and all databases. In the event that the named PI leaves WRNMMC, another WRNMMC investigator will be named through in-place processes), and that new CBCP PI will take full responsibility for the banked samples and data. If under any circumstance a new CBCP PI is not named, then the WRNMMC Institutional Review Board (IRB) will be notified, and the IRB will determine the disposition of this tissue and blood library.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, how the data will be operationally measured, and approvals needed for use of information from DoD databases

a. Method of Data Collection from Study Participants

The main objective of this blood banking and analysis initiative is to collect human blood, along with biological and clinical data, prospectively from all informed and consenting patients enrolled in the blood repository protocols of the CBCP. The patient data collected will include the following categories: demographics, socioeconomic, clinical, pathologic, radiologic, treatment, follow-up, and risk factors. It is emphasized that all samples will be anonymized and all direct patient identifiers of the blood or serum, as well as of the database itself, will be removed from them. All specimens and data will be identified in the research arenas by a “CBCP number”, which will be a unique, 9-digit, individual patient-specific number. This CBCP number will be linked to all patient items via barcoding of samples and questionnaires. Connection between the “CBCP number” and the patient identifiers are located in two places: in patient files, maintained by CBCP laboratory personnel, which will be kept in a gang-locked file cabinet, and in a password-protected, limited-access, secure database to which the Research Protocol Coordinator, pathology, and data team have access. There will be no way for researchers anywhere along the chain of blood, serum, or data collection or analysis, to identify the actual identity of the patient via the barcodes or CBCP number. Other researchers within the CBCP or associated with the CBCP who have permission to use the blood samples may also have access to the clinical information (indeed, this linkage is what makes the CBCP biobank so powerful as a research tool); however, this linkage will not involve the patient’s name, so no researchers will ever know the identity of the specimen’s origin. Other identifiers, i.e., date of birth, date of death, date of surgery, etc. may be identified to researchers pending a separate IRB approved protocol.

Blood samples will be obtained from all participants at sign-up and at all other recommended visits as indicated in this protocol. There will be no patient identifiers sent to the laboratory with the blood samples but all participants will be coded for easy tracking of results and other clinical data. All results will be saved on the CBCP database.

At the time of the initial visit, a research team member will assist the study participant in completing a Case Report Form (CRF). This form contains study participant information such as study ID number, demographics, lifestyle factors, medical history, family history of cancer, pathology, diagnosis and treatment. Certain sections of this form will be completed by a clinician in consultation with the patient’s medical records; the time required for the patient to respond directly to CRF items will be approximately 15 minutes or less. Study participants will be asked to confirm and update the information in the CRF on an annual basis during subsequent visits to the Breast Center as recommended by their treating physician. If a CRF is not fully completed during patient appointments, a Breast Center clinician may contact the patient by telephone, with the patient’s permission, and/or consult the patient’s medical records to complete the CRF. Please see CRF in Appendix 1 to this protocol.

Sample Size / Data Analysis: Please see Section 9.5 (D) 3

b. Source and Type of Data Collected from Existing Data Sources. Answer the questions below after considering the minimum necessary data required for the research study.

i. Have you received a data consultation with a data expert to determine the data elements to be extracted or the data system to access? (Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS data systems, the quality of that data and the methods for encrypting and collapsing data. You may contact a data expert at the following email address: TMADataDetermination@tma.osd.mil

0 Yes, then complete the questions in this subparagraph b according to the information received

from the data consult

1 No, then complete the questions in this subparagraph b according to the best of your knowledge (NOTE: It is highly recommended to get a data consult.)

ii. Indicate whether you will receive a data extract from the MHS or will access a data system to create a data set. A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to a data system means that the researcher may access a data system and create a data set for the research study.

0 Data Extract 1 Access

iii. Do you intend to use only a de-identified data set in your research study?

A de-identified data set is a data set that does not include any of the identifiers listed in the table in 5.5.5 (b)(vi). In addition, the researcher does not have actual knowledge of another way the data can be used alone or in combination with other known information to identify an individual. De-identified data is also data that a person, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines is not individually identifiable in accordance with the conditions outlined in 45 CFR 164.514 (b)(1).

0 Yes 1 No

iv. Will you need MHS data with health information?

Data with health information means any information that is created or received by the MHS that relates to the past, present or future physical or mental health or condition of an individual, the provision of health care to an individual or the past, present or future payment for the provision of health care to an individual. Examples of MHS data with health information includes data maintained on AHLTA, CHCS and ESSENTRIS.

1 Yes 0 No

v. Do you intend to access a data base to obtain personally identifiable information that is not health information (PII)?

1 Yes, will access data base for (PII)

0 No, will not access data base for PII

vi. Include the following table in your protocol and put an “x” in the MHS column next to the categories of data that you are requesting from the MHS. If you are planning to receive a data extract of MHS data that includes a data element that will be de-identified by the MHS, then you do not need to put an “X” in the column corresponding to the category of data for that data element.

Note: Please disregard the table below and see Section 10.9 in its place.

	Study Participant	MHS	Other
1. Names	X		
2. Postal address with only town, city, State and zip code	X		
3. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available	X		

data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.			
4. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older	X	X	

10.3 At any point in the study, will you request, use, or access PII from the Military Health System (MHS)?

◉ Yes ○ No

10.4 Have you consulted with an MHS data expert to determine the data elements to be extracted or the information system(s) to access?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (dha.ncr.pcl.mbx.privacyboard@mail.mil)

○ Yes, then complete the questions below according to the data consult

◉ No, then complete the questions below according to the best of your knowledge (NOTE: It is highly recommended that you work with an MHS data expert)

10.5 Indicate whether you plan to receive a data extract from the MHS or plan to access an information system directly to create a data set:

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

☐ Data Extract

☑ Access

10.6 Do you intend to use only de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:

1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information

2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

○ Yes ◉ No

10.7 If your research study requires access to an MHS information system, please indicate the system to obtain data:

If you do not know which system(s) contain the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or seek guidance from an MHS data expert:

PHI Systems:

MHS Information System		Requesting Data	
:	AHLTA	:	Yes
:	CHCS	:	Yes
:	ESSENTRIS	:	Yes

PII-Only Systems:

MHS Information System	Requesting Data
No records have been added.	

De-Identified Data & Other Systems:

Information System	Requesting Data
Expense Assignment System	
List other system(s):	
List other system(s):	

10.8 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ○ Yes, will merge data
- ◉ No, will not merge data

10.9 Indicate the categories of data that you will request from MHS systems or MHS health care providers about research participants or relatives, employers, or household members of the research participants.

Data Element(s)	MHS	Non-MHS Systems
1. Names		☐ null
2. Postal address with only town, city, state and zip code		☐ null
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000		☐ null
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death		☐ null
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of “age 90 or older”	☐ null	☐ null
6. Telephone numbers		☐ null
7. Fax numbers	☐ null	☐ null
8. Electronic mail addresses	☐ null	☐ null
9. Social Security numbers (SSNs)	☐ null	☐ null
10. Medical record numbers	☐ null	☐ null
11. Health plan beneficiary numbers	☐ null	☐ null
12. Account numbers	☐ null	☐ null
13. Certificate/license numbers	☐ null	☐ null
14. Vehicle identifiers and serial numbers, including license plate numbers	☐ null	☐ null
15. Device identifiers and serial numbers	☐ null	☐ null
16. Web Universal Resource Locators (URLs)	☐ null	☐ null
17. Internet Protocol (IP) address numbers	☐ null	☐ null

18. Biometric identifiers, including finger and voice prints	☐ null	☐ null
19. Full-face photographic images and any comparable images	☐ null	☐ null
20. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)		☐ null

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

Study participants' social security numbers will be collected from MHS and ALTHA and retained in the CBCP database only for the purpose of confirming the identity of a study sample or CRF if a question arises. Social security numbers will not be attached to study samples or data collection instruments.

10.10 Is it possible that the data will become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would be using rank and race together to determine the identity of an individual with a particular health condition

Small cell size means that there are only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30 so the rank category may need to be expanded to include lower ranks

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 19 of Table 1 above, but that could be used to identify an individual. Examples of unique data elements include: 1) a unique number, such as a medical record number or EDIPN; 2) a unique code, such as a diagnosis code or a bar code on an electronic health record; and 3) any unique characteristic, such as the rank of general or admiral, or a race or gender combined with another unique characteristic

- ○ Yes, there is a reasonable possibility the data will become identifiable
- ◉ No, there is no reasonable possibility the data will become identifiable

10.11 HIPAA Privacy Rule and Use of Protected Health Information in Research:

- ○ N/A – will not use or disclose protected health information (PHI)
- ◉ HIPAA Authorization will be obtained
- ○ Use of a limited data set where a data use agreement will be obtained
- ○ Waiver/alteration of HIPAA Authorization is being requested

10.12 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

Please see Section 9.5

10.13 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may

be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed

Please see Section 9.5

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

11.2 Sample Size Estimation:

Please see Section 9.5 (D) 3

11.3 Data Analysis Plan:

Please see Section 9.5 (D) 1 (b)

12.0 Participant Information

12.1 Subject Population:

Please see Section 9.5.1 (A)

12.2 Age Range:

- ☐ 0-17
- ☑ 18-24
- ☑ 25-34
- ☑ 35-44
- ☑ 45-54
- ☑ 55-64
- ☑ 65-74
- ☑ 75+

12.3 Gender:

- ☑ Male
- ☑ Female

12.4 Special categories:

- ☐ Minors /Children - “You must also consider the requirements of 45 CFR 46 Subpart D and DoDI 3216.02, Enclosure 3, paragraph 7.d.”
- ☐ Students
- ☐ Employees - Civilian - “You must also consider the requirements of DoDI 3216.02, paragraph 7.e.”
- ☐ Employees - Contractor
- ☐ Resident/trainee

☐ Cadets /Midshipmen - “You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraphs 7.e. and 12.”

☐ Active Duty Military Personnel - “You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.”

☐ Wounded Warriors - “Depending on your intended subjects’ status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.”

☐ Economically Disadvantaged Persons - “You must also consider the requirements of 32 CFR 219.111(b).”

☐ Educationally Disadvantaged Persons - “You must also consider the requirements of 32 CFR 219.111(b).”

☐ Physically Challenged (Physical challenges include visual and/or auditory impairment)

☐ Persons with Impaired Decisional Capacity - “You must also consider the requirements of 10 USC 980.”

☐ Prisoners - “You must also consider the requirements of 45 CFR 46 Subpart C and DoDI 3216.02, Enclosure 3, paragraphs 7.b. and 7.c.”

☐ Pregnant Women, Fetuses, and Neonates

☐ Non-English Speakers

☐ International Research involving Foreign Nationals - Headquarters Review is necessary

12.5 Inclusion Criteria:

Order Number	Criteria
1	Adult over the age of 18 years
1	High risk beneficiaries
1	Presenting to the Breast Center or the Women's Imaging Center of teh WRNMMC with evidence of possible breast disease
1	Mentally competent and willing to provide informed consent
1	Military health care beneficiaries

12.6 Exclusion Criteria:

Order Number	Criteria
1	Minors under the age of 18
1	Patients with pre-existing coagulopathies
1	Adult subjects with severe mental illness or other conditions that significantly impair memory, such as Alzheimer's disease
1	Patients with any other conditions for which invasive biopsy or surgery is medically contraindicated
1	Non-beneficiaries of the military health care system

13.0 Recruitment and Consent

13.1 Identification and Selection of Subjects:

Please see Section 13.5

13.2 Recruitment Process:

During their clinic visit patients will be offered the opportunity to participate in our studies. If they choose to participate, before signing an informed consent, they will have the study explained to them by a CBCP research team member (e.g. purpose of study, where samples will be stored, the GINA law, how to withdraw from the study) and provided time to discuss any concerns and/or ask questions regarding the study and their participation. They will be offered the opportunity to consent for future research to be performed on their samples. A signed copy of the ICD/HIPAA will be provided to the subject prior to departing.

13.3 Compensation for Participation:

Patients will not be compensated for their participation in this research study.

13.4 Eligibility Assessment Process:

Please see Section 13.5

13.5 Consent Process:

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

During their clinic visit patients will be offered the opportunity to participate in our studies. Printed CBCP informational/recruiting brochures are displayed in the WRNMMC Breast Center clinic area, and a clinician will ask patients if they wish to discuss the study and the informed consent document after their medical appointment. If they choose to learn more about CBCP research studies and to participate, a CBCP research team member will explain the study (e.g. purpose of study, where samples will be stored, the GINA law, how to withdraw from the study) and provide time to discuss any concerns and/or answer the patient's questions regarding the study and their participation. For patients who agree to participate, study procedures will be followed for the initial surgical procedure and any subsequent surgeries at WRNMMC related to their breast disease unless they withdraw from the study. The consent form offers study participants the opportunity to consent for future research to be performed on their samples. In addition, the consent form gives study participants the opportunity to choose whether they are willing to be contacted in the future by a CBCP research team member regarding future research studies that might be of interest to them. A signed copy of the ICD/HIPAA will be provided to the subject prior to departing the Breast Center clinic.

Study participants are informed in the consent form of their right to withdraw from this study at any time. In this case, they are instructed to contact the PI, the Research Coordinator or a CBCP research team member. As stated in the consent form, in the case of study withdrawal, the CBCP research team would retain any previously-collected data necessary to ensure the scientific validity of the research. However, no new blood samples would be collected for this study.

13.6 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

◉ N/A
○ Propose ombudsman

13.7 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Study participants are informed in the consent form of their right to withdraw from this study at any time. In this case, they are instructed to contact the PI, the Research Coordinator or a CBCP research team member. As stated in the consent form, in the case of study withdrawal, the CBCP research team would retain any previously-collected data necessary to ensure the scientific validity of the research. However, no new blood samples would be collected for this study.

If a study participant decides to withdraw from the study, they are instructed to either send their request in writing to the address provided on the consent form or to complete a study withdrawal request form with a CBCP research team member at the time of their Breast Care Center clinical appointment. When a study participant decides to withdraw, they may choose to either: (1) allow the CBCP study team to retain previously-collected blood samples in the CBCP biorepository, and to continue to update their CRF and breast disease status by consulting WRNMMC's medical records system or (2) request that their previously-collected blood samples be destroyed and that the research team discontinue the collection of CRF data and breast disease status information from the medical records.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

This is a minimal risk study. The blood draws associated with this research study may result in mild discomfort, with some pain, swelling or bruising at the needle site. In addition, some people feel dizzy or light-headed for a few minutes after blood is drawn.

Confidentiality of study participants' research records will be protected to the extent possible under existing regulations and laws, but it cannot be guaranteed. Therefore, breach of confidentiality is a potential risk. The chances of this happening, however, are very small because the research records will be promptly de-identified and/or coded.

14.2 Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

ii. When will you destroy the research source documents, data file and the master code?

Research source documents, data files and the master code linking patients to their study ID numbers will be kept for three years from the date the study is closed and then will be destroyed. Consent forms and HIPAA Authorization documents will be kept for six years after the study is closed and then will be destroyed.

iii. Will research data, including Protected Health Information, be sent outside of WRNMMC?

_X__ Yes

If yes and data will be sent out in an electronic format to a third party, a MHS Systems Security

Verification (SSV) form will need to be completed and reviewed by WRNMMC IT department to ensure if an electronic data transmission meets applicable standards. An impact statement from WRNMMC IT department is also required for the SSV review.

___ No

Certificate of Confidentiality

A Certificate of Confidentiality is not required for this study.

14.3 Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

ii. When will you destroy the research source documents, data file and the master code?

Research source documents, data files and the master code linking patients to their study ID numbers will be kept for three years from the date the study is closed and then will be destroyed. Consent forms and HIPAA Authorization documents will be kept for six years after the study is closed and then will be destroyed.

iii. Will research data, including Protected Health Information, be sent outside of WRNMMC?

_X__ Yes

If yes and data will be sent out in an electronic format to a third party, a MHS Systems Security Verification (SSV) form will need to be completed and reviewed by WRNMMC IT department to ensure if an electronic data transmission meets applicable standards. An impact statement from WRNMMC IT department is also required for the SSV review.

___ No

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society
If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

This study does not offer direct benefits to participants but is likely to yield important information about the risk factors, diagnosis, prognosis and treatment of breast disease.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

Please see section 14.1

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

Please see legacy protocol and consent form.

15.0 Study Monitoring

15.1 Data Monitoring Plan:

Describe the plan to monitor the data to verify that data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored and the frequency of monitoring

N/A

15.2 Safety Monitoring Plan:

Describe the plan to monitor the data to ensure the safety of subjects

N/A

15.3 Does your study require independent data and safety monitoring?

○ Yes ◉ No

16.0 Reportable Events

16.1 Reportable Events:

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short term management and any long term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Reportable Events include adverse events (AE), serious adverse events (SAE), unanticipated problems involving risks to subjects or others (UPIRTSO), and protocol deviations as defined by the WRNMMC IRB Handbook.

UPIRTSOs, are unexpected AEs and SAEs, in the opinion of the PI, are possibly related to participation

AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol and must be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within 5 business days.

Expected reportable events and events that are not related to study participation are reported on the Continuing Review (CR) Progress Report. CR is generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

When a deviation occurs, the investigator shall report the occurrence to the IRB. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure. Deviations that are determined to be minor as defined by the WRNMMC IRB Handbook are reported on the Continuing Review (CR) Progress Report.

As a reminder, according to DoDI 3216.02 (November 8, 2011), the IRB shall approve an independent research monitor by name for all DoD-conducted research involving human subjects, determined by the IRB to involve more than minimal risk to human subjects. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or Institutional Official (IO) for research involving human subjects determined to involve minimal risk.

The research monitor may perform oversight functions and will report their observations to the IRB or a designated official. The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have the authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team condu

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs , dietary supplements, biologics, or devices be utilized in this study?

- ☐ Drugs
- ☐ Dietary Supplements
- ☐ Biologics
- ☐ Devices
- ☑ N/A

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- (•) Registration is not required
- ( ) Registration pending
- ( ) Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- (•) Registration is not required
- ( ) Registration pending
- ( ) Registration complete

20.0 References and Glossary

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20.2 Abbreviations and Acronyms:

ATTACHMENT 4:
Blood ICD
(Informed Consent Document)
(3 May 2017)

Last Name_____

WALTER REED NATIONAL MILITARY MEDICAL CENTER (WRNMMC)

This Specimen banking consent form is valid only if it contains the IRB stamped date.

Consent for Voluntary Participation in a Specimen Banking Study Entitled:

"Creation of a Blood Library for the Analysis of Blood for Molecular Changes Associated with Breast Disease and Breast Cancer Development"

Principal Investigator: Craig D. Shriver, COL, MC, General Surgery Service, Department of Surgery

Study site: X WRNMMC

1. INTRODUCTION OF THE STUDY

You are being asked to be in this research study because you are a patient in our Breast Care Center. All patients can participate, those with breast diseases and those without breast cancer or any breast disease. Your participation is entirely voluntary. Refusal to participate will not result in any penalty or loss of benefits to which you are otherwise entitled.

2. PURPOSE OF THE STUDY

The purpose of the study is to store blood samples from patients seen in the Breast Care Center to be used in laboratory studies to identify gene marker and protein expression changes that may be associated with the onset and progression of breast disease and possible breast cancer. By carefully examining blood samples from many different breast conditions and from non-breast disease patients, we hope to improve our understanding of the causes and best treatments for breast disease. Another purpose is to correlate patient clinical information with the results of these laboratory studies.

3. PROCEDURES TO BE FOLLOWED

We propose to carry out this study using blood collected from consenting donors. You would most likely be giving blood for other routine procedures during your visits, and we would like to use some of your blood for our study. However, we may ask for blood even if you are not having blood drawn for other purposes.

If you agree to be in this study, a nurse or another person trained in drawing blood will draw up to 20 cc (about 4 teaspoons) of blood from a vein in your arm. This will take approximately 5 minutes. At any future visits to the Breast Center, or as recommended by your treating doctor for medical care purposes, another blood sample up to 20 cc (about 4 teaspoons) may be taken from a vein in your arm.

In this study, a Clinical Breast Care Project (CBCP) research team member will assist you in completing a Case Report Form (CRF) at the time of your first visit and on an annual basis during subsequent visits to the Breast Center, as recommended by your treating physician. This form contains study participant information such as study ID number, demographics, lifestyle factors, medical history, family history of cancer, diagnosis and treatment. Certain sections of this form will be completed and periodically updated by a clinician who will consult your medical records to monitor the status of your breast disease; the time required for you to respond directly to CRF items with a research team member will be approximately 15 minutes or less. You may refuse to answer any question if you so choose.

The information collected on the CRF will be used to correlate the laboratory research results with your medical history, which may be important in correctly interpreting research results. If a CRF is not fully completed or updated during one of your appointments, a clinician on our staff may follow up with you by telephone, with your permission, or consult your medical records to obtain information to complete the CRF.

4. IDENTIFICATION OF YOUR BLOOD AND/OR SERUM SAMPLES, HOW AND WHERE THEY WILL BE STORED AND WHO WILL HAVE ACCESS TO YOUR SAMPLES

You will be assigned a code number referred to as the CBCP number [not your name or social security number (SSN)], that will be used to code the blood samples, the questionnaire and any clinical information. The only connection between your “CBCP number” and your name or SSN will be kept

in double-locked secure files in the study coordinator's office, and via a password protected secure CBCP database.

The blood samples will be frozen and stored indefinitely in either the Breast Care Center laboratory sites at Walter Reed (WRNMMC), or our off-site facility, Windber Research Institute (WRI), Windber, PA. All samples will be kept in a secured (locked) freezer and identified only by CBCP codes. Only researchers within the CBCP or associated with the CBCP may have access to the samples and related clinical information. The blood samples will undergo the primary research studies as described in the next paragraphs.

The primary research uses of the blood samples are to study the genetic makeup, to examine protein changes, and to look for other markers that may be associated with breast disease. This information will be analyzed and stored in a computer database using your assigned code number.

Any remaining blood samples left over after these primary studies are done will remain frozen indefinitely in the CBCP biorepository until needed for approved research projects, if you consent for future unknown breast disease research. You will be provided the opportunity at the end of this consent form to indicate whether you will allow your blood samples to be used for future breast research. It is not possible at this time to predict all the potential future research uses of the samples.

If future research is to be conducted using these samples, the research will only be conducted after the proposed study protocol has received approval from the appropriate Institutional Research Board (IRB) or the CBCP Principal Investigator (PI) and scientific leadership, as appropriate. You will have the opportunity to give your consent for the use of your samples for future research at the end of this consent form.

Because these research projects are experimental, the results of any research done with your samples will not be given to you or your doctor. These reports will not be put in your health records. The research will not be used in decisions regarding your medical care. Third parties, such as relatives, physicians, and insurance companies, will not have access to your information from these studies.

In addition to this study, there are other research studies ongoing in the Breast Care Center. You may also be asked to participate in these other studies. If you agree to participate in these other studies, any data collected may be linked to the database for this research study. Your name or your SSN will not be in the data.

5. AMOUNT OF TIME FOR YOU TO COMPLETE THIS STUDY

Your participation in this study will consist of the time necessary to read and understand this consent form (about 30 minutes), and to complete the CRF (about 15 minutes). Follow up visits, if any, have already been discussed in Item 3 above. The collection of your blood samples to be used in this study will be done after you have had the study explained to you and you provide written consent. The blood will be collected by one of our research nurses by venipuncture and will take about 5 minutes.

When you agree to take part in this study, we will follow your medical status for as long as the study remains in progress. Your samples will be stored indefinitely or until they are no longer needed for research, or until you request removal of your samples from our repository where the samples are stored. You may withdraw from this study at any time, and you may request that any remaining samples be destroyed. The PI or the Research Coordinator will be the point of contact if you choose to withdraw or if destruction of the samples becomes necessary. Removal of your samples from the bank must be requested in writing to the researcher at the address in section 14 of this consent form or by completing a study withdrawal request form with a study team member during your next visit to the Breast Care Center.

6. NUMBER OF PEOPLE THAT WILL TAKE PART IN THIS STUDY

This study is a multi-site study with participants from several hospitals participating in the study. There are currently over 1,450 people participating in this study.

7. POSSIBLE RISKS OR DISCOMFORTS FROM BEING IN THIS STUDY

We do not anticipate that you will experience any health risks by participating in this study. However, outlined below are some discomforts or risks that could occur.

There may be some discomfort from having your blood drawn, and you may experience some pain, swelling and bruising at the site of the needle stick. In addition, some people feel dizzy or light-headed for a few minutes after blood is drawn.

Confidentiality of your research records will be protected to the extent possible under existing regulations and laws, but it cannot be guaranteed. Therefore, breach of confidentiality is a potential risk. The chances of this happening,

however, are very small because your research records will promptly be de-identified and/or coded.

If something in this study makes you uncomfortable or upset, you may choose to stop taking part in this research at any time without loss of benefits. If a study investigator notes any distress or anxiety associated with the research, you will be referred to your primary care physician or a professional counselor for help.

8. POSSIBLE BENEFITS FROM BEING IN THIS STUDY

You will not benefit directly from being in this study, but the knowledge gained through this research may ultimately lead to a better understanding of the causes of breast cancer and to the development of better ways to prevent, diagnose and treat breast cancer. Possible benefits of future research using your blood specimens would include learning and understanding more about what causes breast cancer and how to prevent and treat it. At the end of this consent form, we will ask for your permission to contact you about future research studies that may be of interest to you.

9. CONFIDENTIALITY/PRIVACY OF YOUR IDENTITY AND YOUR RESEARCH RECORDS

The Principal Investigator will keep your research records in a secure and locked place. These records may be looked at by staff from the WRNMMC Department of Research Programs, the Institutional Review Board (IRB), the Uniformed Services University of the Health Sciences, and other government agencies as part of their duties. These duties include making sure that the research participants are protected. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed. Complete confidentiality cannot be promised, particularly for military personnel, because information related to your health may be required to be reported to appropriate medical or command authorities. Your name will not appear in any published paper or presentation related to this study.

This research study meets the confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA).

10. CONDITIONS UNDER WHICH YOUR PARTICIPATION IN THIS STUDY MAY BE STOPPED WITHOUT YOUR CONSENT

Your taking part in this study may be stopped without your consent if remaining in the study might be dangerous or harmful to you. Your taking

part in this study may also be stopped without your consent if the military mission requires it, or if you lose your right to receive medical care at a military hospital.

11. ELIGIBILITY AND PAYMENT FOR BEING IN THIS STUDY

You will not receive any payment for being in this study.

12. COMPENSATION TO YOU IF INJURED & LIMITS TO YOUR MEDICAL CARE

Should you be injured as a direct result of your participation in this study, you will be provided medical care for that injury at no cost to you. You will not receive any compensation (payment) for injury. You should also understand that this is not a waiver or release of your legal rights.

Medical care is limited to the care normally allowed for Department of Defense (DOD) health care beneficiaries (patients eligible for care at military hospitals and clinics). Necessary medical care does not include in-home care or nursing home care. You should discuss this issue thoroughly with the PI before you enroll in this study.

If at any time you believe you have a study-related injury or illness as a result of participating in this research project, you should contact the PI. For questions about your rights as a research participant, call the Walter Reed National Military Medical Center Institutional Review Board (a group of people who review the research to protect your rights) at 301-295-8239, or the Staff Judge Advocate (SIA) Office at 301-295-2215.

13. COSTS THAT MAY RESULT FROM TAKING PART IN THIS STUDY

There is no charge to you for taking part in this study.

14. IF YOU DECIDE TO STOP TAKING PART IN THIS STUDY AND THE INSTRUCTIONS FOR STOPPING EARLY

You have the right to withdraw from this study at any time. This can be done by contacting the Principal Investigator or the Research Coordinator, at the phone number, mailing address or email address below or by completing a study withdrawal request form with a research team member during your next visit to the Breast Care Center.

The study withdrawal form provides the following two options: (1) no new blood samples will be collected from you, but the study team will retain your previously collected samples in the CBCP biorepository, and will continue to

consult your medical records to update the CRF and follow your medical status or (2) your previously collected blood samples will be destroyed, and the research team will discontinue the collection of CRF data and medical status information from your medical records.

If you choose to withdraw from this study, the research team will continue to use any information that they have already collected to ensure the scientific validity of the research. However, no new blood samples will be collected from you.

You in no way risk losing your right to medical care by leaving the study at any time.

Principal Investigator contact information:

Craig D. Shriver, COL, MC, MD, FACS
P.I., Clinical Breast Care Project
Director, Murtha Cancer Center
Walter Reed National Military Medical Center
America Building, #19, 3rd Floor
Bethesda, MD 20889-5600
(301) 295-8556
craig.d.shriver.mil@mail.mil

15. RESEARCH RESULTS

The results from tests that may be done on the blood that you donate for future research will not be given to you or to your doctor, even if you ask that this be done. The study results will not become part of your hospital medical record because these tests will be done for research purposes only.

Your individual testing results that may be done on the blood that you donate for future research will not be released to any third party, including family members, personal physicians, insurers or employers, under any circumstance unless required by law.

You should understand that there is a chance that the samples you are providing in this study may be used in other research studies related to breast disease. You will not be given any notice of future use of your sample. The confidentiality of your specimens will be protected in the same fashion as stated previously in the description of this study and/or confidentiality section. You will not be personally identified in any published paper of these other research studies. Any other researcher using these samples will be under the direction of the CBCP. No direct identifiers such as your name,

address, social security number, etc. will be provided to these researchers, but they could be provided with some identifying clinical information about you, such as dates of surgery, diagnosis, treatment.

16. YOUR RIGHTS IF YOU TAKE PART IN THIS STUDY

Participating in this study is your choice. You may choose either to participate or not to participate in the study. If you choose to participate in this study, you have the right to withdraw from this study at any time. This can be done by contacting the PI or the Research Coordinator, at the phone number or address in section 14 of this consent form or by completing a study withdrawal request form as described above.

No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits or risk losing your right to medical care.

17. THE NEW FEDERAL LAW – "GENETIC INFORMATION NON-DISCRIMINATION ACT" (GINA)

This new Federal law generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

Health insurance companies and group health plans may not request your genetic information that we get from this research.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans and all employers with 15 or more employees must follow this law.

GINA's health insurance protections do not apply to members of the military who receive their healthcare through TRICARE and for veterans who receive their healthcare through the Veterans' Administration. While GINA's employment protections do not apply to military members and Federal employees presently an Executive Order protects federal employees from genetic discrimination in employment and the military has its own policies in

place that may protect against genetic discrimination. GINA's protections should apply for a military member once he or she leaves the service and enters the private sector.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, so potentially you could experience denial of life, disability or long-term care insurance or higher rates for these kinds of insurance.

18. AUTHORIZATION FOR RESEARCH USE OF PROTECTED HEALTH INFORMATION

The Federal Health Insurance Portability and Accountability Act (**HIPAA**) includes a Privacy Rule that gives special safeguards to Protected Health Information (**PHI**) that is identifiable, in other words, can be directly linked to you (for example, by your name, social security number, etc.). We are required to advise you on how your PHI will be used.

(1) What information will be collected?

For this research study, you will be asked some basic information about your breast health and medical history. A CBCP research team member will assist you in completing a Case Report Form at the time of your first visit and on an annual basis during subsequent clinical visits to the Breast Center as recommended by your treating physician. This form will contain study participant information such as study ID number, demographics, lifestyle factors, medical history, family history of cancer, diagnosis and treatment. Certain sections of this form will be completed and periodically updated by a clinician who will consult your medical records to monitor the status of your breast disease, and who may contact you, with your verbal permission, to update your medical status.

Study participants' social security numbers will be collected from WRNMMC's medical record system and retained in the CBCP database only for the purpose of confirming the identity of a study sample or CRF if a question were to arise. Social security numbers will not be attached to CBCP study samples or data collection forms.

(2) Who may use your PHI within the Military Healthcare System?

The members of the research team will have access to your health information in order to find out if you qualify to participate in this study, and for analyzing research data. Additionally, your PHI may be made available to health oversight groups such as the WRNMMC Department of Research Programs and Institutional Review Board, and other government agencies as

part of their duties. These duties include making sure that research subjects are protected.

(3) What persons outside of the Military Healthcare System who are under the HIPAA requirements will receive your PHI?
Persons outside the Military Healthcare System who operate under HIPAA regulations may receive your PHI for the purpose of performing a guture IRB-approved research study. This information may include your CBCP number and associated information such as dates of surgery, diagnosis, and treatment. Your name, address, social security number and contact information will not be shared.

(4) What is the purpose for using or disclosing your PHI?
The members of the research team need to use your PHI in order to analyze the information related to the specific kind research study being performed. Researchers associated with the CBCP will use your blood samples to study the genetic makeup, protein changes, and other research markers that may be associated with breast disease, and unknown future research. The clinical information is important for performing analysis.

(5) How long will the researchers keep your PHI?
There is no expiration date for this study to maintain your PHI. Since this study collects blood samples for placement within a research blood bank, your samples and PHI will be maintained indefinitely unless you withdraw from this study.

(6) Can you review your own research information?
You will not be able to look at your research information.

(7) Can you cancel this Authorization?
Yes. If you cancel this Authorization, however, you will no longer be included in the research study. The information and samples we have collected from you may be destroyed at your request. The research and samples that may have been used prior to your request will not be able to be destroyed or withdrawn because they will already be among the statistics of the study. If you wish to cancel your HIPAA Authorization, please contact the Principal Investigator or the Research Protocol Coordinator in writing at the address provided in section 14 of this consent form.

(8) What will happen if you decide not to grant this Authorization?
If you decide not to grant this Authorization, you will not be included in this research study. Refusal to grant this Authorization will not result in any loss of medical benefits to which you are otherwise entitled.

(9) Can your PHI be disclosed to parties not included in this Authorization who are not under the HIPAA requirements?
There is a potential that your research information could be shared with another party not listed in this Authorization in order to meet legal or regulatory requirements. Examples of persons who may access your PHI include representatives of the Food and Drug Administration, the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), and the DHHS Office for Civil Rights. This disclosure is unlikely to occur, but in that case, your health information would no longer be protected by the HIPAA Privacy Rule.

(10) Who should you contact if you have any complaints?
If you believe your privacy rights have been violated, you may send a written complaint to the WRNMMC Privacy Officer, located at 8901 Wisconsin Avenue, Bethesda, MD 20889-5600, telephone: 301-319-4775. Your signature at the end of this document acknowledges that you authorize WRNMMC personnel to use and disclose your Protected Health Information (PHI) collected about you for the research purposes as described above.

19. CONTACTS FOR QUESTIONS ABOUT THE STUDY

If you have questions about the study, you should contact either the Principal Investigator or the Research Protocol Coordinator at (301) 295-8556.

20. OTHER FUTURE RESEARCH FOR WHICH YOUR BLOOD SAMPLES TAKEN COLLECTED DURING THIS STUDY COULD BE USED

Please read carefully each sentence below and think about your choices. After reading each sentence, **circle** "yes" or "no", include the date and your initials. If you have any questions please talk to your doctor or a research team member.

BY SIGNING THIS FORM, YOU ARE AGREEING THAT:

a. My serum (blood) samples and clinical data may be kept for use in future research to learn about, prevent, detect, or treat breast cancer, and to better understand how certain genes relate to breast cancer.

YES NO Participant's Initials _____ Date _____

b. The principal investigator (or someone he or she chooses) may contact me in the future to ask me to take part in future research.

YES NO Participant's Initials _____ Date _____

SIGNATURE OF STUDY PARTICIPANT

I have read (or someone has read to me) the information in this consent form. I have been given a chance to ask questions and all of my questions have been answered to my satisfaction.

BY SIGNING THIS CONSENT FORM, YOU FREELY AGREE TO TAKE PART IN THE RESEARCH IT DESCRIBES.

_____

Participant's Signature Date and time

_____ _____ _____

[First name, MI, Last Name]
Participant's **Printed** Name

A signed copy of this consent form will be provided to you.

SIGNATURE OF RESEARCH TEAM MEMBER OBTAINING CONSENT

My signature is intended to attest that the information in the consent document and any other information was explained to and apparently understood, by the subject that questions and concerns were addressed, and that informed consent was freely given.

_____

Printed Name of Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent | Date and time (must be same as subject)

ATTACHMENT 5:
Tissue Protocol
(3 May 2017)

EIRB Protocol Template (Version 1.1)

1.0 General Information

* Please enter the full title of your study:

Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease

* Please enter the Protocol Number you would like to use to reference the protocol:

20704

* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study

Primary Dept?	Department Name
◉	P and R - Walter Reed National Military Medical Center (WRNMMC)

3.0 Assign project personnel access to the project

3.1 * Please add a Principal Investigator for the study:

CRAIG DAVID SHRIVER, MD

Select if applicable

☐ Student ☐ Department Chair ☐ Resident ☐ Fellow

If the Principal Investigator is a Student, Resident, or Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Jeffrey A Hooke

Associate Investigator

JOEL T MONCUR

Associate Investigator

Denise Marchand Thigpen

Associate Investigator

B) Research Support Staff

KAY FRANCES KELLEY

Research Coordinator

Julie Clyman Lee

Team Member

Sara Denman Sakura

Research Coordinator

Marianne V Spevak, BSHS

Team Member

Robert Stewart

Department Representative

3.3 Please add a Protocol Contact:

CRAIG DAVID SHRIVER, MD

Sara Denman Sakura

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Philip Perdue

Department Chair

CRAIG DAVID SHRIVER, MD

Department Chair

Robert Stewart

Department Chair

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 Is this a research study?

◉ Yes ○ No

4.2 What type of research is this?

☑ Biomedical Research
☐ Clinical trial (FDA regulated)
☐ Behavioral Research
☐ Educational Research
☐ Psychosocial Research
☐ Oral History
☐ Other

4.4 Is this human subjects research (Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects) and DoDI 3216.02)?

◉ Yes ○ No

4.5 Do you believe this human subjects research is exempt from IRB review?

○ Yes ◉ No

5.0 Personnel Details

5.1 Will you have a Research Monitor for this study?

○ Yes
○ No
◉ N/A

Research Monitor Role:

If applicable, you may nominate an individual to serve as the Research Monitor:

	Selected Users
No Users have been selected.	

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount		
No records have been added.				

Total amount of funding:

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

8.0 Study Locations

8.1 Has another IRB reviewed this study?

○ Yes ◉ No

8.2 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

○ Yes ◉ No

9.0 Study Details

9.1 Abstract/ Summary:

Summarize the proposed study in 500 words or less, to include the purpose, the subject population, the

study's design type, and procedures

Purpose

Although there have been remarkable improvements in breast cancer diagnosis and management, most of the complex molecular mechanisms associated with the onset, progression and/or severity of breast cancer are still not well understood. The Clinical Breast Care Project (CBCP) is a congressionally mandated and funded military-civilian collaboration between Windber Medical Center (WMC) in Windber, PA, Walter Reed National Military Medical Center (WRNMMC) Bethesda, MD, and the U.S. Army Medical Research and Material Commend (USAMRMC) in Fort Detrick, MD. As part of the CBCP, we propose to carry out molecular, biochemical and histologic analysis of breast tissue and/or blood to provide more insights on the molecular mechanisms that may be relevant in breast cancer development and breast diseases.

Research Design

The proposed study is designed as a minimal risk, prospective acquisition and archiving of patient serum, leucocytes, and breast tissue removed in the course of diagnostic, therapeutic or elective treatment, but not otherwise required for diagnostic or therapeutic purposes. Portions of these tissues will then be analyzed for global expression pattern screening analyses utilizing high-throughput genome and proteome research technologies, the results of which will be analyzed using standard bioinformatics tools.

Methodology /Technical Approach

The population for this study includes military health care beneficiaries over the age of 18 years presenting with the diagnosis of breast cancer or any radiologic or clinical breast lesion requiring biopsy or tissue diagnosis.

In 2014, 253 patients who presented to WRNMMC's Breast Care Center received a surgical procedure (including biopsy or other tissue diagnosis). Based on CBCP study subject enrollment in recent years, we anticipate continued study accrual of about 200 patients per year.

Tissue and blood samples for this study will be obtained from two general subject groups:

1) Consenting adult patients presenting to the Breast Care Center or the Women's Imaging Center of the WRNMMC with known breast cancer,
2) Consenting adult patients presenting to the Breast Care Center or the Women's Imaging Center of the WRNMMC with evidence of breast disease requiring clinical need for some form of tissue biopsy.

As stated in the informed consent form for this protocol, study procedures will apply for the subject's current and all subsequent surgeries related to their breast disease, unless they withdraw from the study.

9.2 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

9.3 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Literature Review

Breast cancer is the second leading cause of cancer-related deaths in American women and the most common cause of cancer-related deaths between the ages 15 and 54[1]. The National Cancer Institute's

Surveillance, Epidemiology and End Results (SEER) program reported that 32% of all malignancies among women are breast cancer (1). Over the past forty years the incidence rate of breast cancer has been steadily increasing worldwide with a rate of one to two percent per year in the United States. The American Cancer Society estimated that 192,370 new invasive cases of breast cancer were diagnosed in the USA in the year 2009, as well as an estimated 62,280 additional cases of in situ breast cancer. With this high incidence rate, even small improvements in treatment could represent tens of thousands of lives saved every year. For a systematic study of breast disorders, a large supply of good quality breast tissue specimens is needed.

The success of research translating to the clinic will partly depend on the availability of good quality and well characterized biospecimens from consented donors. These specimens will allow scientists to study the development and progression of diseases at the molecular level. The establishment of dedicated research biobanks as the source of biospecimens by academic and private companies is playing a significant role in biomedical research. The desire to find a cure for breast cancer has spurred increased interest in breast tumor tissue banks across the United States and Canada. One example is the National Institute of Canada-Manitoba Breast Tumor Bank Project that was established in 1993. This tumor bank provides a national resource consisting of a pre-assembled data set of matched samples of paraffin-embedded and frozen tissue with corresponding pathological and clinical data[7]. In the first three years of operation, the bank accrued over 1,000 cases and has provided support for 20 research projects in 16 laboratories in Canada. As of 2014, the CBCP biobank holds more than 57, 000 biospecimen that have been donated by over 6, 000 donors. The biobank has provided CBCP scientists with good quality and well-annotated specimens which have led to a long list of peer reviewed research activities. These breast specimens have also been utilized for the NCI funded TCGA (The Cancer Genome Atlas) project which resulted in ground breaking breast cancer research.[8]

High throughput gene and protein evaluation through techniques such as microarrays, mass spectrometry and next-generation sequencingis on the forefront in the battle to understand the mechanisms associated with breast cancer development, progression and severity.These techniques require high-quality genomic (blood) and tissue specimens to identify DNA variants, and gene and protein expression level differences in diseased compared to non-diseased patients and specimens.

To draw any useful conclusions concerning the association between molecular alterationsand disease, it is necessary to analyze a large number of good quality samples from many patients with similar clinical characteristics and well-documented case history.This protocol aims to establish a blood and tissue repository that will provide good quality specimens for studies aimed at identifying molecular, biochemical, and histologic mechanisms associated with breast cancer and its development.

The ability to analyze entire genomes and/or thousands of genes and proteins simultaneously has many potential impacts. It allows researchers to study the gene's relationship to breast cancer and to understand the pathways of disease development and progression. These discoveries will enable researches to develop novel drugs targeting disease pathways and disease-specific targets. Additionally, research application of these technologies may yield more specific and clinically relevant classification and subtyping of breast disease.

We aim to create a large library of fresh and formalin-fixed paraffin-embedded (FFFE) breast tissue, and analyze it with high-throughput technologies in our CBCP laboratories. This tissue will be collected as part of that obtained during the course of clinically required treatment for breast disorders or other clinically indicated breast surgeries. This would provide us with the resources to study the evolution of breast disease from normal epithelium to cancerous tumor at the genetic level. A concomitant blood library will be used by our functional genomics and proteomic laboratory to investigate gene and protein marker expressions in patients with various forms of breast disease, and in those patients at above average risk for developing breast cancer (Risk Reduction Clinic patients). The biologically relevant information generated from the laboratory will then be linked with our clinical database to identify and/or understand associations between biological properties of the tissue and clinical presentations. Such a multidisciplinary, linked database will enable researchers and clinicians to follow patients longitudinally, and ultimately will facilitate the correlation between discoveries made in the lab and patient care.

The current standard of care for treating breast diseases and breast cancer is based on a multidisciplinary model that integrates prevention, screening, diagnosis, treatment, and continuing care. The CBCP is modeled after this multidisciplinary approach. However, the CBCP is unique in its field. It incorporates advances in breast cancer risk reduction, informatics, tissue banking, and research. The present protocol represents one aspect of this integrated approach. It will interdigitate and synergize with the clinical, informatics, and research components of the CBCP, to achieve the overall objective of improving breast care and reducing the morbidity and mortality associated with breast disease.

In 2002, a panel of microsatellite markers was developed to assess allelic imbalance (AI) at the 26 most

commonly altered regions in breast cancer. This panel was used to investigate how tumors develop and progress. For example, this panel was applied to 42 columnar cell lesions (CCL) and 31 atypical ductal hyperplasias (ADH), both non-neoplastic diseases of the breast. Of note, we assessed genetic changes only in pure CCL and ADH without concomitant DCIS or invasive breast cancer (IBC). This approach was quite different than the then current body of literature that had evaluated synchronous non-neoplastic lesions and, based on shared genetic changes between the neoplastic and non-neoplastic diseases, suggested that CCL and ADH were non-obligatory precursors to DCIS/IBC. Our study was one of the first to look at pure CCL and ADH, and unlike the other studies, we found very few genetic changes, suggesting that these lesions are genetically naïve and that earlier models of progression based on synchronous lesions may not accurately reflect tumor progression[14].

In contrast, the 100 pure DCIS lesions we assayed shared many of the same alterations found in IBC, suggesting that DCIS lesions are genetically advanced[15]. We also found that low-grade DCIS and IBC are genetically distinct from high-grade DCIS and IBC, based largely on high rates of loss of chromosome 16q in low-grade disease and high rates of alterations at 9p21, 11q23, 13q14, 17p13.1 and 17p12[16, 17]. These data suggest that high-grade disease does not progress from low-grade disease but rather that low- and high-grade disease are distinct diseases.

CBCP has been investigating molecular changes in the tumor microenvironment. Tumor epithelial and corresponding adjacent stroma < 850 m from the tumor were laser microdissected from 30 formalin-fixed, paraffin-embedded tumor specimens and evaluated using the allelic imbalance panel. Discordant patterns of LOH/AI between epithelial and stromal components were detected such that hierarchical clustering samples from the same patient rarely clustered together[18]. In a second study evaluating LOH/AI data generated from archival breast quadrants from 21 patients who underwent mastectomy, levels of LOH/AI were significantly higher ($P<$ 0.05) in the tumor-adjacent (15.4%) compared to distant (3.7%) tissues, suggesting that chromosomal alterations in stroma close to the tumor may promote tumorigenesis[19]. These data lead to the invitation to write review papers for *Lancet Oncology* and *Expert Reviews in Molecular Diagnosis*[20, 21].

We have also had an interest in health care disparities between Caucasian (CW) and African American women (AAW) with breast cancer. Enrollment of patients within the DOD health-care system affords us the opportunity to evaluate clinical, epidemiological and molecular differences in patients treated within an equal-access health-care system, thus minimizing the impact of disparate access to quality-health care seen in the general population. Recruitment of African Americans into the Clinical Breast Care Project (CBCP) has been effective: in 2007, 25% of the patients enrolled were self-described AAW[22]. No differences in education levels, breast health practices (e.g., self-breast exam, routine screening mammograms) or reproductive histories were seen between AAW and CW with invasive breast cancer, however, AAW were more likely to use oral contraceptives, less likely to use HRT or to breastfeed and were more likely to be obese and have extremely high fat-intake. Breast tumors from AAW were also more likely to be diagnosed at a younger age, and are larger, more frequently ER negative and/or triple negative, and of higher grade. Evaluation of gene expression patterns between AAW and CW matched by age, grade and ER status revealed differentially expression of 23 genes, suggesting that tumors from AAW and CW are molecularly different and these differences may contribute to the less favorable outcome in AAW[23].

We have also performed a number of studies to determine the molecular mechanisms of metastasis. Using our AI panel, we evaluated patterns of chromosomal changes in primary breast tumors and matched metastatic lymph node tumors and found disparate patterns of alterations between the two tumor types, suggesting that metastatic cells diverge early in tumorigenesis[24]. A follow-up study evaluated genetic changes between primary tumors (n=26) and multiple lymph node tumors (n=146) to determine how metastasis spreads. Divergent patterns of chromosomal alterations were seen between lymph nodes and the primary tumor, but also between metastatic lymph node tumors from the same patients. This genetic heterogeneity may impact response to adjuvant therapy, recurrence, and survival, and thus may be important to improving clinical management of breast cancer patients[25]. Gene expression analysis was also performed on primary breast tumors and matched metastatic lymph node tumors to improve our understanding of the metastatic process. Fifty-one genes were differentially expression ($P< 1x10^{-5}$, >2-fold differences). Genes expressed at higher levels in the primary tumors were involved in degradation of the extracellular matrix, enabling cells with metastatic potential to disseminate, while genes expressed at higher levels in metastases were involved in transcription, signal transduction and immune response, providing cells with proliferation and survival advantages. These data improve our understanding of the biological processes involved in successful metastasis and provide new targets to arrest tumor cell dissemination and metastatic colonization[21]. Evaluation of primary tumors from patients with metastases and those without has also been performed; however, in this study we were unable to identify a molecular signature that could

effectively classify the two types of tumors[26]. The inability to derive molecular profiles of metastasis in primary tumors may reflect tumor heterogeneity, paucity of cells within the primary tumor with metastatic potential, influence of the microenvironment, or inherited host susceptibility to metastasis[27].

Biomedical Informatics (BMIX) has been focused on: 1) development and implementation of an infrastructure system that supports the acquisition, storage, and maintenance of the clinical and molecular data generated in the study, and 2) application of existing algorithms and methods, and development of new ones as needed, for biomedical informatics research as well as for supporting other scientific research in the study. Our work has resulted in an advanced and recognized infrastructure system that supports translational research[28, 29], a number of peer-reviewed publications and conference presentations, and competitive extramural funding. The following is a high-level summary of the activities and achievements in BMIX.

Quality Control (QC) and Quality Assurance (QA). To obtain high-quality data we have developed a set of QA programs, and many of the QC/QA procedures have been embedded into our SOPs. For example, the clinical QA program consists of: 1) a visual inspection of missing values and obvious inconsistencies, 2) double data-entry to reduce data entry errors, 3) a computer program named QAMetrics that deploys established QA rules to check for data integrity across the whole questionnaire, and 4) a web-based QA Issue Tracking system to enable efficient communications between WRI and the clinical sites for resolving QA problems of the clinical data[30-33]. In addition, we have developed a microarray QA program to identify outlier arrays from a population of similar arrays[34, 35]. Additional QA programs have been developed or are in development to ensure the quality of the data generated at WRI. These QA programs are evolving as data collection and generation technologies develop.

The Laboratory Information Management System (LIMS). A LIMS is needed to track and manage the sheer volume of data involved in translational research. Our clinical and tissue banking activities are tracked by the Clinical Laboratory Workflow System that we co-developed with Cimarron Software that was deployed in 2004[36]. To support the evolving needs of breast cancer studies, we are now in the process of developing a replacement system of the CLWS using up-to-date IT technologies. Through the years of practice, we concluded that for tracking the lab experimental activities, a lightweight LIMS is most appropriate, recording experimental results and essential information that is needed for experimental results interpretation. We plan to develop such a lightweight system after the replacement system of the CLWS is developed.

The Data Warehouse for Translational Research (DW4TR). We have developed the DW4TR to integrate internally collected and generated clinicopathological data and molecular data from all the platforms. The development is done with our IT development partner, InforSense Ltd (currently part of IDBS). We have developed an innovative patient-centric, modularly-structured data model for clinicopathologic data, which contains disease-independent and disease-specific submodules to enable easy expansion to support the study of new diseases. A specimen-centric data model has been developed for molecular data. We have also developed a temporal data model to resolve the problem of the temporal information alignment between the data and specimens that were collected at multiple points of the time. The DW4TR has two major intuitive interfaces, one is the Aggregated Biomedical-information Browser and the other is the Individual Subject Information Viewer. The DW4TR has successfully supported the Clinical Breast Care Project with a total of 799 data elements, and has been expanded to support additional translational research programs[37-40].

Other Applications: We have developed a Biomedical Informatics Portal, using the InforSense analytical workflow platform, to host additional applications deployed or developed by us to facilitate integrative biomedical research. For example, we have developed a specimen selection tool for scientists to use to select specimens in our tissue bank using the temporal and other information in the DW4TR[41]. The user can specify the inclusion/exclusion criteria. We have also developed a Data Correction Utility to enable correction of data errors in the DW4TR.

Research: Our research focuses on clinicopathologic risk factors of breast cancers, biomarker identification, and mechanistic understanding of primary and metastatic breast cancer, and we do so mostly by applying existing data mining methods[42, 43]. We also have developed new algorithms and visualization tools for clinicopathologic risk factor analysis, and reported interesting new breast disease co-occurrence patterns among other findings[44-50]. We found ethnicity-specific benign breast disease co-occurrence with breast cancer[51, 52], reported different characteristics of invasive breast cancer between Caucasian and African American women[53], and identified subtype-specific clinicopathologic properties of breast cancers[54, 55]. We worked closely with laboratory scientists in identifying biomarkers of breast cancer and breast cancer metastasis, and used bioinformatics tools to seek mechanistic understanding of breast cancer development and metastasis[56-58], and we collaborated with external scientists as well in study human diseases[59, 60]. In performing a peripheral blood gene expression analysis, we have identified differential enrichment of signaling pathways between breast cancer patients and normal subjects[61]. In another project

using breast cancer tissues we have identified significant difference between lymph node positive and lymph node negative cases in a carefully stratified population. We also performed a transcription factor-centric computational analysis of genes differentially expressed in healthy breast tissues from African American and Caucasian women[62]. We used the semantic similarity measures to characterize human metabolic and regulatory pathways which will help us to understand human disease development mechanisms[63, 64].

Preliminary Data and/or Findings.

Please see section 9.3 (Background and Significance)

Scientific Justification.

The rapid advances in basic research and data mining technologies fuels a growing demand for tissue banks. Technologies such as polymerase chain reaction (PCR), microarray and proteomic technologies, and laser microdissection (LMD) has made it possible to examine gene expression in very small tumor samples and at high throughput. Tissue banks allow these researchers to test their hypotheses rapidly and in a cost effective manner. By linking such molecular information to clinical data, we propose to translate knowledge from the laboratory to the clinic. These new technologies coupled with the information that can be generated with resources available in a tissue bank, will inspire researchers in the field of breast cancer to ask questions and develop hypotheses that 10 years ago were inconceivable.

Human Subjects Justification.

The purpose of using human subjects for this study is to prospectively collect human tissue and blood specimens in order to study breast cancer and disease.This minimal risk study is likely to yield important information about the risk factors, diagnosis, prognosis and treatment of breast disease. Please also see Section 3.1 (Medical Application).

9.4 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

As part of the CBCP, we propose to carry out molecular, biochemical and histologic analysis of breast tissue and/or blood to provide more insights on the molecular mechanisms that may be relevant in breast cancer development and breast diseases. To achieve this aim, a large supply and a wide variety of good quality tissue samples is needed. Unfortunately, good quality donor breast tissue samples are extremely scarce and when available is often not backed by a comprehensive medical history and/or not a good representation of the target population or study area. The non-availability of a steady and consistent supply of good quality breast tissue samples limits the systematic analysis of tissues and negatively impacts the generation of biologically useful information in the laboratories and in clinical practice. The objectives of this project are therefore:

1.
Acquisition and banking of breast tissue, lymph nodes, and/or blood from informed and consenting donors,
2.
Experimental analysis of DNA, RNA and/or proteins isolated from donor tissues for molecular, biochemical, and/or histopathological analysis,
3.
Establishment of standardized procedures for tissue collection, processing and storage through biospecimen science research activities. This research data will feed evidence based standard operating procedures of the biobank and will allow the maintenance of the biospecimen integrity throughout the biospecimens' life-cycle.
4.
Establishment of an integrated and relational database for human biospecimens studied and patient clinical characteristics that will provide the resources necessary to achieve the following future goals:

1. Identify single nucleotide polymorphisms (SNPs) present in DNA from diseased breast tissue (as defined by histologic criteria) as compared to breast tissue without disease, lymph nodes with and without metastatic deposits, and/or DNA derived from patient leucocytes
2. Identify differences in mRNA and protein expression associated with breast disease (as defined by histologic criteria) as compared to normal breast tissue and lymph nodes with and without metastatic deposits
3. Correlate SNPs and differences in mRNA and protein expression associated with diseased breast and nodal tissue (as defined by histologic criteria) with the corresponding clinical patient database
4. Identify factors within patient serum, plasma and/or blood-derived cellular components that correlate with patient risk factors or clinical status as defined in the corresponding clinical patient database.

9.5 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data/specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

The proposed study is designed as minimal risk, prospective acquisition and archiving of patient serum, leucocytes, and breast tissue removed in the course of diagnostic, therapeutic or elective treatment, but not otherwise required for diagnostic or therapeutic purposes. Portions of these tissues will then be analyzed for global expression pattern screening analyses utilizing high-throughput genome and proteome research technologies, results of which will be analyzed using bioinformatics tools. Informed patient consent for archiving and later experimental use will be obtained prior to procedures involving tissue removal. The tissue will be handled and processed for archiving under the supervision of a licensed pathologist, and the remaining tissue will be coded and released for archiving only after all diagnostic tissue needs have been satisfied as determined by the supervising pathologist. Blood samples will be obtained (as described in

section d). Each patient will be assigned a unique, 9-digit coded identifier (CBCP number) and all associated tissue, serum, and/or blood samples to be archived will be assigned an 8-digit barcode. Both the CBCP numbers and the corresponding sample barcodes will be registered into the clinical database. Under separate approved protocols (WRNMMC IRB#20704 and WRNMMC IRB#20705) a clinical database continues to be maintained which describes the characteristics of the blood and tissue donors. Linkage between the patient and research samples will be kept in a password protected-limited access database and in individual patient records held in gang-locked cabinets.

Tissues will be employed for molecular, biochemical and histological investigations that will be generally described to the prospective patients at the time of counseling for the tissue bank. Portions of these tissues will be used for DNA and RNA sequencing analysis, including but not limited to whole-exome and whole genome sequencing, targeted gene analysis, and single-cell sequencing. Portions of these tissues will also be used for global expression pattern screening analyses utilizing high-throughput genomic and proteomic research technologies. These molecular biologic investigations will be carried out at the CBCP's research facility, Windber Research Institute, located in Windber, PA. Along with the global genome and proteome expression profiling studies, other CBCP sponsored studies and collaborations with outside organizations utilizing CBCP tissue and blood-based specimens will be defined, reviewed and approved per the scientific (clinical and basic science) leadership of the CBCP. These additional studies will be supported by separate research protocols and collaborative agreements in compliance with WRNMMC IRB regulations and guidelines.

All specimens will be held in CBCP freezers for up to an indefinite period of time into the future. Exceptions to this will occur when specimens are exhausted (consumed) due to their use in the approved research within CBCP labs and elsewhere, or when previously consented patients withdraw their consent, at which time that patient's specimens will be withdrawn from the repository and destroyed. Specimens are carefully monitored for the amount of each sample remaining, and a "No Further Use" block is placed on the specimen when it reaches a minimum threshold. The PI would make the final decision as to whether the last remaining sample would be utilized further for research. The CBCP PI is responsible for maintaining the integrity of the tissue bank, and all databases. In the event that the named PI leaves WRNMMC, another WRNMMC investigator will be named (through in-place processes), and that new CBCP PI will take full responsibility for the banked samples and data. If under any circumstance a new CBCP PI is not named, then the WRNMMC Institutional Review Board (IRB) will be notified, and the IRB will determine the disposition of this tissue and blood library.

1. Methodology:

The approach to sample and data collection is as follows, based on the following study subject groupings (corresponding to the subject groups in section 2.3 above).

a. Patients already diagnosed with breast cancer: This group will consist of patients who already have undergone a breast biopsy of any type, at WRNMMC or at another institution (after confirmation of the pathology diagnosis at that other institution), with a confirmed cancer diagnosis that requires further surgical therapy as per the consensus recommendation of the multidisciplinary breast conference.

b. All consenting adult patients presenting to the Breast Center or the Women's Imaging Center at WRNMMC with evidence of breast disease for which a breast tissue biopsy (to include ductal lavage, open breast biopsy, tru-cut biopsy, image-directed biopsy) is clinically indicated. After consent is obtained, patients will be prepared for procedure or surgery.

2. Sample and Data Collection and Processing:

The following sample and data collection procedures will be followed for the study participant's current and all subsequent surgeries related to their breast disease for the duration of their participation in the study.

a. At the time of initial consent for this research study, or prior to the patient's initial surgical procedure, up to 20 cc of blood will be obtained via a peripheral venous access. At the time of any subsequent surgical procedures, up to 20 cc of blood may also be drawn for this research study. In the absence of a new event relating to the patient's breast disease that requires surgery, the patient will have up to 20 cc of blood drawn, at least annually, during their routine follow-up visits with their clinician.

b. Once the patient's breast tissue is surgically removed, as clinically indicated, the specimen(s) will be taken to the pathology laboratory where a licensed pathologist will ensure that the tissue is adequate for routine pathology analyses (diagnosis, margin status assessment, and other indicated purposes). Then and only then, if any actual excess tissue (cancerous or benign) remains, samples of that tissue will be harvested for archiving in the tissue bank. This archival tissue will be divided and preserved

using several methods: the tissue will be OCT embedded in a cryomold and frozen on dry ice, the tissue will be placed in a vial and flash-frozen in liquid nitrogen, and/or the tissue will be placed in a tissue cassette for paraffin embedding.

c. The OCT-embedded and flash-frozen tissue samples will be labeled with an 8-digit coded identifier and placed into the CBCP Tissue Bank freezer at temperatures -80C pending shipment to WRI.

d. Blood samples will be fractionated into their components using a centrifuge. The blood components will be aliquotted into labeled cryovials and placed into the -80C freezer.

e. This tissue will remain in the freezer at the breast care center laboratory site for at least a two-week period of time, or longer if needed to fulfill the requirement set in section (ii) below. During this time, no analyses will be performed on the specimen; this period of time will be known as the "Fail-Safe" time period. The Fail-Safe time period is intended to allow the diagnostic pathologists the opportunity to withdraw banked tissue for any additional diagnositic testing they determine is necessary to patient care.

f. After the pathologist determines with final certainty, by the publishing of the official final pathologic report with no outstanding addenda, that there is no diagnostic pathologic requirement for the frozen specimen(s), then the archived specimen(s) on that patient (identified only by a unique 8-digit barcode) will be released to the CBCP for research analyses. This will include transfer of the tissues to offsite locations for specialized studies (to include functional genomics, proteomics analyses). Similarly research-collected FFPE tissue will be appropriately labeled and transferred to offsite facilities for immunohistochemical analysis and tissue microarray construction.

g. The blood components will, after appropriate labeling and removal of all patient identifiers, linked only to the patient via a unique coded identifier be transferred to WRI CBCP offsite research facility for genomic and proteomic analysis.

Data Collection

Either at the time of initial visit and consent to this protocol, during recovery from surgery or at a follow up visit, a CBCP research team member will assist the patient in completing a Case Report Form (CRF). This form contains study participant information such as study ID number, demographics, lifestyle factors, medical history, family history of cancer, pathology, diagnosis and treatment.

Certain sections of this form will be completed by a clinician in consultation with the patient's medical records; the time required for the patient to respond directly to CRF items will be approximately 15 minutes or less. Study participants will be asked to confirm and update the information in the CRF on an annual basis during subsequent visits to the Breast Center as recommended by their treating physician. If a CRF is not fully completed during patient appointments, a Breast Center clinician may contact the patient by telephone (with patient's verbal permission) and/or consult the patient's medical records to obtain information to complete the CRF. A CBCP study team member will periodically consult the study participant's medical records to update CRF data for the duration of the study subject's participation in the study.

3. Primary Uses of the Biopecimens (Data Analysis Plan):

The known primary uses under this protocol for the acquired tissues and serums/blood fall into six major subsections listed below. Additional topics of investigation for internal (CBCP) and external (CBCP collaborations with outside institutions) will be identified and approved by CBCP leadership and supported as required by separate research protocols and collaborative agreements in compliance with WRNMMC IRB guidelines.

a. Tissue Banking – this includes sample definition and receiving, freezing/labeling/storage, OCT (Optimal Cutting Temperature) embedding, labeling (putting identifier codes on each tissue sample for subsequent tracking/storage), and inventory/tracking. The inventory and tracking of all samples will be done electronically with unique identifiers (8-digit barcodes) using Clinical Laboratory Workflow System (CLWS), which tracks each specimen throughout its lifetime in the repository.

b. Imaging/Microscopy – after sample definition, receiving, and fixation fluorescence in situ hybridization (FISH) will be performed on tumor samples. Laser microdissection (LMD) will be performed by our LMD-trained CBCP pathologist/Histologists (trained at NCI in laser capture microdissection) RNA will be isolated from laser captured material and utilized for down stream processes such as cDNA synthesis, array analysis, and in-situ RT-PCR. Image acquisition will be performed on digital microscopes and images archived in the CBCP server(s) and/or data warehouse.

c. Gene Expression Profiling – RNA will be extracted from tissues using various kits as appropriate to the storage conditions of the tissues (i.e., flash frozen, OCT, and FFPE tissues and PAXGene blood samples). RNA will be used for Northern Analysis, RT-PCR, and mRNA expression analysis using Affymetrix arrays and in future RNA Seq analysis.

d. Sequencing –Traditional and next-generation sequencing approaches are performed on genomic DNA from diseased tissues, histologically normal tissues, and blood.

e. Genotyping – Tissues/blood will undergo DNA quantification followed by PCR set-up, thermal cycling, SNP (single nucleotide polymorphism) reaction clean-up, capillary electrophoresis set-up, genotype calling, and genotype QC. Genotyping is also performed using Affymetrix arrays.

f. Protein Expression Analysis– Current mass spectrometry analysis will be conducted for protein identification and quantification.

At the end of each of the above six laboratory workflows, the data will be QA'd, analyzed using powerful genomics/proteomics software tools, and placed into the CBCP database / data warehouse. QA of the data involves using software tools that interrogate the fields of the data that come out of the workflow stations, to ensure the data has consistency and is within expected or known ranges; any data found to be outside of expected ranges is not necessarily flawed, but is then identified for closer analysis by researchers.

CBCP Resource Utilization Oversight

The CBCP Scientific and Data Review Committee provides internal review and oversight for all CBCP research protocols and projects, as well as CBCP budgetary oversight, review and approval. This committee includes members from WRNMMC, Windber Research Institute and the Henry Jackson Foundation. All requests to utilize CBCP tissue and blood specimens and/or data, either for internal CBCP protocols or collaborations with outside organizations, require the completion of the WRI-CBCP Project/Sample Approval Form. This form must be reviewed, approved and signed by the CBCP PI and CBCP Scientific and Data Review Committee before new CBCP research studies can begin.

9.6 Target Population:

Describe the population to whom the study findings will be generalized

Please see legacy protocol.

9.7 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

One of the major challenges facing researchers and clinicians today is to understand the mechanisms associated with the evolution of benign breast disease and/or transition of breast disorders to breast cancer. The creation of a comprehensive tissue/blood bank is essential to the application of modern molecular and genetic analysis of breast diseases. Amongst other goals, this entire (overall CBCP) project will: (a) establish a repository of high quality breast tissue and related (lymph nodal, blood) specimens for research on breast cancer and associated breast diseases, and (b) Permit the establishment of a single relational database with accurate and comprehensive biologically and clinically relevant information on breast diseases. Since the standard of care for treating breast diseases and breast cancer is based on a multidisciplinary model that integrates prevention, screening, diagnosis, treatment and management, this CBCP project will provide the necessary framework for such an integrated approach, which will positively impact the future management of breast cancer.

10.0 Study Procedures and Data management

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

The population for this study includes military health care beneficiaries over the age of 18 years presenting with the diagnosis of breast cancer or any radiologic or clinical breast lesion requiring biopsy or tissue diagnosis.

In 2014, 253 patients who presented to WRNMMC's Breast Care Center received a surgical procedure (including biopsy or other tissue diagnosis). Based on CBCP study subject enrollment in recent years, we anticipate continued study accrual of about 200 patients per year.

Tissue and blood samples for this study will be obtained from two general subject groups:

1) Consenting adult patients presenting to the Breast Care Center or the Women's Imaging Center of the WRNMMC with known breast cancer,

2) Consenting adult patients presenting to the Breast Care Center or the Women's Imaging Center of the WRNMMC with evidence of breast disease requiring clinical need for some form of tissue biopsy.

As stated in the informed consent form for this protocol, study procedures will apply for the subject's current and all subsequent surgeries related to their breast disease, unless they withdraw from the study.

Anticipated start date: 2002

Anticipated completion: Indefinite

Study procedures ongoing

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, how the data will be operationally measured, and approvals needed for use of information from DoD databases

a. Method of Data Collection from Study Participants.

The main objective of this tissue banking and analysis initiative is to collect tissue, along with biological and clinical data, prospectively from all informed and consenting patients enrolled in the tissue repository protocols of the CBCP. Patient data will be collected in a Case Report Form including items such as demographics, lifestyle factors, family history of cancer, medical history, and diagnostic, pathologic and treatment information.(See CRF in Appendix 1). It is emphasized that all tissue samples will be coded and all direct patient identifiers of the tissue and/or serum, as well as of the database itself, will be removed from them. All tissue and data will be identified in the research arenas by a "CBCP number," which will be a unique, 9-digit, individual patient-specific number. This CBCP number will be linked to all patient items via barcoding of samples and questionnaires. Connection between the "CBCP number" and the patient identifiers are located in two places: in patient files, maintained by CBCP laboratory personnel, which will be kept in a gang-locked file cabinet, and in a password-protected, limited-access, secure database to which the Research Protocol Coordinator, pathology, and data team have access. There will be no way for researchers anywhere along the chain of tissue, serum, or data collection or analysis, to identify the actual identity of the patient via the barcodes or CBCP number. Other researchers within the CBCP or associated with the CBCP who have permission to use the blood or tissue samples may also have access to the clinical information (indeed, this linkage is what makes the tissue bank so powerful as a research tool); however, this linkage will not involve the patient's name, so no researchers will ever know the identity of the specimen's origin. Other identifiers, i.e., date of birth, date of death, date of surgery, etc. may be identified to researchers pending a separate IRB approved protocol.

The data collection instruments and protocol that will accompany the tissue of the diagnosed breast cancer patients and patients not diagnosed with breast cancer, but requiring clinically-directed tissue biopsies of any type, or elective reduction mammoplasty were previously submitted to the former WRAMC DCI, and were IRB-approved in December 2000 (WU# 00-2006).

Other institutions are intended to join in this protocol. These other sites will be both military and civilian. As with multi-center protocols, a Principal Investigator will be responsible at each separate institution for overseeing the protocol, conforming the protocol and consent form to their own institutional IRB requirements, and for achieving their own institution's IRB approval prior to proceeding.

10.3 At any point in the study, will you request, use, or access PII from the Military Health System (MHS)?

(•) Yes ( ) No

10.4 Have you consulted with an MHS data expert to determine the data elements to be extracted or the information system(s) to access?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (dha.ncr.pcl.mbx.privacyboard@mail.mil)

( ) Yes, then complete the questions below according to the data consult
(•) No, then complete the questions below according to the best of your knowledge (NOTE: It is highly recommended that you work with an MHS data expert)

10.5 Indicate whether you plan to receive a data extract from the MHS or plan to access an information system directly to create a data set:

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

[ ] Data Extract
[x] Access

10.6 Do you intend to use only de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:

1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information

2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

( ) Yes (•) No

10.7 If your research study requires access to an MHS information system, please indicate the system to obtain data:

If you do not know which system(s) contain the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or seek guidance from an MHS data expert:

PHI Systems:

MHS Information System		Requesting Data	
:	AHLTA	:	Yes
:	CHCS	:	Yes
:	ESSENTRIS	:	Yes

PII-Only Systems:

MHS Information System	Requesting Data
No records have been added.	

De-Identified Data & Other Systems:

Information System	Requesting Data	
Expense Assignment System		
List other system(s):ACTUR (DoD Cancer Registry)	:	Yes
List other system(s):WRNMMC Radiology PACS	:	Yes

10.8 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ○ Yes, will merge data
- ◉ No, will not merge data

10.9 Indicate the categories of data that you will request from MHS systems or MHS health care providers about research participants or relatives, employers, or household members of the research participants.

Data Element(s)	MHS	Non-MHS Systems
1. Names		☐ null
2. Postal address with only town, city, state and zip code	☐ null	☐ null
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000	☐ null	☐ null
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death		☐ null
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of “age 90 or older”		☐ null
6. Telephone numbers		☐ null
7. Fax numbers	☐ null	☐ null
8. Electronic mail addresses	☐ null	☐ null
9. Social Security numbers (SSNs)		☐ null
10. Medical record numbers		☐ null
11. Health plan beneficiary numbers	☐ null	☐ null
12. Account numbers	☐ null	☐ null
13. Certificate/license numbers	☐ null	☐ null
	☐ null	☐ null

14. Vehicle identifiers and serial numbers, including license plate numbers		
15. Device identifiers and serial numbers	☐ null	☐ null
16. Web Universal Resource Locators (URLs)	☐ null	☐ null
17. Internet Protocol (IP) address numbers	☐ null	☐ null
18. Biometric identifiers, including finger and voice prints	☐ null	☐ null
19. Full-face photographic images and any comparable images	☐ null	☐ null
20. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)		☐ null

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

Study participants' social security numbers will be collected from MHS and ALTHA and retained in the CBCP database only for the purpose of confirming the identity of a study sample or CRF if a question arises. Social security numbers will not be requested on the study consent form and will not be attached to study samples or data collection instruments.

10.10 Is it possible that the data will become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would be using rank and race together to determine the identity of an individual with a particular health condition

Small cell size means that there are only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30 so the rank category may need to be expanded to include lower ranks

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 19 of Table 1 above, but that could be used to identify an individual. Examples of unique data elements include: 1) a unique number, such as a medical record number or EDIPN; 2) a unique code, such as a diagnosis code or a bar code on an electronic health record; and 3) any unique characteristic, such as the rank of general or admiral, or a race or gender combined with another unique characteristic

- ○ Yes, there is a reasonable possibility the data will become identifiable
- ◉ No, there is no reasonable possibility the data will become identifiable

10.11 HIPAA Privacy Rule and Use of Protected Health Information in Research:

- ○ N/A – will not use or disclose protected health information (PHI)
- ◉ HIPAA Authorization will be obtained
- ○ Use of a limited data set where a data use agreement will be obtained
- ○ Waiver/alteration of HIPAA Authorization is being requested

10.12 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

Please see Section 9.5

10.13 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed

Please see Section 9.5

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

Sample Size Estimation

No sample size justification is required as this is an open-ended tissue repository protocol, and will not undergo specific data analysis per se. However, we do have an expected (estimated) number of patients per year that will be enrolled at WRNMMC in the tissue protocols. We estimate that the number of patients newly diagnosed with breast cancer and treated at WRNMMC will average 132 per year.. The number of patients undergoing some form of a breast biopsy or tissue diagnosis for any reason at our institution averaged 272 over the last three years.

11.2 Sample Size Estimation:

Please see 11.1 text

11.3 Data Analysis Plan:

The known primary uses under this protocol for the acquired tissues and serums/blood fall into six major subsections listed below. Additional topics of investigation for internal (CBCP) and external (CBCP collaborations with outside institutions) will be identified and approved by CBCP leadership and supported as required by separate research protocols and collaborative agreements in compliance with WRNMMC IRB guidelines.

1.
Tissue Banking – this includes sample definition and receiving, freezing/labeling/storage, OCT (Optimal Cutting Temperature) embedding,labeling (putting identifier codes on each tissue sample for subsequent tracking/storage), and inventory/tracking.The inventory and tracking of all samples will be done electronically with unique identifiers (8-digit barcodes) using Clinical Laboratory Workflow System (CLWS), which tracks each specimen throughout its lifetime in the repository.

2.
Imaging/Microscopy – after sample definition, receiving, and fixation fluorescence in situ hybridization (FISH) will be performed on tumor samples. Laser microdissection (LMD) will be performed by our LMD-trained CBCP pathologist/Histologists (trained at NCI in laser capture microdissection) RNA will be isolated from laser captured material and utilized for downstream processes such as cDNA synthesis, array analysis, and in-situ RT-PCR.Image acquisition will be performed on digital microscopes and images archived in the CBCP

server(s) and/or data warehouse.

3.
Gene Expression Profiling – RNA will be extracted from tissues using various kits as appropriate to the storage conditions of the tissues (i.e., flash frozen, OCT, and FFPE tissues and PAXGene blood samples).RNA will be used for Northern Analysis, RT-PCR, and mRNA expression analysis using Affymetrix arrays and in future RNA Seq analysis.

4. Sequencing - Traditional and next-generation sequencing approaches are performed on genomic DNA from diseased tissues, histologically normal tissues, and blood.

5. Genotyping - Tissues/blood will undergo DNA quantification followed by PCR set-up, thermal cycling, SNP (single nucleotide polymorphism) reaction clean-up, capillary electrophoresis set-up, genotype calling, and genotype QC.Genotyping is also performed using Affymetrix arrays.

6.
Protein Expression Analysis– Current mass spectrometry analysis will be conducted for protein identification and quantification.

At the end of each of the above six laboratory workflows, the data will be QA'd, analyzed using powerful genomics/proteomics software tools, and placed into the CBCP database / data warehouse. QA of the data involves using software tools that interrogate the fields of the data that come out of the workflow stations, to ensure the data has consistency and is within expected or known ranges; any data found to be outside of expected ranges is not necessarily flawed, but is then identified for closer analysis by researchers.

12.0 Participant Information

12.1 Subject Population:

The population for this study includes military health care beneficiaries over the age of 18 years presenting with the diagnosis of breast cancer or any radiologic or clinical breast lesion requiring biopsy or tissue diagnosis.

In 2014, 253 patients presenting to WRNMMC's Breast Center received a surgical procedure (including biopsy or other tissue diagnosis). Based on CBCP study subject enrollment in recent years, we anticipate continued study accrual of about 200 patients per year.

Tissue and blood samples for this study will be obtained from two general subject groups:

1) Consenting adult patients presenting to the Breast Care Center or the Women's Imaging Center of the WRNMMC with known breast cancer,

2) Consenting adult patients presenting to the Breast Care Center or the Women's Imaging Center of the WRNMMC with evidence of breast disease requiring clinical need for some form of tissue biopsy.

Evidence of breast disease shall include potentially malignant breast lesions detected by mammography or ultrasound, palpable breast mass(es), abnormal breast discharge, abnormal physical breast morphology consistent with possible breast cancer, or axillary adenopathy without a known pre-existing condition. The far majority of patients will be female, however, 1% of all breast cancers occur in males and these male patients with breast cancer ("1" above), as well as males undergoing breast tissue biopsy ("2" above).

12.2 Age Range:

- ☐ 0-17
- ☑ 18-24
- ☑ 25-34
- ☑ 35-44
- ☑ 45-54
- ☑ 55-64
- ☑ 65-74
- ☑ 75+

12.3 Gender:

☑ Male
☑ Female

12.4 Special categories:

☐ Minors /Children - “You must also consider the requirements of 45 CFR 46 Subpart D and DoDI 3216.02, Enclosure 3, paragraph 7.d.”
☐ Students
☐ Employees - Civilian - “You must also consider the requirements of DoDI 3216.02, paragraph 7.e.”
☐ Employees - Contractor
☐ Resident/trainee
☐ Cadets /Midshipmen - “You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraphs 7.e. and 12.”
☐ Active Duty Military Personnel - “You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.”
☐ Wounded Warriors - “Depending on your intended subjects’ status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.”
☐ Economically Disadvantaged Persons - “You must also consider the requirements of 32 CFR 219.111(b).”
☐ Educationally Disadvantaged Persons - “You must also consider the requirements of 32 CFR 219.111(b).”
☐ Physically Challenged (Physical challenges include visual and/or auditory impairment)
☐ Persons with Impaired Decisional Capacity - “You must also consider the requirements of 10 USC 980.”
☐ Prisoners - “You must also consider the requirements of 45 CFR 46 Subpart C and DoDI 3216.02, Enclosure 3, paragraphs 7.b. and 7.c.”
☐ Pregnant Women, Fetuses, and Neonates
☐ Non-English Speakers
☐ International Research involving Foreign Nationals - Headquarters Review is necessary

12.5 Inclusion Criteria:

Order Number	Criteria
1	Military healthcare system beneficiary.
1	Adult over the age of 18 years.
1	Presenting to the Breast Center or the Women's Imaging Center of the WRNMMC with evidence of possible breast disease and scheduled to have part or all breast tissue removed as directed by WRNMMC physician.
1	Mentally competent and willing to provide informed consent.

12.6 Exclusion Criteria:

Order Number	Criteria
1	Patients with any other conditions for which invasive biopsy or surgery is medically contraindicated.
1	Minors under the age of 18.
1	Adult subjects with severe mental illness or other conditions that significantly impair memory, such as Alzheimer's disease.
1	Non-beneficiaries of the military healthcare system.

13.0 Recruitment and Consent

13.1 Identification and Selection of Subjects:

Please see Section 13.2

13.2 Recruitment Process:

During their clinic visit patients will be offered the opportunity to participate in our studies. Printed CBCP informational/recruiting brochures are displayed in the WRNMMC Breast Center clinic area, and a clinician will ask patients if they wish to discuss the study and the informed consent document after their medical appointment. If they choose to learn more about CBCP research studies and to participate, a CBCP research team member will explain the study (e.g. purpose of study, where samples will be stored, the GINA law, how to withdraw from the study) and provide time to discuss any concerns and/or answer the patient's questions regarding the study and their participation.

13.3 Compensation for Participation:

Patients will not be compensated for their participation in this research study.

13.4 Eligibility Assessment Process:

Please see Section 13.5.

13.5 Consent Process:

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

For patients who agree to participate, study procedures will be followed for the initial surgical procedure and any subsequent surgeries at WRNMMC related to their breast disease unless they withdraw from the study. In the absence of a new event relating to the patient's breast disease that requires a surgical procedure, the patient will have up to 20 cc of blood drawn for this research study, at least annually, during their routine follow-up visits with their clinician. The consent form offers study participants the opportunity to consent for future research to be performed on their samples. In addition, the consent form gives study participants the opportunity to choose whether they are willing to be contacted in the future by a CBCP research team member regarding research studies that might be of interest to them. A signed copy of the ICD/HIPAA will be provided to the subject prior to departing the Breast Center clinic.

Study participants are informed in the consent form of their right to withdraw from this study at any time. In this case, they are instructed to contact the PI, the Research Coordinator or a CBCP research team member. As stated in the consent form, in the case of study withdrawal, the CBCP research team would retain any previously-collected data necessary to ensure the scientific validity of the research. However, no new tissue or blood samples would be collected for this study.

13.6 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

◉ N/A

○ Propose ombudsman

13.7 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Study participants are informed in the consent form of their right to withdraw from this study at any time. In this case, they are instructed to contact the PI, the Research Coordinator or a CBCP research team member. As stated in the consent form, in the case of study withdrawal, the CBCP research team would retain any previously-collected data necessary to ensure the scientific validity of the research. However, no new tissue or blood samples would be collected for this study.

If a study participant decides to withdraw from the study, they are instructed to either send their request in writing to the address provided on the consent form or to complete a study withdrawal request form with a CBCP research team member at the time of their Breast Care Center clinical appointment.When a study participant decides to withdraw, they may choose to either : (1) allow the CBCP study team to retain previously-collected tissue and blood samples in the CBCP biorepository, and to continue to update their CRF and medical status by consulting WRNMMC's medical records system or (2) request that their previously-collected tissue and blood samples be destroyed and that the research team discontinue the collection of CRF data and medical status information from the medical records.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

This is a minimal risk study. The blood draws associated with this research study may result in mild discomfort, with some pain, swelling or bruising at the needle site. In addition, some people feel dizzy or light-headed for a few minutes after blood is drawn.

Confidentiality of study participants' research records will be protected to the extent possible under existing regulations and laws, but it cannot be guaranteed. Therefore, breach of confidentiality is a potential risk. The chances of this happening, however, are very small because the research records will be promptly de-identified and/or coded.

14.2 Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

Please see Section 14.1 and 14.3

14.3 Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

When will you destroy the research source documents, data file and the master code?

Research source documents, data files and the master code linking patients to their study ID numbers will be

kept for three years from the date the study is closed and then will be destroyed. Consent forms and HIPAA Authorization documents will be kept for six years after the study is closed and then will be destroyed.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society
If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

This study does not offer direct benefits to participants but is likely to yield important information about the risk factors, diagnosis, prognosis and treatment of breast disease.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

Please see Sections 14.1 and 14.3.

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

This protocol does not allow for the study team to share research results or incidental findings with study participants or their health care providers.

15.0 Study Monitoring

15.1 Data Monitoring Plan:

Describe the plan to monitor the data to verify that data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored and the frequency of monitoring

Please see legacy protocol.

15.2 Safety Monitoring Plan:

Describe the plan to monitor the data to ensure the safety of subjects

Please see legacy protocol.

15.3 Does your study require independent data and safety monitoring?

○ Yes ◉ No

16.0 Reportable Events

16.1 Reportable Events:

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short term management and any long term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

Reportable Events include adverse events (AE), serious adverse events (SAE), unanticipated problems involving risks to subjects or others (UPIRTSO), and protocol deviations as defined by the WRNMMC IRB Handbook.

UPIRTSOs, are unexpected AEs and SAEs, in the opinion of the PI, are possibly related to participation AND places subjects or others at a greater risk of harm that was previously known or recognized in the protocol and must be reported to the IRB and Research Monitor via email or telephone within 24 hours of discovery and a written follow up report within 5 business days.

Expected reportable events and events that are not related to study participation are reported on the Continuing Review (CR) Progress Report. CR is generally performed on a 12-month cycle. More frequent Progress Reports may be required at the discretion of the IRB.

When a deviation occurs, the investigator shall report the occurrence to the IRB. The investigator is required to make the determination whether the deviation meets the criteria for an unanticipated problem involving risks to subjects or others. The IRB Chair or IRB staff member shall also make the determination if the protocol deviation meets the definition of an unanticipated problem involving risks to participants or others. If the IRB Chair or IRB Staff member determines and documents that the deviation is an unanticipated problem involving risks to subjects or others or the deviation resulted from serious or continuing noncompliance, the IRB staff member shall place the deviation on the agenda of the next available IRB meeting for review. If the IRB Chair or IRB Staff member determines and documents that the deviation is not an unanticipated problem involving risks to subjects or others, the IRB Chair or staff member shall acknowledge the submission and complete the review through an administrative review procedure. Deviations that are determined to be minor as defined by the WRNMMC IRB Handbook are reported on the Continuing Review (CR) Progress Report.

As a reminder, according to DoDI 3216.02 (November 8, 2011), the IRB shall approve an independent research monitor by name for all DoD-conducted research involving human subjects, determined by the IRB to involve more than minimal risk to human subjects. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or Institutional Official (IO) for research involving human subjects determined to involve minimal risk.

The research monitor may perform oversight functions and will report their observations to the IRB or a designated official. The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have the authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs , dietary supplements, biologics, or devices be utilized in this study?

- ☐ Drugs
- ☐ Dietary Supplements
- ☐ Biologics
- ☐ Devices
- ☑ N/A

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

- ◉ Registration is not required
- ○ Registration pending
- ○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

- ◉ Registration is not required
- ○ Registration pending
- ○ Registration complete

20.0 References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms:
N/A

ATTACHMENT 6:
Tissue ICD
(Informed Consent Document)
(3 May 2017)

Last Name_____

WALTER REED NATIONAL MILITARY MEDICAL CENTER (WRNMMC)

This Specimen banking consent form is valid only if it contains the IRB stamped date.

Consent for Voluntary Participation in a Specimen Banking Study Entitled:

"Tissue and Blood Library Establishment for Molecular, Biochemical and Histologic Study of Breast Disease"

Principal Investigator: Craig D. Shriver, COL, MC, General Surgery Service, Department of Surgery, 301-295-8556

Study Sites: X WRNMMC

1. INTRODUCTION OF THE STUDY

You are being asked to be in this research study because you are scheduled to have part or all of your breast tissue surgically removed as part of your clinical care. Your participation is voluntary. Refusal to participate will not result in any penalty or loss of benefits to which you are otherwise entitled.

Please read the information below, and ask questions about anything you do not understand, before deciding whether to take part in the study.

2. PURPOSE OF THE STUDY

The purpose of this study is to gather samples of breast tissue, lymph node, and blood for use in future research studies. As part of your medical care, small amounts of breast tissue and lymph node are usually left over after all the clinical testing has been done. With your consent, we would like to keep some of this leftover tissue and take some blood samples from you. By carefully examining breast cells from many different breast conditions, we hope to improve our understanding of the causes and best treatments of these medical problems. All normal hospital regulations will be followed in sending the tissue removed from your body to Pathology for diagnosis.

3. PROCEDURES TO BE FOLLOWED

If you agree to participate in this study, the tissue, blood and data collection procedures described below will be followed for this surgery and any subsequent surgeries at WRNMMC related to your breast disease unless you decide to stop participating in this study. You may decide to withdraw from this study at any time by notifying the Principal Investigator (PI) or Research Coordinator and following the steps in Section 14 of this consent form.

All necessary diagnostic tests will be performed by the WRNMMC pathologist on your surgically removed breast tissue prior to the release of any excess tissue by the pathologist. Then, if you agree to be in this study, a small amount of excess breast tissue will be obtained from the pathologist. Only tissue that would otherwise be thrown away will be used for this study. If your surgical procedure also involves the removal of any lymph node(s), then a small amount of lymph node will also be obtained from the pathologist.

We will also take small amounts of blood from you during your routine clinical visits on at least an annual basis for the duration of your participation in the study. Three tube(s) of blood (up to 20cc or about 4 teaspoons) will be drawn at the time of your consent for this research study or prior to your initial surgical procedure. If additional surgical procedures are required in the future, you may have up to 20 cc of blood drawn at the time of these procedures for the purposes of this study. If additional surgeries related to your breast disease are not required, you will provide a blood sample (up to 20 cc) at least annually during your routine follow-up visits with your clinician for as long as your choose to participate in this study.

Participating in this study will not delay the processing of your pathology report and will not add to the time of your surgery. No additional surgery will be done on you to obtain these samples and only tissue that would otherwise be thrown away will be used for this study. In other words, all necessary diagnostic tests will be done first, prior to release of any excess tissue by the pathologist. If your breast tissue is being removed for therapeutic reasons and you consent to participate in this study, it is important for us to study the normal breast tissue because it allows our researchers to learn what non-diseased, normal breast tissue looks like at the genetic and protein levels, which we are analyzing in this study.

In this study, a Clinical Breast Care Project (CBCP) research team member will assist you in completing a Case Report Form (CRF) at the time of your first visit and on an annual basis during subsequent clinical visits to the Breast Care Center as recommended by your treating physician. This form will contain study participant information such as study ID number, demographics, lifestyle factors, medical history, family history of cancer, diagnosis and treatment.

Certain sections of this form will be completed and periodically updated by a clinician in consultation with your medical records. The time required for you to respond directly to CRF items with a research team member will be approximately 15 minutes or less. You will be asked to confirm and update the information in the CRF on an annual basis during subsequent clinical visits to the Breast Center. You may refuse to answer any question if you so choose.

The information collected on the CRF will be used to correlate the laboratory research results with your medical history, which may be important in correctly interpreting research results. If the CRF is not fully completed or updated during one of your appointments, a clinician on our staff may follow up with you by telephone with your permission.

4. IDENTIFICATION OF YOUR BLOOD AND/OR TISSUE SAMPLES, HOW AND WHERE THEY WILL BE STORED AND WHO WILL HAVE ACCESS TO YOUR SAMPLES

You will be assigned a code number referred to as the "CBCP number" (not your name or social security number), that will be used to code the blood and tissue samples, the questionnaire and any clinical information. The only connection between your CBCP number and your name or social security number will be kept in double-locked secure files in the study coordinator's office, and via a password protected secure CBCP database.

The blood samples will be frozen and stored indefinitely in either the Breast Care Center laboratory sites at Walter Reed or in our off-site facility, Windber Research Institute (WRI), Windber, PA. All samples will be kept in a secured (locked) freezer and identified only by CBCP codes. Only researchers within the CBCP or associated with the CBCP may have access to the samples and related clinical information. The tissue and blood samples will be used in the primary research studies as described in the next paragraphs.

This breast tissue can be used for many types of laboratory research looking at cell changes during breast cancer development, identification of risk factors that lead to breast cancer, breast tissue biology, and learning why and how breast cancer spreads to lymph nodes. The primary research uses of the blood and tissue samples are to study the genetic makeup, to examine protein changes, and to look for other markers that may be associated with breast disease. This information will be analyzed and stored in a CBCP computer database using your assigned code number.

Any remaining blood and tissue samples left over after these primary studies are done will remain frozen indefinitely in the CBCP biorepository until needed for approved research projects, if you consent for future breast disease

research. You will be provided the opportunity at the end of this consent form to indicate whether you will allow your blood and tissue samples to be used for future breast disease research. It is not possible at this time to predict all the potential future research uses of the samples.

If future research is to be conducted using these samples, the research will only be conducted after the proposed study protocol has received approval from the local Institutional Research Board (IRB) or the CBCP PI and scientific leadership, as appropriate. You will have the opportunity to give your consent for the use of your samples for future research at the end of this consent form.

Because these research projects are experimental, the results of any research done with your tissue will not be given to you or your doctor. These reports will not be put in your health records. The research will not be used in decisions regarding your medical care. Third parties, such as relatives, physicians, and insurance companies, will not have access to your information from these studies.

5. AMOUNT OF TIME FOR YOU TO COMPLETE THIS STUDY

Your participation in this study will consist of the time necessary to read and understand this consent form (about 30 minutes), and to complete the CRF (about 15 minutes). The collection of all of the tissue samples to be used in this study will be done at the time of your surgery or surgeries. The blood draws will occur prior to your IV placement for your surgical procedure(s), or will be done separately at the time of your clinically recommended follow-up visits and will take about 5 minutes.

When you agree to take part in this study, we will follow your breast disease status for as long as the study remains in progress. Your samples will be stored indefinitely or until they are no longer needed for research, or until you request removal of your samples from our repository where the samples are stored. You may withdraw from this study at any time, and you may request that any remaining samples be destroyed. The PI or the Research Coordinator will be the point of contact if you choose to withdraw or if destruction of the samples becomes necessary. Removal of your samples from the bank must be requested in writing to the researcher at the address in section 14 of this consent form or by completing a study withdrawal request form during your next visit to the Breast Care Center.

6. NUMBER OF PEOPLE THAT WILL TAKE PART IN THIS STUDY

This study is called a multi-site study because participants from several hospitals will be enrolled in the study. There are currently over 7,000 people enrolled in this study.

7. POSSIBLE RISKS OR DISCOMFORTS FROM BEING IN THIS STUDY

We do not anticipate that you will experience any health risks by participating in this study. However, outlined below are some discomforts or risks that could possibly occur.

There may be some discomfort from having your blood drawn, and you may experience some pain, swelling and bruising at the site of the needle stick. In addition, some people feel dizzy or light-headed for a few minutes after blood is drawn.

Confidentiality of your research records will be protected to the extent possible under existing regulations and laws, but it cannot be guaranteed. Therefore, breach of confidentiality is a potential risk. The chances of this happening, however, are very small because your research records will be promptly de-identified and/or coded.

If something in this study makes you uncomfortable or upset, you may choose to stop taking part in this research at any time without loss of benefits. If a study investigator notes any distress or anxiety associated with the research, you will be referred to your primary care physician or a professional counselor for help.

8. POSSIBLE BENEFITS FROM BEING IN THIS STUDY

You will not benefit directly from being in this study, but the knowledge gained through this research may ultimately lead to a better understanding of the causes of breast cancer and to the development of better ways to prevent, diagnose and treat breast cancer. At the end of this consent form, we will ask for your permission to contact you about future research studies that may involve clinical trials or other research related matters that may be of interest to you.

9. CONFIDENTIALITY/PRIVACY OF YOUR IDENTITY AND YOUR RESEARCH RECORDS

The PI will keep your research records in a secure and locked place. These records may be looked at by staff from the WRNMMC Department of Research Programs, the Institutional Review Board (IRB), the Uniformed Services University of the Health Sciences, and other government agencies as part of their duties. These duties include making sure that the research participants are protected. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed. Complete confidentiality cannot be promised, particularly for military personnel, because

information related to your health may be required to be reported to appropriate medical or command authorities. Your name will not appear in any published paper or presentation related to this study.

This research study meets the confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA).

10. CONDITIONS UNDER WHICH YOUR PARTICIPATION IN THIS STUDY MAY BE STOPPED WITHOUT YOUR CONSENT

Your taking part in this study may be stopped without your consent if remaining in the study might be dangerous or harmful to you. Your taking part in this study may also be stopped without your consent if the military mission requires it, or if you lose your right to receive medical care at a military hospital.

11. ELIGIBILITY AND PAYMENT FOR BEING IN THIS STUDY

You will not receive any payment for being in this study.

12. COMPENSATION TO YOU IF INJURED AND LIMITS TO YOUR MEDICAL CARE

Should you be injured as a direct result of your participation in this study, you will be provided medical care for that injury at no cost to you. You will not receive any compensation (payment) for injury. You should also understand that this is not a waiver or release of your legal rights.

Medical care is limited to the care normally allowed for Department of Defense (DOD) health care beneficiaries (patients eligible for care at military hospitals and clinics). Necessary medical care does not include in-home care or nursing home care. You should discuss this issue thoroughly with the PI before you enroll in this study.

If at any time you believe you have a study-related injury or illness as a result of participating in this research project, you should contact the PI. For questions about your rights as a research participant, contact the Human Protections Administrator, Department of Research Programs (DRP) in Building 17 at 301-295-8273 or the Staff Judge Advocate (SJA) office at 301-295-2215.

13. COSTS THAT MAY RESULT FROM TAKING PART IN THIS STUDY

There is no charge to you for taking part in this study.

14. IF YOU DECIDE TO STOP TAKING PART IN THIS STUDY AND THE INSTRUCTIONS FOR STOPPING EARLY

You have the right to withdraw from this study at any time. This can be done by contacting the PI or the Research Coordinator at the phone number, mailing address, or email address below or by completing a study withdrawal request form with a research team member during your next visit to the Breast Care Center.

The study withdrawal form provides the following two options: (1) no new tissue and blood samples will be collected from you, but the study team will retain your previously collected samples in the CBCP biorepository, and will continue to consult your medical records to update the CRF and follow your medical status or (2) your previously collected tissue and blood samples will be destroyed, and the research team will discontinue the collection of CRF data and medical status information from your medical records.

If you withdraw from this study, the research team will continue to use any information that they have already collected to ensure the scientific validity of the research. However, no new samples will be collected from you. By leaving this study at any time, you in no way risk losing your right to medical care.

Principal Investigator contact information:

Craig D. Shriver, COL, MC, MD, FACS
P.I., Clinical Breast Care Project
Director, Murtha Cancer Center
Walter Reed National Military Medical Center
America Building #19, 3rd Floor
Bethesda, MD
(301) 295-8556
craig.d.shriver.mil@mail.mil

15. RESEARCH RESULTS

The results from tests that may be done on the (blood and/or tissue) that you donate for future research will not be given to you or to your doctor, even if you ask that this be done. The study results will not become part of your hospital medical record because these tests will be done for research purposes only.

Your individual testing results that may be done on the blood and/or tissue that you donate for future research will not be released to any third party, including family members, personal physicians, insurers or employers, under any circumstance unless required by law.

You should understand that the samples you are providing in this study may be used in other research studies related to breast disease. You will not be given any notice of future use of your sample. The confidentiality of your specimens will be protected in the same fashion as stated previously in the description of this study and/or confidentiality section. You will not be personally identified in any published paper of these other research studies. Any other researcher using these samples will be under the direction of the CBCP; no direct identifiers such as your name, address, social security number, etc. will be provided to these researchers, but they could be provided with some identifying clinical information about you, such as dates of surgery, diagnosis, treatment.

16. YOUR RIGHTS IF YOU TAKE PART IN THIS STUDY

Participating in this study is your choice. You may choose either to participate or not to participate in the study. If you choose to participate in this study, you have the right to withdraw from this study at any time. This can be done by contacting the PI or the Research Coordinator at the phone number or address in section 14 of this consent form, or by completing a study withdrawal request form as described above.

No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits or risk losing your right to medical care.

17. THE NEW FEDERAL LAW – "GENETIC INFORMATION NON-DISCRIMINATION ACT" (GINA)

This new federal law generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

Health insurance companies and group health plans may not request your genetic information that we get from this research.

Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans and all employers with 15 or more employees must follow this law.

GINA's health insurance protections do not apply to members of the military who receive their healthcare through TRICARE, for veterans who receive their healthcare through the Veterans' Administration, and for federal employees enrolled in the Federal Employee Health Benefits Plan. While GINA's employment protections do not apply to military members and federal employees, presently an Executive Order protects federal employees from genetic discrimination in employment, and the military has its own policies in place that may protect against genetic discrimination. GINA's protections should apply for a military member once he or she leaves the service and enters the private sector.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

18. AUTHORIZATION FOR RESEARCH USE OF PROTECTED HEALTH INFORMATION

The Federal Health Insurance Portability and Accountability Act (**HIPAA**) includes a Privacy Rule that gives special safeguards to Protected Health Information (**PHI**) that is identifiable, in other words, can be directly linked to you (for example, by your name, social security number, etc.). We are required to advise you on how your PHI will be used.

(1) What information will be collected?

For this research study, you will be asked some basic information about your breast health and medical history. A CBCP research team member will assist you in completing a Case Report Form at the time of your first visit and on an annual basis during subsequent clinical visits to the Breast Center as recommended by your treating physician. This form will contain study participant information such as study ID number, demographics, lifestyle factors, medical history, family history of cancer, diagnosis and treatment.

Certain sections of this form will be completed and periodically updated by a clinician who will consult your medical records to monitor the status of your breast disease, and who may contact you, with your verbal permission, to update your medical status.

Study participants' social security numbers will be collected from WRNMMC's medical record system and retained in the CBCP database only for the purpose of confirming the identity of a study sample or document if a question were to arise. CBCP study samples and data collection forms will be coded using CBCP study identification numbers.

(2) Who may use your PHI within the Military Healthcare System?
The members of the research team will have access to your health information in order to find out if you qualify to participate in this study, and to analyze research data. Additionally, your PHI may be made available to health oversight groups such as the WRNMMC Department of Research Programs and Institutional Review Board, and other government agencies as part of their duties. These duties include making sure that research subjects are protected.

(3) What persons outside of the Military Healthcare System who are under the HIPAA requirements will receive your PHI?
Persons outside the Military Healthcare System who operate under HIPAA regulations may receive your PHI for the purpose of performing a future IRB-approved research study. This information may include your CBCP number and associated information such as dates of surgery, diagnosis and treatment. Your name, address, social security number and contact information will not be shared.

(4) What is the purpose of using or disclosing your PHI?
The members of the research team need to use your PHI in order to analyze the information related to the specific kind of research study being performed. Researchers associated with the CBCP will use your blood and/or tissue samples to study the genetic makeup, protein changes, and other factors that may be associated with breast disease, and to conduct unknown future research. The clinical information is important for performing analysis.

(5) How long will the researchers keep your PHI?
There is no expiration date for this study to maintain your PHI. Since this study collects samples for placement within a tissue bank, your samples and PHI will be maintained indefinitely unless you withdraw from this study.

(6) Can you review your own research information?
You will not be able to review your own research information.

(7) Can you cancel this Authorization?
Yes. If you cancel this Authorization, however, you will no longer be included in the research study. The information and samples we have collected from you may be destroyed at your request. The research and samples that may have been used prior to your request will not be able to be destroyed or withdrawn because they will already be among the statistics of the study. If you wish to cancel your HIPAA Authorization, please contact the Principal Investigator or the Research Protocol Coordinator in writing at the address provided in section 14 of this consent form.

(8) What will happen if you decide not to grant this Authorization?
If you decide not to grant this Authorization, you will not be included in this research study. Refusal to grant this Authorization will not result in any loss of medical benefits to which you are otherwise entitled.

(9) Can your PHI be disclosed to parties not included in this Authorization who are not under the HIPAA requirements?
There is a potential that your research information could be shared with another party not listed in this Authorization in order to meet legal or regulatory requirements. Examples of persons who may access your PHI include representatives of the Food and Drug Administration, the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), and the DHHS Office for Civil Rights. This disclosure is unlikely to occur, but in that case, your health information would no longer be protected by the HIPAA Privacy Rule.

(10) Who should you contact if you have any complaints?
If you believe your privacy rights have been violated, you may send a written complaint to the WRNMMC Privacy Officer, located at 8901 Wisconsin Avenue, Bethesda, MD 20889-5600, telephone: 301-319-4775.

Your signature at the end of this document acknowledges that you authorize WRNMMC personnel to use and disclose your Protected Health Information (PHI) collected about you for the research purposes described above.

19. CONTACTS FOR QUESTIONS ABOUT THE STUDY

If you have questions about this study, you may contact either the PI or the Research Coordinator at (301) 295-8556. For questions about your rights as a research subject, contact the Human Protections Administrator, WRNMMC Department of Research Programs in Building 17 at (301) 295-8273 or WRNMMC Staff Judge Advocate Office at (301) 295-2215.

20. OTHER FUTURE RESEARCH FOR WHICH YOUR BLOOD AND/OR TISSUE SAMPLES COLLECTED DURING THIS STUDY COULD BE USED

Please read carefully each sentence below and think about your choices. After reading each sentence, **circle** “yes” or “no”, include the date and your initials. If you have any questions please talk to your doctor or a research team member.

BY SIGNING THIS FORM, YOU ARE AGREEING THAT:

a. My tissue and serum (blood) samples, clinical data and imaging data may be kept for use in future research to learn about, prevent, detect, or treat breast cancer, and to better understand how genes relate to breast cancer:

YES NO Participant's Initials _____ Date _____

b. The Principal Investigator (or someone he or she chooses) may contact me in the future to ask me to take part in future research:

YES NO Participant's Initials _____ Date _____

SIGNATURE OF RESEARCH STUDY PARTICIPANT

I have read (or someone has read to me) the information in this consent form. I have been given a chance to ask questions and all of my questions have been answered to my satisfaction.

BY SIGNING THIS CONSENT FORM, YOU FREELY AGREE TO TAKE PART IN THE RESEARCH IT DESCRIBES.

_____ _____

Participant's Signature Date and time

_____

Printed First name MI **Printed** Last Name

A signed copy of this consent form will be provided to you.

SIGNATURE OF RESEARCH TEAM MEMBER OBTAINING CONSENT

My signature is intended to attest that the information in the consent document and any other information was explained to and apparently understood by the subject, that questions and concerns were addressed, and that informed consent was freely given.

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date and time (must be same as subject)

ATTACHMENT 7:
Case Report Form (CRF)

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Clinical Breast Care Project/WRNMMC
Breast Cancer Case Report Form©

Date completed _____ / _____ / _____

Initials _____ / _____ / _____

CBCP Number	___ ___ ___ ___ ___ ___ ___ ___ ___
Date	____/____/_____ *(mm/dd/yyyy)*
Patient Pathologic Category	☐ Benign ☐ Not applicable ☐ Atypical ☐ Not reported / Unknown ☐ In Situ ☐ Invasive ☐ Malignant, NOS
Vital status	☐ Living: Date of last visit ____ / ____ / _____ ☐ AWD ☐ NED ☐ Not reported / Unknown Date of last activity ____ / ____ / _____ *OR* ☐ Deceased: Date of death ____ / ____ / _____ ☐ Date of death not reported or unknown ☐ Dead of disease (DOD) ☐ Dead of other causes (DOC) (specify) _____ ☐ Cause of death not reported or unknown
PART I: CLINICAL DATA SECTION A: DEMOGRAPHICS	
Date of birth	____/____/_____ *(mm/dd/yyyy)*
Age	___ ___ ___
Gender	☐ Female ☐ Male
Race *(If multiracial, check all that apply)*	☐ White ☐ Black or African American ☐ Asian ☐ American Indian/Alaska Native ☐ Native Hawaiian or other Pacific Islander ☐ Other _____ ☐ Not reported / Unknown
Ethnicity	☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Ashkenazi Jewish descent ☐ Not reported / Unknown
Current Marital Status	☐ Single ☐ Married ☐ Divorced ☐ Widowed ☐ Separated ☐ Unmarried (Living with partner) ☐ Not reported / Unknown

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Education	Highest level of education completed: ☐ Grade School ☐ High School graduate or equivalency (GED) ☐ Vocational or Trade School ☐ Some college, no degree ☐ Associate's degree ☐ Bachelor's Degree ☐ Graduate or Professional Degree ☐ Not reported / Unknown
Military Status	What is your current military status? ☐ Active Duty ☐ Retired ☐ Reserves ☐ Not Applicable (Patient is not in the military) ☐ Not reported/Unknown ☐ Other: _____
Military Association	What branch of the military are you or your spouse associated with? ☐ Army ☐ Navy ☐ Air Force ☐ Marine Corps ☐ Coast Guard ☐ National Guard ☐ U.S. Public Health Service Commissioned Corps ☐ Foreign Military ☐ Department of Defense ☐ Other: _____ ☐ Not Applicable (Patient is not a beneficiary) ☐ Not reported/Unknown

SECTION B: LIFESTYLE FACTORS

Measurements	Weight ☐ ___ ___ ___ lbs. ☐ Not reported / Unknown Height ☐ _____ ft. _____ in. ☐ Not reported / Unknown Body Mass Index ☐ _____ (calculated) ☐ Not evaluable (Height and/or Weight unknown)	
Tobacco Products	(1) Has the patient smoked at least 100 cigarettes in their lifetime? *(equivalent of 5 packs)*	☐ Yes ☐ No *(End of Section)* ☐ Not reported / Unknown
	(2) How many total years did patient smoke? *(Do not include times when patient quit)*	☐ __ __ years ☐ Not reported / Unknown
	(3) When smoking, how many packs per day did patient smoke?	☐ Less than ½ pack per day ☐ Half to 1 pack per day ☐ 1 to 2 packs per day ☐ Greater than 2 packs per day ☐ Not reported / Unknown

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Tobacco Products ***(continued)***	(4) Does patient currently smoke?	☐ Yes (end of section) ☐ No ☐ Not reported / Unknown
	(5) At what age did patient stop smoking?	☐ ___ ___ years ☐ Not reported / Unknown
Physical Activity	On average, does patient engage in moderate-intensity aerobic activity 150 minutes/week? ☐ Yes ☐ No ☐ Not reported / Unknown	
SECTION C: REPRODUCTIVE HISTORY		
Age at menarche	☐ _____ Years ☐ Not reported / Unknown	
Pregnancy History	☐ Gravidity: _____ *(if G is "0", end of section)* ☐ Not reported / Unknown ☐ Parity: _____ ☐ Not reported / Unknown ☐ Age at first pregnancy: _____ ☐ Not reported / Unknown ☐ Age at last pregnancy: _____ ☐ Not reported /Unknown ☐ Age at first live birth: _____ ☐ Not reported / Unknown ☐ Breastfeeding, cumulative: _____ months ☐ Not reported / Unknown	
Hormone Replacement Therapy	☐ No ☐ Yes ⇒ ☐ Duration: _____ years ☐ Duration: Not reported / Unknown ☐ Not reported / Unknown	
Menopausal status	What is the patient's current menopausal status? ☐ Pre-menopausal ☐ Post-menopausal Age: _____ ☐ Not reported / Unknown ☐ Surgically menopausal Age: _____ ☐ Not reported / Unknown ☐ Not reported / Unknown	
Fertility Treatment	Has patient ever been treated for infertility? ☐ Yes ☐ No ☐ Not reported / Unknown	

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

SECTION D: FAMILY HISTORY OF CANCER

Does patient have any family members diagnosed with cancer? (blood relatives, including ½ relatives)

☐ Yes ⇒ Please complete **Family Cancer History Grid**
☐ No ⇒ Move on to Section 'E'
☐ Not reported / Unknown ⇒ Move on to Section 'E'

SECTION E: PATIENT MEDICAL HISTORY (NON-CANCER)

Lesion Detection	Is this patient currently being evaluated for a breast lesion? ☐ No ☐ Not reported / Unknown ☐ Yes ⇒ Please check one ☐ Symptomatic (Lesion detected by self or physician) ☐ Imaging (Lesion detected through routine mammogram or other imaging modality)
Medical Conditions	Does patient have a history of any of the following physician diagnosed conditions? ☐ No ☐ Not reported / Unknown ☐ Yes ⇒ Please check all that apply: ☐ Alcoholism ☐ Benign breast disease, detected by biopsy ☐ Colon or rectal polyps ☐ Diabetes ☐ High blood pressure / hypertension ☐ High cholesterol ☐ Thyroid disorders
Medications	Does patient currently take medication on a *regular basis* for any *chronic*, physician diagnosed conditions? ☐ No ☐ Not reported / Unknown ☐ Yes (please list condition and medication below)

Condition	Medication(s)

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / ______

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other __________________

SECTION F: PATIENT MEDICAL HISTORY (NON-BREAST MALIGNANCIES)

Non-Breast Malignancies *(squamous cell and basal cell carcinomas of the skin excluded)* ☐ Yes ☐ No ☐ Not reported / Unknown

Organ of origin ________________

Histologic type ________________

Histologic grade ________________

Tumor stage ________________

Date of diagnosis ____/____/________

Treatment *(check all that apply)*:

☐ Resection ☐ Radiation ☐ Chemotherapy ☐ Not reported / Unknown

Comment:

Organ of origin ________________

Histologic type ________________

Histologic grade ________________

Tumor stage ________________

Date of diagnosis ____/____/________

Treatment *(check all that apply)*:

☐ Resection ☐ Radiation ☐ Chemotherapy ☐ Not reported / Unknown

Comment:

Organ of origin ________________

Histologic type ________________

Histologic grade ________________

Tumor stage ________________

Date of diagnosis ____/____/________

Treatment *(check all that apply)*:

☐ Resection ☐ Radiation ☐ Chemotherapy ☐ Not reported / Unknown

Comment:

STOP

This is the end of the Clinical Data Section.

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Part II: PATHOLOGY

SURGICAL PROCEDURES ***(Including all benign and malignant)*** ☐ Yes ☐ No ☐ Not reported / Unknown

Procedure codes

01 Core needle biopsy	04 Mastectomy, for tumor	07 Sentinel lymph node biopsy	11 Body fluid
02 Excisional biopsy	05 Mastectomy, prophylactic	08 Axillary lymph node dissection	12 Other
03 Re-excision	06 Skin biopsy	09 Lymph node biopsy, other	13 Mammoplasty
		10 Fine needle aspirate	16 Imaging, NOS

Laterality codes

L Left **R** Right **N/A** Not applicable **U** Unknown/Not reported

	Laterality	Procedure	Site, if non-breast	Date of Procedure	N	R	Pathology #
1.	_____	_____	_____	____/____/_____	☐	☐	_____
2.	_____	_____	_____	____/____/_____	☐	☐	_____
3.	_____	_____	_____	____/____/_____	☐	☐	_____
4.	_____	_____	_____	____/____/_____	☐	☐	_____
5.	_____	_____	_____	____/____/_____	☐	☐	_____
6.	_____	_____	_____	____/____/_____	☐	☐	_____
7.	_____	_____	_____	____/____/_____	☐	☐	_____
8.	_____	_____	_____	____/____/_____	☐	☐	_____
9.	_____	_____	_____	____/____/_____	☐	☐	_____
10.	_____	_____	_____	____/____/_____	☐	☐	_____
11.	_____	_____	_____	____/____/_____	☐	☐	_____
12.	_____	_____	_____	____/____/_____	☐	☐	_____
13.	_____	_____	_____	____/____/_____	☐	☐	_____
14.	_____	_____	_____	____/____/_____	☐	☐	_____
15.	_____	_____	_____	____/____/_____	☐	☐	_____

N= Post-Neoadjuvant, R = Recurrence

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

PATHOLOGIC DIAGNOSES- MASTER LIST

Date _____/_____/_____ to _____/_____/_____ **Laterality** ☐ Left ☐ Right ☐ Not applicable

Path Category

☐ Benign ☐ Invasive
☐ Atypical ☐ Malignant, NOS
☐ In Situ

Inflammatory and Reactive Lesions

[001] ☐ Fat necrosis
[002] ☐ Post−surgical changes
[003] ☐ Radiation/chemotherapy changes
[004] ☐ Breast infarct
[005] ☐ Galactocele
[006] ☐ Silicone mastitis/granulomas
[007] ☐ Mammary duct ectasia
[008] ☐ Granulomatous lobular mastitis
[009] ☐ Plasma cell mastitis
[010] ☐ Lymphocytic mastitis
[011] ☐ Acute mastitis/abscess
[012] ☐ Subareolar abscess
[013] ☐ Tuberculous mastitis
[014] ☐ Mycotic mastitis
[015] ☐ Parasitic mastitis
[016] ☐ Other infectious
[017] ☐ Sarcoidosis
[018] ☐ Vasculitis
[019] ☐ Collagen vascular disease
[020] ☐ Diabetic mastopathy
[021] ☐ Amyloid tumor

Miscellaneous Benign Lesions

[022] ☐ Microcalcifications
[023] ☐ Atrophy
[024] ☐ Fibrocystic changes
[025] ☐ Stromal fibrosis
[026] ☐ Cysts
[027] ☐ Apocrine metaplasia
[028] ☐ Clear cell metaplasia
[029] ☐ Lactational change/ metaplasia
[030] ☐ Sclerosing adenosis
[031] ☐ Apocrine adenosis
[032] ☐ Tubular adenosis
[033] ☐ Blunt duct adenosis
[034] ☐ Florid adenosis
[035] ☐ Microglandular adenosis
[133] ☐ Nodular sclerosing adenosis
[036] ☐ Adenosis, not otherwise specified
[037] ☐ Radial scar
[038] ☐ Collagenous spherulosis
[039] ☐ Tubular adenoma
[040] ☐ Lactating adenoma
[041] ☐ Ductal adenoma
[042] ☐ Pleomorphic adenoma
[043] ☐ Adenomyoepithelioma
[044] ☐ Myoepithelioma

Papillary Lesions

[045] ☐ Solitary (central) papilloma
[046] ☐ Multiple (peripheral) papillomas
[047] ☐ Intracystic papilloma
[048] ☐ Sclerosing papilloma
[049] ☐ Atypical papilloma

Biphasic Tumors

[052] ☐ Fibroadenoma
[053] ☐ Fibroadenomatoid change
[054] ☐ Juvenile fibroadenoma
[055] ☐ Gynecomastia
[056] ☐ Phyllodes tumor, benign
[057] ☐ Phyllodes tumor, low−grade malignant/border
[058] ☐ Phyllodes tumor, malignant

Hyperplasias and Columnar Cell Lesions

[059] ☐ Intraductal hyperplasia, mild
[060] ☐ Intraductal hyperplasia, moderate
[061] ☐ Intraductal hyperplasia, florid
[063] ☐ Atypical ductal hyperplasia
[064] ☐ Atypical apocrine hyperplasia
[066] ☐ Atypical lobular hyperplasia
[128] ☐ Columnar cell change
[129] ☐ Columnar cell change with atypia
[062] ☐ Columnar cell hyperplasia
[065] ☐ Columnar cell hyperplasia with atypia

In Situ Carcinomas

[132] ☐ Ductal carcinoma in situ, NOS
[069] ☐ Lobular carcinoma in situ
[135] ☐ Lobular carcinoma in situ, pleomorphic
[050] ☐ In situ papillary carcinoma

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Infiltrating Carcinomas: Common and Familiar Types

[070] ☐ Infiltrating ductal carcinoma
[071] ☐ Microinvasive ductal carcinoma
[072] ☐ Infiltrating lobular carcinoma
[073] ☐ Tubular carcinoma
[131] ☐ Tubulolobular carcinoma
[074] ☐ Infiltrating carcinoma, mixed, NOS
[075] ☐ Mucinous carcinoma
[076] ☐ Medullary carcinoma

Infiltrating Carcinomas: Special Types

[051] ☐ Invasive papillary carcinoma
[134] ☐ Invasive micropapillary carcinoma
[077] ☐ Inflammatory carcinoma
[078] ☐ Metaplastic carcinoma
[079] ☐ Apocrine carcinoma
[080] ☐ Carcinoma with neuroendocrine features
[081] ☐ Secretory carcinoma
[082] ☐ Lipid−rich carcinoma
[083] ☐ Clear−cell (glycogen−rich) carcinoma
[084] ☐ Invasive cribriform carcinoma
[085] ☐ Carcinoma with osteoclast giant cells
[086] ☐ Adenoid cystic carcinoma

Diseases of the Nipple

[087] ☐ Paget's disease
[088] ☐ Nipple duct adenoma
[089] ☐ Syringomatous adenoma
[090] ☐ Basal cell carcinoma
[091] ☐ Hyperkeratosis
[092] ☐ Accessory nipple

Benign Mesenchymal Lesions

[093] ☐ Fibromatosis
[094] ☐ Fibrous tumor
[095] ☐ Pseudoangiomatous stromal hyperplasia
[096] ☐ Myofibroblastoma
[097] ☐ Granular cell tumor
[098] ☐ Neurofibroma/Neurolemoma
[099] ☐ Leiomyoma
[100] ☐ Hamartoma
[101] ☐ Myxoma
[102] ☐ Mucinosis
[103] ☐ Lipoma
[104] ☐ Hemangioma
[105] ☐ Angiomatosis
[106] ☐ Papillary endothelial hyperplasia
[107] ☐ Aneurysm

Sarcomas

[108] ☐ Angiosarcoma
[109] ☐ Hemangiopericytoma
[110] ☐ Liposarcoma
[111] ☐ Osteogenic sarcoma
[112] ☐ Leiomyosarcoma
[113] ☐ Rhabdomyosarcoma
[114] ☐ Malignant fibrous histiocytoma

Lymphoid and Hematopoietic Tumors

[115] ☐ Non−Hodgkin's lymphoma
[116] ☐ Hodgkin's disease
[117] ☐ Plasmacytoma
[118] ☐ Leukemic infiltration
[119] ☐ Granulocytic sarcoma

Axillary Lymph Nodes

[120] ☐ No metastatic tumor
[130] ☐ Isolated tumor cells (<= 0.2 mm)
[122] ☐ Micrometastasis (> 0.2 mm but <= 2.0 mm)
[121] ☐ Metastasis (>2.0 mm)

Miscellaneous

[123] ☐ Recurrent/residual breast carcinoma
[136] ☐ Lymphovascular invasion
[124] ☐ Distant metastasis (excludes metastasis to supraclavicular nodes)
[125] ☐ Metastasis to breast (non−hematopoietic), type:
_____
[126] ☐ No abnormalities
[127] ☐ Other (specify) _____

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Premalignant Disease of Breast	☐ Yes ☐ No ☐ Not reported / Unknown

Event: ☐ Recurrence ☐ New disease

Laterality: ☐ Left ☐ Right ☐ Not applicable ☐ Not reported / Unknown

Date of diagnosis ____/____/_____

Diagnosis *(check all that apply)*:

- ☐ Atypical ductal hyperplasia (ADH)
- ☐ Ductal carcinoma in situ (DCIS)
  - ☐ Low (nuclear grade 1)
  - ☐ Intermediate (nuclear grade 2)
  - ☐ High (nuclear grade 3)
  - ☐ Intraluminal necrosis
- ☐ Atypical lobular hyperplasia (ALH)
- ☐ Lobular carcinoma in situ (LCIS)

Treatment:

- ☐ Surgical excision
- ☐ Radiation
- ☐ Pharmacologic therapy
- ☐ Not reported / Unknown

Comment:

Event: ☐ Recurrence ☐ New disease

Laterality: ☐ Left ☐ Right ☐ Not applicable ☐ Not reported / Unknown

Date of diagnosis ____/____/_____

Diagnosis *(check all that apply)*:

- ☐ Atypical ductal hyperplasia (ADH)
- ☐ Ductal carcinoma in situ (DCIS)
  - ☐ Low (nuclear grade 1)
  - ☐ Intermediate (nuclear grade 2)
  - ☐ High (nuclear grade 3)
  - ☐ Intraluminal necrosis
- ☐ Atypical lobular hyperplasia (ALH)
- ☐ Lobular carcinoma in situ (LCIS)

Treatment:

- ☐ Surgical excision
- ☐ Radiation
- ☐ Pharmacologic therapy
- ☐ Not reported / Unknown

Comment:

Distant Metastases

- ☐ M0 No distant metastasis
- ☐ M1 Distant metastasis
- ☐ M0(i+) Disseminated tumor cells
- ☐ MX Unknown status

If M1, Please indicate if site known:

- ☐ Not reported / Unknown
- ☐ Yes *(please check all that apply):*
  - ☐ Lung ____/____/_____
  - ☐ Liver ____/____/_____
  - ☐ Bone ____/____/_____
  - ☐ Brain ____/____/_____
  - ☐ Other: ____/____/_____

Comment:

If M0(i+),*

Site of involvement	Date of diagnosis
☐ Bone marrow	____/____/_____
☐ Blood (circulating tumor cells)	____/____/_____
☐ Other tissue _____	____/____/_____

**Presence of either disseminated tumor cells (DTCs) detectable in bone marrow or circulating tumor cells or found incidentally in other tissues (e.g., ovary removed prophylactically) if ≤0.2 mm.*

Comment:

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Locoregional Recurrence and New Disease	☐ Yes ☐ No ☐ Not reported / Unknown

Event: ☐ Recurrence ☐ New disease

Laterality: ☐ Left ☐ Right ☐ N/A ☐ Not reported / Unknown

Date of diagnosis _____/_____/_____

Site:
- ☐ Breast
- ☐ Skin of the breast
- ☐ Chest wall
- ☐ Axillary lymph node(s)
- ☐ Other_____

Tumor#: _____ **Description:** _____

Histologic type (enter code from Master List):
- ☐ ___ ___ ___
- ☐ Not reported / Unknown

For Invasive patients only, please complete the following section:

Histologic grade	☐ G1 ☐ G2 ☐ G3 Nottingham score _____ Tubules/nuclei/mitoses ____ /____ / ____ ☐ Not reported / Unknown
Tumor location (check all that apply)	☐ Upper outer (UO) ☐ Lower mid (LM) ☐ Upper inner (UI) ☐ Mid outer (MO) ☐ Upper mid (UM) ☐ Mid inner (MI) ☐ Lower outer (LO) ☐ Central (C) ☐ Lower inner (LI) ☐ Unknown
Tumor size	☐ Microinvasive only (≤1.0 mm) ☐ Macroinvasive, tumor size = _____ mm ☐ Cannot be determined or unknown (TX)

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

PRIMARY TUMOR PATHOLOGY	
Laterality	☐ Left ☐ Right ☐ N/A ☐ Not reported / Unknown
Date of diagnosis	____/____/_____
Tumor distribution	☐ Multicentric ☐ Multifocal ☐ Heterogenic ☐ Not applicable ☐ Not reported / Unknown
Neoadjuvant Chemotherapy	☐ Yes ☐ No
Tumor # _____	**Description:**
Histologic type (Enter code from Master List)	☐ ___ ___ ___ ☐ Not reported / Unknown
Histologic grade	☐ G1 ☐ G2 ☐ G3 Nottingham score _____ Tubules/nuclei/mitoses ____ /____ / ____ ☐ Not reported / Unknown
Tumor location (check all that apply)	☐ Upper outer (UO) ☐ Lower mid (LM) ☐ Upper inner (UI) ☐ Mid outer (MO) ☐ Upper mid (UM) ☐ Mid inner (MI) ☐ Lower outer (LO) ☐ Central (C) ☐ Lower inner (LI) ☐ Unknown
Tumor size	☐ Microinvasive only (≤1.0 mm) ☐ Macroinvasive, tumor size = _____ mm ☐ Cannot be determined or unknown (TX)
Tumor # _____	**Description:**
Histologic type (Enter code from Master List)	☐ ___ ___ ___ ☐ Not reported / Unknown
Histologic grade	☐ G1 ☐ G2 ☐ G3 Nottingham score _____ Tubules/nuclei/mitoses ____ /____ / ____ ☐ Not reported / Unknown

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Tumor location (check all that apply)	☐ Upper outer (UO) ☐ Lower mid (LM) ☐ Upper inner (UI) ☐ Mid outer (MO) ☐ Upper mid (UM) ☐ Mid inner (MI) ☐ Lower outer (LO) ☐ Central (C) ☐ Lower inner (LI) ☐ Unknown
Tumor size	☐ Microinvasive only (≤1.0 mm) ☐ Macroinvasive, tumor size = _____ mm ☐ Cannot be determined or unknown (TX)
Tumor # _____	**Description:**
Histologic type (Enter code from Master List)	☐ ___ ___ ___ ☐ Not reported / Unknown
Histologic grade	☐ G1 ☐ G2 ☐ G3 Nottingham score _____ Tubules/nuclei/mitoses ____ /____ / ____ ☐ Not reported / Unknown
Tumor location (check all that apply)	☐ Upper outer (UO) ☐ Lower mid (LM) ☐ Upper inner (UI) ☐ Mid outer (MO) ☐ Upper mid (UM) ☐ Mid inner (MI) ☐ Lower outer (LO) ☐ Central (C) ☐ Lower inner (LI) ☐ Unknown
Tumor size	☐ Microinvasive only (≤1.0 mm) ☐ Macroinvasive, tumor size = _____ mm ☐ Cannot be determined or unknown (TX)

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Tumor # _____	**Description:**
Histologic type (Enter code from Master List)	☐ ___ ___ ___ ☐ Not reported / Unknown
Histologic grade	☐ G1 ☐ G2 ☐ G3 Nottingham score _____ Tubules/nuclei/mitoses ____ /____ / ____ ☐ Not reported / Unknown
Tumor location (check all that apply)	☐ Upper outer (UO) ☐ Lower mid (LM) ☐ Upper inner (UI) ☐ Mid outer (MO) ☐ Upper mid (UM) ☐ Mid inner (MI) ☐ Lower outer (LO) ☐ Central (C) ☐ Lower inner (LI) ☐ Unknown
Tumor size	☐ Microinvasive only (≤1.0 mm) ☐ Macroinvasive, tumor size = _____ mm ☐ Cannot be determined or unknown (TX)
CASE PATHOLOGY	
Extension to chest wall or skin *(clinical diagnosis)*	☐ No ☐ Yes *If yes,* ☐ T4a Extension to chest wall (excluding pectoralis) ☐ T4b Skin edema, ulceration, or satellite nodules ☐ T4c Both T4a and T4b ☐ T4d Inflammatory carcinoma
In situ component (Check all that apply)	☐ Low (nuclear grade 1) ☐ Intermediate (nuclear grade 2) ☐ High (nuclear grade 3) ☐ Intraluminal necrosis

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Lymph/vascular invasion	☐ No ☐ Yes
Dermal lymphatic invasion	☐ No ☐ Yes
Paget's disease	☐ No ☐ Yes
Axillary lymph nodes (path) *Isolated tumor cells: ≤0.2 mm or ≤200 cells* *Micrometastasis: >0.2 mm to 2.0 mm* *Macrometastasis: >2.0 mm*	☐ Negative ☐ Isolated tumor cells (ITCs), #LN _____ ☐ Micro- or macrometastasis , #LN _____ ☐ Micrometastasis only ☐ Nodes not sampled or unknown status (NX) Total axillary nodes sampled: _____ Largest metastasis _____ mm Extranodal extension: ☐ No ☐ Yes
Other regional lymph nodes (path) *IM = internal mammary* *IC = infraclavicular (level III axillary)* *SC = supraclavicular*	IM: ☐ Neg ☐ SLN+ ☐ Clin+ ☐ NX IC: ☐ Neg ☐ Pos ☐ NX SC: ☐ Neg ☐ Pos ☐ NX
Lymph nodes (clinical)	☐ Not applicable ☐ Negative ☐ Positive ☐ Cannot be assessed or unknown status (NX) If clinically positive, check all that apply, ☐ Movable level I, II axillary lymph node(s) ☐ Fixed or matted level I, II axillary lymph nodes ☐ Internal mammary lymph node(s) ☐ Infraclavicular lymph node(s) ☐ Supraclavicular lymph node(s)

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Tumor stage	T _____ N _____ M _____ ☐ **Stage 0** Tis / N0 / M0 ☐ **Stage IA** T1/N0/M0 ☐ **Stage IB** T0 / N1mi / M0 T1 / N1mi / M0 ☐ **Stage IIA** T0 / N1 / M0 T1 / N1 / M0 T2 / N0 / M0 ☐ **Stage IIB** T2 / N1 / M0 T3 / N0 / M0 ☐ **Stage IIIA** T0 / N2 / M0 T1 / N2 / M0 T2 / N2 / M0 T3 / N1 / M0 T3 / N2 / M0 ☐ **Stage IIIB** T4 / N0 / M0 T4 / N1 / M0 T4 / N2 / M0 ☐ **Stage IIIC** Any T / N3 / M0 ☐ **Stage IV** Any T / Any N / M1 ☐ Other: _____ ☐ TNM unknown, Stage unknown ☐ AJCC Staging Edition _____
Comment	

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

POST-TREATMENT TNM STAGING (NEOADJUVANT CASES ONLY)	
Tumor size	_____ mm *(invasive component only)* ☐ Cannot be determined or unknown status (TX)
Axillary lymph nodes (path) *Isolated tumor cells: ≤0.2 mm or ≤200 cells* *Micrometastasis: >0.2 mm to 2.0 mm* *Macrometastasis: >2.0 mm*	☐ Negative ☐ Isolated tumor cells (ITCs), #LN _____ ☐ Micro- or macrometastasis , #LN _____ ☐ Micrometastasis only ☐ Nodes not sampled or unknown status (NX) Total axillary nodes sampled: _____ Largest metastasis: _____ mm Extranodal extension: ☐ No ☐ Yes
Other regional lymph nodes (path) *IM = internal mammary* *IC = infraclavicular (level III axillary)* *SC = supraclavicular*	IM: ☐ Neg ☐ SLN+ ☐ Clin+ ☐ NX IC: ☐ Neg ☐ Pos ☐ NX SC: ☐ Neg ☐ Pos ☐ NX
Tumor stage *(Stage will also be calculated)*	T _____ N _____ M _____ ☐ **Stage 0** Tis / N0 / M0 ☐ **Stage IA** T1/N0/M0 ☐ **Stage IB** T0 / N1mi / M0 T1 / N1mi / M0 ☐ **Stage IIA** T0 / N1 / M0 T1 / N1 / M0 T2 / N0 / M0 ☐ **Stage IIB** T2 / N1 / M0 T3 / N0 / M0 ☐ **Stage IIIA** T0 / N2 / M0 T1 / N2 / M0 T3 / N1 / M0 T3 / N2 / M0 ☐ **Stage IIIB** T4 / N0 / M0 T4 / N1 / M0 T4 / N2 / M0 ☐ **Stage IIIC** Any T / N3 / M0 ☐ **Stage IV** Any T / Any N / M1 ☐ Other: _____ ☐ TNM unknown, Stage unknown ☐ AJCC Staging Edition _____

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

Response to neoadjuvant therapy	☐ Complete response (CR) ☐ Residual DCIS ☐ Partial response (PR) ☐ Decrease in tumor volume ☐ Decrease in positive nodes ☐ No response (NR)
Comment	

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

BIOMARKER STUDIES		☐ Yes ☐ No ☐ Not reported / Unknown
Record Pos/Neg status only if details not available.	**Laterality:** ☐ Left ☐ Right ☐ Not applicable **Surgical Pathology ID:** _____ **Block** _____ **Tumor #:** _____ **Description:** ☐ Recurrence ☐ Neoadjuvant therapy ☐ In situ ☐ Invasive ☐ Metastatic, lymph node ☐ Metastatic, distant ☐ Malignant,NOS	
Estrogen receptor	☐ Pos ☐ Neg ☐ Unk	Nuclear staining _____ % *or* Range _____ to _____ % Intensity: ☐ Weak ☐ Moderate ☐ Strong Pattern: ☐ Homogeneous ☐ Heterogeneous
Progesterone receptor	☐ Pos ☐ Neg ☐ Unk	Nuclear staining _____ % *or* Range _____ to _____ % Intensity: ☐ Weak ☐ Moderate ☐ Strong Pattern: ☐ Homogeneous ☐ Heterogeneous
HER2 /*neu* IHC	☐ Pos ☐ Neg ☐ Unk	IHC Score: ☐ 0 ☐ 1+ ☐ 2+ ☐ 3+
HER2 /*neu* FISH or CISH	☐ Pos ☐ Neg ☐ Unk	☐ FISH ☐ CISH HER2 mean copy # _____ HER2 ratio _____ CEP17 mean copy # _____
Ki-67	☐ Unk	Nuclear staining _____ % *or* Range _____ to _____ % Intensity: ☐ Weak ☐ Moderate ☐ Strong Pattern: ☐ Homogeneous ☐ Heterogeneous
p53	☐ Unk	Nuclear staining _____ % *or* Range _____ to _____ % Intensity: ☐ Weak ☐ Moderate ☐ Strong Pattern: ☐ Homogeneous ☐ Heterogeneous
Comments:		

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / _____

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other _____

PROGNOSTIC STUDIES		☐ Yes ☐ No ☐ Not reported / Unknown
Study	**Date of study**	**Result**
☐ BRCA 1 or 2 mutation	____/____/_____	☐ BRCA 1 Positive ☐ Negative ☐ BRCA 2 Positive ☐ Variant of undetermined significance ☐ Variant _____
☐ Oncotype DX	____/____/_____	Recurrence score: _____
☐ Gail Model	____/____/_____	5-year patient risk: _____% 5-year average risk: _____% Lifetime patient risk (to age 90): _____% Lifetime average risk (to age 90): _____%
☐ Other:	____/____/_____	☐ _____
☐ Other:	____/____/_____	☐ _____
☐ Other:	____/____/_____	☐ _____
Comment		

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / ______

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other ____________________

RADIATION THERAPY ☐ Yes ☐ No ☐ Not reported / Unknown

Location: ☐ Locoregional ☐ Distant Metastasis

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ____________________________

Laterality: ☐ Left ☐ Right ☐ Not applicable

Field treated: ____

Start/end date: ____/____/________ to ____/____/________

Fractions: _________ Dose / Fraction : _________ Total Dose: __________ cGy

Comment:

Location: ☐ Locoregional ☐ Distant Metastasis

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ____________________________

Laterality: ☐ Left ☐ Right ☐ Not applicable

Field treated: ____

Start/end date: ____/____/________ to ____/____/________

Fractions: _________ Dose / Fraction : _________ Total Dose: __________ cGy

Comment:

Location: ☐ Locoregional ☐ Distant Metastasis

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ____________________________

Laterality: ☐ Left ☐ Right ☐ Not applicable

Field treated: ____

Start/end date: ____/____/________ to ____/____/________

Fractions: _________ Dose / Fraction : _________ Total Dose: __________ cGy

Comment:

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / ______

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other ___________________

PHARMACOLOGIC THERAPY ☐ Yes ☐ No ☐ Not reported / Unknown

Drug ______________________

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ___________________________

Dose (per cycle): __________ or Dose range (if varied) _________ to _________

Dose unit: ______

Cycles: ________ # Doses: ________ Dosing schedule: ____________________

Start/end date: ____/____/________ to ____/____/________ or ☐ Active medication

☐ Dose Reduction

Comment:

Drug ______________________

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ___________________________

Dose (per cycle): __________ or Dose range (if varied) _________ to _________

Dose unit: ______

Cycles: ________ # Doses: ________ Dosing schedule: ____________________

Start/end date: ____/____/________ to ____/____/________ or ☐ Active medication

☐ Dose Reduction

Comment:

Drug ______________________

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ___________________________

Dose (per cycle): __________ or Dose range (if varied) _________ to _________

Dose unit: ______

Cycles: ________ # Doses: ________ Dosing schedule: ____________________

Start/end date: ____/____/________ to ____/____/________ or ☐ Active medication

☐ Dose Reduction

Comment:

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / ______

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other ____________________

Drug _______________________

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ____________________________

Dose (per cycle): __________ or Dose range (if varied) _________ to _________

Dose unit: ______

Cycles: ________ # Doses: ________ Dosing schedule: _____________________

Start/end date: ____/____/________ to ____/____/________ or ☐ Active medication

☐ Dose Reduction

Comment:

Drug _______________________

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ____________________________

Dose (per cycle): __________ or Dose range (if varied) _________ to _________

Dose unit: ______

Cycles: ________ # Doses: ________ Dosing schedule: _____________________

Start/end date: ____/____/________ to ____/____/________ or ☐ Active medication

☐ Dose Reduction

Comment:

Drug _______________________

Indication: ☐ Neoadjuvant ☐ Adjuvant ☐ Progression ☐ Recurrence ☐ Other ____________________________

Dose (per cycle): __________ or Dose range (if varied) _________ to _________

Dose unit: ______

Cycles: ________ # Doses: ________ Dosing schedule: _____________________

Start/end date: ____/____/________ to ____/____/________ or ☐ Active medication

☐ Dose Reduction

Comment:

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / ______

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other ____________________

Tissue Sample Attributes							
Sample ID	**Sample Date**	**Laterality** ☐ Left ☐ Right ☐ N/A	**Tumor #**		**Usage Code** ☐ Green ☐ Yellow ☐ Red		
Tissue ☐ Breast ☐ SLN ☐ Non-SLN ☐ LN, extra-axillary ☐ Skin ☐ Other:	**Sample Type** ☐ OCT ☐ FF ☐ Paraffin ☐ Slide(s)	**Location in Breast** ☐ UOQ ☐ Mid outer ☐ UIQ ☐ Mid inner ☐ Upper mid ☐ Central ☐ LIQ ☐ Unknown ☐ LOQ ☐ N/A ☐ Lower mid	**Dist. From Tumor** ☐ Adjacent ☐ _____ cm ☐ Unknown ☐ N/A	**Tissue Weight** _____ g	**Ischemia Interval** _____min	**Diagnostic Category** ☐ Benign ☐ Atypical ☐ In situ ☐ Invasive ☐ Metastatic ☐ Malignant,NOS	**Diagnosis Codes** __
Comment:							

Tissue Sample Attributes							
Sample ID	**Sample Date**	**Laterality** ☐ Left ☐ Right ☐ N/A	**Tumor #**		**Usage Code** ☐ Green ☐ Yellow ☐ Red		
Tissue ☐ Breast ☐ SLN ☐ Non-SLN ☐ LN, extra-axillary ☐ Skin ☐ Other:	**Sample Type** ☐ OCT ☐ FF ☐ Paraffin ☐ Slide(s)	**Location in Breast** ☐ UOQ ☐ Mid outer ☐ UIQ ☐ Mid inner ☐ Upper mid ☐ Central ☐ LIQ ☐ Unknown ☐ LOQ ☐ N/A ☐ Lower mid	**Dist. From Tumor** ☐ Adjacent ☐ _____ cm ☐ Unknown ☐ N/A	**Tissue Weight** _____ g	**Ischemia Interval** _____min	**Diagnostic Category** ☐ Benign ☐ Atypical ☐ In situ ☐ Invasive ☐ Metastatic ☐ Malignant,NOS	**Diagnosis Codes** __
Comment:							

Tissue Sample Attributes							
Sample ID	**Sample Date**	**Laterality** ☐ Left ☐ Right ☐ N/A	**Tumor #**		**Usage Code** ☐ Green ☐ Yellow ☐ Red		
Tissue ☐ Breast ☐ SLN ☐ Non-SLN ☐ LN, extra-axillary ☐ Skin ☐ Other:	**Sample Type** ☐ OCT ☐ FF ☐ Paraffin ☐ Slide(s)	**Location in Breast** ☐ UOQ ☐ Mid outer ☐ UIQ ☐ Mid inner ☐ Upper mid ☐ Central ☐ LIQ ☐ Unknown ☐ LOQ ☐ N/A ☐ Lower mid	**Dist. From Tumor** ☐ Adjacent ☐ _____ cm ☐ Unknown ☐ N/A	**Tissue Weight** _____ g	**Ischemia Interval** _____min	**Diagnostic Category** ☐ Benign ☐ Atypical ☐ In situ ☐ Invasive ☐ Metastatic ☐ Malignant,NOS	**Diagnosis Codes** __
Comment:							

CBCP # __ __ __ __ __ __ __ __ __ **Date** ___ / ___ / ______

Site ☐ WRNMMC ☐ AAMC ☐ JMBCC ☐ Other ___________________

Tissue Sample Attributes							
Sample ID	**Sample Date**	**Laterality** ☐ Left ☐ Right ☐ N/A	**Tumor #**		**Usage Code** ☐ Green ☐ Yellow ☐ Red		
Tissue ☐ Breast ☐ SLN ☐ Non-SLN ☐ LN, extra-axillary ☐ Skin ☐ Other:	**Sample Type** ☐ OCT ☐ FF ☐ Paraffin ☐ Slide(s)	**Location in Breast** ☐ UOQ ☐ Mid outer ☐ UIQ ☐ Mid inner ☐ Upper mid ☐ Central ☐ LIQ ☐ Unknown ☐ LOQ ☐ N/A ☐ Lower mid	**Dist. From Tumor** ☐ Adjacent ☐ _____ cm ☐ Unknown ☐ N/A	**Tissue Weight** _____ g	**Ischemia Interval** _____min	**Diagnostic Category** ☐ Benign ☐ Atypical ☐ In situ ☐ Invasive ☐ Metastatic ☐ Malignant,NOS	**Diagnosis Codes** __
Comment:							

Tissue Sample Attributes							
Sample ID	**Sample Date**	**Laterality** ☐ Left ☐ Right ☐ N/A	**Tumor #**		**Usage Code** ☐ Green ☐ Yellow ☐ Red		
Tissue ☐ Breast ☐ SLN ☐ Non-SLN ☐ LN, extra-axillary ☐ Skin ☐ Other:	**Sample Type** ☐ OCT ☐ FF ☐ Paraffin ☐ Slide(s)	**Location in Breast** ☐ UOQ ☐ Mid outer ☐ UIQ ☐ Mid inner ☐ Upper mid ☐ Central ☐ LIQ ☐ Unknown ☐ LOQ ☐ N/A ☐ Lower mid	**Dist. From Tumor** ☐ Adjacent ☐ _____ cm ☐ Unknown ☐ N/A	**Tissue Weight** _____ g	**Ischemia Interval** _____min	**Diagnostic Category** ☐ Benign ☐ Atypical ☐ In situ ☐ Invasive ☐ Metastatic ☐ Malignant,NOS	**Diagnosis Codes** __
Comment:							

Tissue Sample Attributes							
Sample ID	**Sample Date**	**Laterality** ☐ Left ☐ Right ☐ N/A	**Tumor #**		**Usage Code** ☐ Green ☐ Yellow ☐ Red		
Tissue ☐ Breast ☐ SLN ☐ Non-SLN ☐ LN, extra-axillary ☐ Skin ☐ Other:	**Sample Type** ☐ OCT ☐ FF ☐ Paraffin ☐ Slide(s)	**Location in Breast** ☐ UOQ ☐ Mid outer ☐ UIQ ☐ Mid inner ☐ Upper mid ☐ Central ☐ LIQ ☐ Unknown ☐ LOQ ☐ N/A ☐ Lower mid	**Dist. From Tumor** ☐ Adjacent ☐ _____ cm ☐ Unknown ☐ N/A	**Tissue Weight** _____ g	**Ischemia Interval** _____min	**Diagnostic Category** ☐ Benign ☐ Atypical ☐ In situ ☐ Invasive ☐ Metastatic ☐ Malignant,NOS	**Diagnosis Codes** __
Comment:							

ATTACHMENT 8:
Annual Retreat Agendas
2015, 2016 and 2017

Clinical Breast Care Project (CBCP) Retreat

USUHS, Sanford Auditorium
Friday, July 24, 2015

7:30 – 8:00 AM	Registration and Continental Breakfast	
8:00 – 8:05 AM	Welcome and Announcements	Jaime Boone, MBA
8:05 – 8:20 AM	Opening Remarks	Craig D. Shriver, MD, FACS (Director/PI)
8:20 – 8:35 AM	Greetings from WRI	Tom Kurtz, President (CEO WRI/WMC)
8:35 – 8:55 AM	CBCP Research Update	Hai Hu, PhD
8:55 – 9:15 AM	Tissue Bank	Stella Somiari, PhD
9:15 – 9:35 AM	Biomedical Informatics Infrastructure	Leonid Kvecher, MS
9:35 – 9:55 AM	Translational Breast Research Update	Rachel Ellsworth, PhD
9:55 – 10:05 AM	Break	
10:05 – 10:25 AM	Pathology Update	Al Kovatich, Scientist
10:25 – 10:45 AM	Research Update	Juliana Slavik, MS for George Iida, PhD
10:45 – 11:05 AM	Genetics Update	Raymond Weiss, MD
11:05 – 11:15 AM	Nurse Navigators	Becky Trupp, RN (Hilton, RN/Ganster, RN)
11:15 – 11:30 AM	AAMC Breast Center	Dr. Lorrain Tafra, MD
11:30 – 11:45 AM	JMBCC Breast Center	Dr. Deborah Sims, MD
11:45 – 12:00 PM	Discussion Wrap Up of Morning	Craig D. Shriver, MD
12:00 – 12:15 PM	Group Photo	Outdoor Quad Area
12:15 – 1:15 PM	Lunch on Your Own	USUHS Cafeteria
1:15 – 1:45 PM	Status of CBCP protocols / New CRF	Sara Sakura, PsyD, CCRP Leigh Campbell, M.S., P.A. (ASCP), CCRP
1:45 – 3:45 PM	Discussion / Visioning for Future	Craig D. Shriver, MD / Group
3:45 – 4:00 PM	Concluding Remarks	Craig D. Shriver, MD

Murtha Cancer Center (MCC) Retreat

USUHS, Sanford Auditorium
Friday, July 29, 2016

7:30 – 8:00 AM	**Registration and Continental Breakfast**	
8:00 – 8:05 AM	**Welcome and Opening Remarks**	**Craig D. Shriver, MD (MCC Director)**
8:05 – 8:15 AM	**Greetings from Leadership**	**Dean Arthur Kellermann/CAPT Eric Elster**
8:15 – 8:40 AM	**MCC Overview**	**Craig D. Shriver, MD**
8:40 – 9:10 AM	**GYN CoE Overview**	**George Maxwell, MD**
9:10 – 9:40 AM	**CPDR CoE Overview**	**Inger Rosner, MD / Dr. Shiv Srivastava**
9:40 – 9:55 AM	**NCI Collaboration Update**	**Dr. Patricia Steeg/ Dr. Stanley Lipkowitz**
9:55 – 10:15 AM	**CBCP CoE Overview**	**Craig D. Shriver, MD**
10:15 – 10:30 AM	**Break**	
10:30 – 11:15 AM	**Visioning for Future – Research**	**Craig D. Shriver, MD / Group**
11:15 – 12:00 PM	**Visioning for Future – Admin/Regulatory**	**Craig D. Shriver, MD / Group**
12:00 – 12:15 PM	**Group Photo**	**Outdoor Quad Area**
12:15 – 1:00 PM	**Lunch on Your Own**	**USUHS Cafeteria**
1:00 – 1:15 PM	**MCC Recognition**	**Craig D. Shriver, MD**
1:15 – 2:15 PM	**Visioning for Future – Informatics**	**Craig D. Shriver, MD / Group**
2:15 – 3:15 PM	**Visioning for Future – Biobank**	**Craig D. Shriver, MD / Group**
3:15 – 3:45 PM	**Discussion / Wrap Up**	**Craig D. Shriver, MD / Group**
3:45 – 4:00 PM	**Concluding Remarks**	**Craig D. Shriver, MD / Group**

Murtha Cancer Center (MCC) Retreat

USUHS, Sanford Auditorium
Friday, July 28, 2017

7:30 – 8:00 AM	Registration and Continental Breakfast	
8:00 – 8:05 AM	Welcome and Opening Remarks	COL Craig D. Shriver, MD (MCC Director)
8:05 – 8:15 AM	Greetings from Leadership	Dean Arthur Kellermann/CAPT Eric Elster
8:15 – 8:45 AM	MCC Overview	COL Craig D. Shriver, MD
8:45 – 9:15 AM	GYN CoE Overview	Thomas Conrads, PhD
9:15 – 9:45 AM	CPDR CoE Overview	COL Inger Rosner, MD / Shiv Srivastava, PhD
9:45 – 10:00 AM	NCI Collaboration Update	Dr. Stanley Lipkowitz
10:00 – 10:15 AM	CBCP CoE Overview	COL Craig D. Shriver, MD
10:15 – 10:30 AM	Break	
10:30 – 10:45 AM	Overall Vision of APOLLO	COL Craig D. Shriver, MD
10:45 – 11:15 AM	GYN CoE and APOLLO	Thomas Conrads, PhD
11:15 – 11:45 AM	CPDR CoE and APOLLO	COL Inger Rosner, MD / Dr. Shiv Srivastava
11:45 – 12:00 PM	Tissue Bank at the CSSIOMM	Caroline Larson (Manager, Biobank)
12:00 – 12:15 PM	Group Photo	Sanford Auditorium
12:15 – 1:00 PM	Lunch on Your Own	USUHS Cafeteria
1:00 – 1:15 PM	MCC Recognition	COL Craig D. Shriver, MD
1:15 – 1:45 PM	Data and APOLLO	Hai Hu, PhD
1:45 – 2:00 PM	APOLLO 5 Protocol	Sara Sakura, PhD
2:00 – 2:30 PM	Biobanking (MCC, MTFs, AAMC, APOLLO and ORIEN)	LTC Justin Wells, MD
2:30 – 3:15 PM	Early Results - APOLLO	Harvey Pollard, MD, PhD/Clifton Dalgard, PhD Matthew Wilkerson, PhD (TAGC)
3:15 – 3:45 PM	Open Discussion (WRIKE display)	COL Craig D. Shriver, MD / Group
3:45 – 4:00 PM	Closing Remarks / Adjourn	COL Craig D. Shriver, MD

ATTACHMENT 9: National Accreditation Programs of Breast Centers (NAPBC) Certificate

NAPBC®

NATIONAL ACCREDITATION PROGRAM FOR BREAST CENTERS

Awards this

Certificate of Accreditation

to

Breast Center at

Walter Reed National Military Medical Center

Three-Year Full Accreditation

September 2015 - September 2018

James L. Connolly

James L. Connolly, MD, FCAP
Chair
National Accreditation Program for Breast Centers

Terry Sarantou MD

Terry Sarantou, MD, FACS
Chair, Standards and Accreditation Committee
National Accreditation Program for Breast Centers

AMERICAN COLLEGE OF SURGEONS
Inspiring Quality:
Highest Standards, Better Outcomes

ATTACHMENT 10: College of American Pathologists (CAP) Accreditation Certificate

Advancing Excellence

Accredited Laboratory

The College of American Pathologists

certifies that the laboratory named below

Windber Research Institute
Biorepository
Windber, Pennsylvania
Stella B. Somiari, PhD

CAP Number: 8076297
AU-ID: 1708765

has met all applicable standards for accreditation and is hereby accredited by the College of American Pathologists' Biorepository Accreditation Program. Reinspection should occur prior to April 7, 2018 to maintain accreditation.

Accreditation does not automatically survive a change in director, ownership, or location and assumes that all interim requirements are met.

Chair, Commission on Laboratory Accreditation

FCAP
President, College of American Pathologists