DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Report to Congress:

Use of Funds Received for Semipostal Stamp for Breast Cancer Research

Fiscal Year 2019

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Introduction

On December 20, 2019, Congress reauthorized the Stamp Out Breast Cancer Act, which extended the authority of the U.S. Postal Service to issue a semipostal stamp to raise funds for breast cancer research through 2027. A provision of this law requires that the National Institutes of Health (NIH) and the Department of Defense each submit an annual report concerning the use of any amounts received from the sale of the stamps, including a description of any significant advances or accomplishments, to Congress and the Government Accountability Office (GAO) (39 U.S.C. 414). To fulfill this requirement, the following report has been prepared by the National Cancer Institute (NCI), NIH, Department of Health and Human Services.

This report highlights the research currently funded by proceeds from the semipostal stamp for breast cancer research. Additional information related to the Breast Cancer Research Stamp is available electronically on the NCI website at http://www.cancer.gov/aboutnci/overview/contributing.

Background

In the United States, breast cancer is the most common non-skin cancer and the second leading cause of cancer death, after lung and bronchus cancer, among women. According to the Annual Report to the Nation 2019, it is estimated that there will be an estimated 268,600 new cases of breast cancer among women in the United States in 2019, and 41,760 women will die from the disease this year.[1]

Since 1998, increased support for breast cancer research has come from funding through the highly successful Stamp Out Breast Cancer Act. The breast cancer research stamp is offered through the United States Postal Service as an alternative to a first class postage stamp. The Stamp Out Breast Cancer Act (The Stamp Act), which Congress initially enacted in 1997, stipulates that 70 percent of the proceeds from the stamp surcharge be directed to the NIH for breast cancer research and 30 percent to the Department of Defense for the same purpose. Congress reauthorized the Stamp Act in 2019, extending the sales period through December 31, 2027.

In November 1998, NCI began receiving Breast Cancer Research Stamp proceeds from the United States Postal Service. Since then, the NCI has allocated the proceeds – totaling $62.2 million – to eligible research. Of this amount, NCI obligated $53.4 million by the close of fiscal year 2019 through multiple extramural grant programs, as well as some NCI intramural research programs. NCI senior leadership considers a program's potential to make significant progress against breast cancer when selecting programs for funding.

The sections of this report that follow discuss the NCI research programs in detail. The studies currently funded include awards supported through the Molecular and Cellular Characterization of Screen-Detected Lesions Consortium and two randomized trial studies that include only female study subjects, the Breast Cancer Weight Loss (BWEL) Study and the Tomosynthesis Mammographic Imaging Screening Trial (TMIST).

[1] https://seer.cancer.gov/report_to_nation/statistics.html

NCI receives the Breast Cancer Research Stamp funds in May and November of each fiscal year. The table below lists the annual amounts received during each fiscal year since the inception of the program.

Breast Cancer Research Stamp Act Collections	
FY	**Total**
1999	$4,150,210.00
2000	$3,101,033.00
2001	$5,556,224.67
2002	$3,594,619.80
2003	$5,175,938.00
2004	$4,813,994.00
2005	$4,372,191.62
2006	$4,467,540.23
2007	$3,006,105.81
2008	$4,855,539.01
2009	$3,403,204.50
2010	$2,344,610.59
2011	$2,048,555.12
2012	$1,622,774.59
2013	$1,403,656.57
2014	$1,160,055.41
2015	$1,251,477.38
2016	$1,707,408.51
2017	$1,387,066.59
2018	$1,293,677.44
2019	$1,449,512.98
Total	**$62,165,395.82**

Projects Currently Funded by Stamp Act Proceeds

During fiscal year 2015, NCI began funding meritorious breast cancer applications, with consideration also given to funding priorities and public health significance, among other factors, submitted in response to the RFAs entitled, "Molecular and Cellular Characterization of Screen-Detected Lesions" (RFA-CA-14-010 and RFA-CA-14-011), with Stamp Act proceeds. NCI continued to fund these projects in fiscal year 2019.

Molecular and Cellular Characterization of Screen-Detected Lesions Consortium

This NCI initiative addresses one of the most challenging problems in oncology: predicting more precisely whether lesions that are detected by sensitive screening tests are indolent (hence, not requiring extensive treatment) or progressive and potentially life threatening. The overarching goal of this initiative is to identify cellular and molecular characteristics that distinguish progressive from non-progressive lesions.

NCI published two Funding Opportunity Announcements (RFA-CA-14-010 and RFA-CA-14-011) soliciting applications from multi-disciplinary teams in the extramural community to undertake a comprehensive molecular characterization of tumor tissue, cell, and microenvironment components of screen-detected early lesions, as well as interval, and symptom-detected cancers in one or more of the following tumor sites: breast, prostate, lung, melanoma, and pancreas. The use of enabling approaches and technologies was encouraged to determine the cellular and molecular phenotypes of early lesions, to assess the degree to which the behavior of these lesions is predictable or not, and to allow better predictions of the fate of such lesions.

From fiscal years 2015 through 2020, the NCI used the Breast Cancer Research Stamp Fund to support the following three meritorious applications received in response to these solicitations that are specifically focused on breast cancer:

University of Vermont and State Agricultural College (CA196383) – The goal of this project is to identify tumor microenvironment signatures that predict the aggressiveness of early stage, screen-detected breast cancers by minimally invasive methods. The researchers will leverage and refine state-of-the-art technologies to characterize aggressive signatures based on the cellular composition and gene expression of specific cell populations within the tumor microenvironment of interval (i.e., tumors missed by annual screening) and symptom-detected invasive breast cancers. The researchers will then determine whether the presence of these aggressive tumor microenvironment signatures in early stage, screen-detected breast cancer is associated with disease progression. Identifying aggressive and indolent (i.e., slow growing) tumor microenvironment signatures will promote the development of more conservative treatment strategies for the subset of women with favorable prognoses and suggest novel targets for therapeutic intervention in cases with less favorable prognoses. Researchers have constructed large-scale tissue microarrays containing symptom and interval detected tumor/stroma samples and are using advanced imaging and computational methods to characterize distinct stromal cell populations and distinguish invasive tumor and benign stroma. Recently, investigators found that the novel non-coding RNA, Mitotically-Associated lncRNA (MANCR), affects genome stability and is upregulated in aggressive breast cancers and associated

with poor overall patient survival.

University of California-San Francisco (CA196406) – The goal of this project is to identify better ways to screen for and treat the most aggressive cancers and avoid overdiagnosis and overtreatment, as well as develop evidence to avoid the inadvertent labeling of indolent lesions as cancers. The project intends to develop better biologic discriminators among indolent, ultralow, low, and interval cancers (i.e., cancers missed by screening tests) by harnessing a network of research collaborators and unique data sets. Assays developed through this research can be tested in samples from a unique, prospectively randomized trial of annual vs. personalized screening across the five University of California (UC) Medical Centers and the Sanford Health system in the rural Midwest. Germline profiling will be available on all women in the personalized arm, and expression profiling will be available for all tumors diagnosed. The project also aims to find out who is at risk for specific subtypes of breast cancer, with the ultimate goal of adjusting screening and prevention activities to mitigate overdiagnosis and overtreatment for both in situ (i.e., tumors that have not migrated) and invasive lesions. Further, the project plans to address the specific features of interval cancers that may generate a better approach to screening and prevention than the current imaging-based screening paradigm. The overall approach seeks to retrospectively optimize and prospectively validate new and emerging molecular, morphometric, and tumor immune microenvironment assays, and to prospectively add the context of germline predisposition. Thus far, researchers have identified five distinct immune subtypes in breast cancer involving either elevated or reduced levels of inflammatory cells or cytokines with significant outcome differences, including response to immune checkpoint inhibitor-based therapies. Investigators also validated the 70-gene MammaPrint (MP) signature, showing that an ultra-low MP threshold identifies women with extremely low risk of progression to metastasis after surgery alone.

Baylor College of Medicine (CA196386) – This grant supports the Baylor College of Medicine as the Coordinating and Data Management Group (CDMG) for the Molecular Characterization Labs (MCLs). NCI has used the Breast Cancer Research Stamp funds partly support the CDMG for breast cancer-related efforts, including statistical support and computational analysis of MCL breast cancer site-generated data. The CDMG has recently described two testing methods – Marcenko-Pastur Distribution and Tracy-Widom Tests – that may support a more accurate prediction of biologically relevant outcomes from observable genomic variables, including breast cancer-associated variables. Furthermore, NCI has used the Breast Cancer Research Stamp funds partially support the CDMG in protocol development for collaborative breast cancer projects aimed at the validation of molecular signatures distinguishing indolent from aggressive, screen-detected and interval/symptom-detected lesions and for the prospective collection of biospecimens by the individual breast cancer MCL sites. CDMG-related efforts led to the recent development of an integrated data sharing platform to facilitate the acquisition, processing and distribution of data sets between MCL breast cancer partner sites and the consortium at large.

The list of grant awards, affiliations, and funding information are in Appendix 5.

New Programs funded in Fiscal Years 2017-2019

Breast Cancer Weight Loss (BWEL)

The BWEL Study is a randomized trial comparing the impact of a supervised weight loss intervention plus health education materials against health education materials alone upon invasive disease-free survival in overweight and obese women with stage II-III breast cancer. BWEL is a rigorously designed trial conducted by the Alliance National Clinical Trials Network (NCTN) Group. The study will enroll 3,136 women with stage II-III hormone receptor positive or triple negative breast cancer diagnosed within the previous 14 months who have a BMI ≥ 27 kg/m2. Women will enroll in BWEL after completing surgery, chemotherapy, and radiation (if indicated) and be randomized to either a 2-year intervention of a supervised weight loss program + health education materials or health education materials alone. The primary endpoint is disease-free survival with secondary endpoints that include the impact of the weight loss intervention on overall survival, development of other medical problems, quality of life, and correlative science objectives that evaluate specific translational mechanisms linking obesity with breast cancer. NCI has used the Breast Cancer Research Stamp Fund to provide partial support for this study.

Over the past year, enrollment in the BWEL trial has continued to meet target goals. To date, 2569 patients have completed all baseline data collection and have been randomized to the weight loss intervention or health education control group, representing approximately 82% of the target enrollment. Enrollment is expected to be completed in late summer 2020. Participants have been enrolled from 49 states and 7 Canadian provinces, with approximately 50% of participants enrolling through community-based practice sites. The study population is relatively diverse, with more than 25% of enrolled participants representing racial and/or ethnic minority groups. The study intervention is offered in both English and Spanish, and efforts are on-going through community-based outreach and development of additional Spanish recruitment materials to increase enrollment of Hispanic participants over the next year.

The BWEL study also passed an interim weight loss analysis in March of 2019, demonstrating that participants randomized to the weight loss intervention had >4% loss of baseline weight as compared to controls.

The list of grant awards, affiliations, and funding information are in Appendix 6.

Tomosynthesis Mammographic Imaging Screening Trial (TMIST)-- Processing and Storage of Biospecimens

During fiscal year 2017, the NCI began supporting the Tomosynthesis Mammographic Imaging Screening Trial (TMIST), a large nationwide randomized trial of the two most commonly used mammography screening technologies: tomosynthesis (TM) and digital mammography (DM). The purpose of the trial is to evaluate whether the newer technology (TM) produces a stage shift through earlier detection of the most aggressive tumors or merely detection of additional cancers that may not be dangerous to the woman. Through long-term follow-up, this study should also provide information on the relative impact of the new technology on breast cancer mortality. TMIST will also provide measurements of the diagnostic accuracy of the currently available technologies in women undergoing current state-of-the-art treatments.

In addition, through the analysis and correlation of the genetic features of all breast lesions undergoing biopsy in the TMIST participants during the trial, this study should substantially increase the understanding of the biology of breast cancers detected through screening and how those factors vary by method of detection. These specimens will provide a rich biorepository for future hypothesis generation and testing in this domain. NCI will use the Breast Cancer Research Stamp funds to support the repository of these specimens that are stored at the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) Central Biorepository and Pathology Facility, MD Anderson Cancer Center.

As of January 28, 2020, 22,000 women have been randomized in the trial. There are 92 participating practices that have enrolled women and 30 practices in the credentialing phase. It is anticipated that 150 sites will participate during the next fiscal year. International sites include Canada and South American and others are being vetted or awaiting State Department clearance. Consenting and collection of biospecimens can be performed at any time during the duration of the screening component of the trial. As of December 2019, 25, 969 women have consented to submitting specimens, and 9, 675 specimens have been collected. The study team has partnered with other stakeholders, including the Centers for Disease Control and Prevention and Komen Foundation to enhance accrual.

The list of grant awards, affiliations, and funding information are in Appendix 7.

Conclusion

Breast cancer research has benefited from the innovative funding source that Congress established in the Stamp Out Breast Cancer Act. The additional funding has allowed cancer researchers to increase the public's knowledge of genetics and molecular biology in ways that may support the development of more effective and less toxic treatments for breast cancer. Moreover, through the Molecular and Cellular Characterization of Screen-Detected Lesions Consortium funded by Stamp Act proceeds, the NCI supports investigations to distinguish screen-detected lesions that are life threatening from those that are indolent. These investigations and others funded with Stamp Act proceeds have the potential to contribute to the prevention, detection, and treatment of breast cancer malignancies, while also appropriately protecting women from unnecessary, aggressive treatments. The Stamp Act proceeds afford NCI the ability to support the most innovative laboratory research and clinical trials to transform today's data into tomorrow's most groundbreaking clinical discoveries.

The summary below lists all the programs that NCI has supported or currently supports with Breast Cancer Research Stamp collections:

Fiscal Year(s) Funded	NCI Program Title	Obligated	Projected Funding for Future Years	Stamp Funds Balance
2000-2002	Insight Awards	$9,409,783		
2003-2008	Exceptional Opportunities in Breast Cancer Research	$12,345,462		
2006	TAILORx Trial	$4,566,019		
2006-2014	Breast Pre-Malignancy Program funding both intramural and extramural research projects	$14,267,031		
2015-2019	Molecular and Cellular Characterization of Screen-Detected Lesions	$8,085,650		
2018-2021	Breast cancer Weight Loss (BWEL)	$2,000,000	$2,000,000	
2018-2024	Tomosynthesis Mammographic Imaging Screening Trial (TMIST)-	$2,709,686	$4,701,779	
Total		**$53,383,631**	**$6,701,779**	**$8,726,898**

Note: Some amounts displayed in this table may be different than amounts displayed in reports from prior years. The primary reason for such differences relates to funding balances that were not fully expended on project activities and were reclaimed through the grant accounting process.

*Planned Future Projects: Future projects are pending anticipated collections.
**Stamp Funds Balance: The NIH conducted an audit of the BCS resources and found approximately $6.6 million of available resources that were not properly allocated to the BCS program. These additional resources relate to recoveries of previous obligations that occurred in the early 2000s and were returned to the NCI.

Appendix 1. Summaries for Completed Programs Funded with Proceeds from the Breast Cancer Research Stamp

Insight Awards to Stamp Out Breast Cancer (2000-2002)

The Insight Awards to Stamp Out Breast Cancer program was designed to support research grants considered high risk, with the potential for high reward. One of the central aims of this initiative was to challenge existing paradigms and to develop new methodologies and technologies in breast cancer research. Using funds from the proceeds made available via Breast Cancer Research Stamp Act, NCI awarded 86 Insight Awards totaling nearly $9.4 million to extramural research investigators located at universities and medical schools across the country.

The list of grant awards, affiliations, and funding information are in Appendix 2.

Exceptional Opportunities in Breast Cancer Research (2003-2008)

Under the Exceptional Opportunities in Breast Cancer Research program, NCI used the Breast Cancer Research Stamp proceeds to support high-quality and peer-reviewed breast cancer grant applications that were outside the funding ability for NCI in that fiscal year. Through this initiative, NCI provided grant support for a maximum of four years to 36 Exceptional Opportunities Awards, totaling $12.4 million. Breast cancer research benefited from the Institute's ability to expand its research portfolio and focus on the many critical areas of breast cancer by supporting these additional grants.

The list of awards, affiliations, and funding information are in Appendix 3.

Trial Assigning Individualized Options for Treatment (TAILORx) (2006)

In 2006, NCI used Breast Cancer Research Stamp proceeds to support the Trial Assigning Individualized Options for Treatment (TAILORx). The goal of TAILORx is examining whether genes that are frequently associated with risk of recurrence for women with early-stage breast cancer can be used to assign patients to the most appropriate and effective treatment. The trial completed accrual in October 2010 and is ongoing. In June 2018, results were reported from an analysis of women in the intermediate risk-group. Findings showed that adjuvant hormone therapy alone worked as well as hormone therapy and chemotherapy together. After 9 years of follow-up, the rates of invasive disease-free survival were 83.3% for hormone therapy alone and 84.3% for hormone therapy and chemotherapy; for overall survival, the rates were 93.9% and 93.8%, respectively. Additionally, in September 2015, results were reported from an analysis of the women in the lowest- risk group. The findings showed that at 5 years, rates of distant relapse-free survival were 99.3 percent, of invasive disease-free survival were 93.8 percent, and of overall survival were 98.0 percent. These results provide prospective evidence that the gene expression test identifies women with a low risk of recurrence who can be spared chemotherapy. More information can be found at: http://www.cancer.gov/types/breast/research/tailorx.

Breast Pre-Malignancy Program (2006-2014)
The Trans-NCI Breast Pre-Malignancy Program represented a comprehensive program in breast cancer pre-malignancy research that includes the areas of prevention, etiology, biology, diagnosis, and molecular epidemiology. The program consisted of both NCI researchers located on the NIH campuses in Bethesda and Frederick, Maryland, and extramural research programs, which support investigations underway in universities, medical schools, hospitals, and research institutions across the country. The Trans-NCI Breast Pre-Malignancy Program consists of six research components supporting research on pre-malignant lesions, cancer prevention techniques, and methods for detecting breast cancer or pre-cancers earlier. The program involved work on characterization and imaging of breast cancer stem cells, the biology of breast pre-malignancy, molecular epidemiology of mammographic density, strategies to improve accuracy of mammography interpretation, the evaluation of decision-making approaches used by women recruited for chemoprevention trials, molecular target identification (biomarkers), imaging, and translational research.

Previously Funded Intramural Research:

- *Development and Characterization of Affibody®-Based Biconjugates for Molecular Imaging and Targeted Therapy of HER2-PositiveBreast Cancers*
- *Isolation, Propagation, Characterization, and Imaging of Breast Cancer Stem Cells to Improve Early Diagnosis and Therapy in Breast Cancer*
- *Image Guided Therapy with Targeted SPIO Carbon-Nanostructure*
- *Preclinical Consortium for Brain Metastases of Breast Cancer*
- *Personalized Medicine Approach to Triple-Negative Breast Cancers*
- *Analysis of Gene Expression Patterns Downstream of Multiple Metastasis Suppressor Genes Identifies New Potential Therapeutic Targets for Breast Cancer*
- *Maternal Pregnancy Factors and Breast Cancer Risk*

Previously Funded Extramural Research:

- *Multi-parameter Monitoring of Breast Cancer Progression and Therapeutic Response (CA135650)*
- *Characterizing the Evolution of Pre-malignant Tissues at High Risk for Malignancy (CA135626)*
- *A Study to Evaluate Different Decision-Making Approaches Used by Women Known to*
- *be at High Risk for Breast Cancer (Grant Supplement) (CA37377)*
- *PARP Inhibition in BRCA Mutation Carriers – A Pilot Study (CA037403)*
- *Assessing and Improving Mammography (AIM) Study*

Breast Radiology Evaluation and Study of Tissues (BREAST) Stamp Project (Intramural) (2010-2014)
The NCI Breast Radiology Evaluation and Study of Tissues (BREAST) Stamp Project is a molecular epidemiologic study of mammographic density (MD), one of the strongest breast cancer risk factors, undertaken by NCI researchers in partnership with the University of Vermont (UVM), an NCI Breast Cancer Surveillance Consortium (BCSC) site. Funded by the NCI through Breast Cancer Research Stamp funds and intramural funding between 2006 and 2009, 465 women who were referred for diagnostic image-guided breast biopsy were enrolled from 2007 to 2010. Participants consented to 10 years of passive follow-up, and analyses are ongoing. Participants provided risk factor data and donated blood, oral rinses and breast tissues. As the data from this study have become available, researchers

continue to conduct analyses for an increasing number of projects utilizing this rich resource.

A novel component of the BREAST Stamp Project has been the incorporation of cutting-edge methods to measure MD as a volume, in addition to its traditional measure as a two-dimensional area. Researchers found that area and volumetric MD measures exhibit some overlap in risk factor associations, but divergence as well, particularly for body mass index, suggesting that breast cancer risk assessments may vary depending on the MD measurement technique used (Cancer Epidemiol Biomarkers Prev. 2014;23:2338-48). Circulating markers that influence or reflect increased cellular proliferation may also relate to elevated MD and breast cancer risk. Researchers observed that women with diagnoses of cellular proliferation had longer leukocyte telomeres (protective ends of chromosomes). If replicated, this finding may suggest that leukocyte telomere length is a marker of risk for proliferative breast disease among women referred for biopsy based on breast imaging (BMC Cancer. 2015;15:823). Investigators also utilized a highly reproducible assay to measure serum estrogens and estrogen metabolites and evaluate their relationship with MD. Their findings suggest that elevated serum estrogen profiles are associated with higher MD (Horm Cancer. 2015;6:107-19). The biopsy tissues collected from study participants have also offered remarkable opportunities to better understand the determinants of elevated MD at the tissue level. Their findings suggest that associations of MD with breast cancer may partly reflect amounts of at-risk epithelium (Cancer Prev Res [Phila]. 2016;9:149-58 and Breast Cancer Res. 2016;18:24).

The list of grant awards, affiliations, and funding information are in Appendix 4.

The Breast Cancer Metabolomics Project (Intramural) (2010-2014)

The primary aim of NCI's Breast Cancer Metabolomics Project, which NCI supported through Breast Cancer Research Stamp funding between 2010 and 2014, was to identify metabolic profiles that precede the development of breast cancer. The research team used the most advanced metabolic profiling technology to simultaneously characterize levels of more than 500 circulating metabolites, including lipids, proteins, and sex hormones in prediagnostic blood samples through two different studies. The first study included 360 breast cancer cases and 360 women without breast cancer from a large, well-characterized cohort of women residing in Shanghai, China. The second study included 500 breast cancer cases and 500 women without breast cancer from a large, well-characterized cohort of women residing in the United States.

The project was designed to proceed in three stages. In 2010-2011, the research team completed the first stage, which involved evaluating four leading metabolic profiling labs using six different metabolic profiling technologies, and selecting a lab to perform the work for future stages. In 2011-2012, the team completed the second stage of the study, which entailed identifying metabolic profiles for two breast cancer-related exposures, excess body weight and physical activity. By analyzing samples from nearly 1,000 study participants from the U.S. and Shanghai, the research team identified 40 body weight-related metabolites, many with no previously known link to body weight. They also identified three novel metabolites correlated with physical activity levels, as measured by wearable physical activity monitors. Two manuscripts have been published describing results from this second stage. The third stage of the study – metabolomics analysis of the breast cancer cases and controls – was initiated in August 2012 and completed in 2014.

The preliminary data from this project has been highly informative and formed the basis for two recent successful grant applications by the research team to expand their analyses into a breast cancer replication study and a pancreatic cancer study. The research team published papers supported by this grant on metabolomics and epidemiology (Cancer Epidemiol Biomarkers Prev April 2013 22; 6312013), on metabolic correlates of body mass index (Metabolomics [2014] 10:259–269), and on plasma metabolic profiles of type 2 diabetes risk (Metabolomics [2016] 12:3).

Maternal Pregnancy Factors and Breast Cancer Risk Study (Intramural) (2010-2014)
The goal of this study, which NCI supported through Breast Cancer Research Stamp funds from 2010 to 2014, was to identify possible links between pregnancy factors and breast cancer risk. Investigators at the NCI, in collaboration with researchers at the Fred Hutchinson Cancer Research Center in Seattle, Washington, compared pregnancy-related information from women who delivered babies prior to a breast cancer diagnosis to the information from women without breast cancer who had deliveries during the same period. The study results suggest that delivery of a large (4,000 grams or more) infant and bleeding in the first trimester and later in the pregnancy may be associated with an increased risk of breast cancer. In addition, having a pregnancy complicated by preeclampsia or carrying a twin or multiple gestation may be associated with a decreased risk of breast cancer. These results were published in Cancer Epidemiology, Biomarkers and Prevention (2013;22:835-47).

Using data from the study, researchers are conducting a second record linkage to the participant's offspring birth records to improve their ability to examine associations for factors related to a participant's own pregnancy. Moreover, including information from all case/control offspring birth and fetal death records allows researchers to consider not only factors associated with a woman's most recent pregnancy, but also to evaluate summary factors across all pregnancies (for example, the number of pregnancies affected by preeclampsia or other conditions) using data collected at the time of the pregnancy compared to information based on what a subject may recall. Researchers are currently developing this data set for analysis. NCI researchers have also conducted a population-based nested case control study of breast cancer among female members of Washington State birth cohorts and are drafting a paper on how in utero and early life exposures may impact subsequent cancer risk of offspring.

The Biology of Estrogen Receptor-Negative Breast Cancer in Various Racial and Ethnic Groups (2010-2014)
The objectives and goals of this component of the trans-NCI program were to identify the differences between estrogen receptor positive (ER +) and estrogen receptor negative (ER -) human breast cancers; identify the subtypes or heterogeneity within ER-breast cancers using human samples (normal and malignant); and determine possible differences in the biology of ER-breast cancers among various racial and ethnic groups. Through this Request for Applications (RFA), NCI awarded three grants in September 2010, each for five years. The NCI used Breast Cancer Research Stamp funding to support these grants until fiscal year 2014.

> ***Stanford University (CA154209)***: The team analyzed the genome of individual cancer cells to resolve seemingly contradictory findings regarding normal stem cells in the mammary glands. One research group has identified normal human mammary stem cells as being negative or low in key markers known as CD49f and EPCAM, while another claimed that these cells positively

express both markers. The results from this work have demonstrated that mouse repopulating units (MRU) with the same phenotypes have similar mammary gland regeneration capacity. Since each population can give rise to the other, their data shows these are likely two different physiological stem cell states.

Ohio State University (CA154200): Androgen receptors, a certain type of cell receptor, have been associated with the development of triple negative breast cancer, but its role in the different subtypes has not been clearly defined. The investigators studied the expression of androgen receptors in 678 breast cancers, including 396 triple negative cancers (TNBC). They found that androgen receptor expression was associated with a better prognosis in a subtype of TNBC known as non-basal TNBC. These findings confirm the use of androgen receptor expression as an important prognostic tool in non-basal triple negative breast cancers, and also suggest targeting of new androgen receptor-related molecular pathways in patients with these cancers.

University of Michigan (CA154224): The investigators have focused on understanding the molecular factors in the development of the highly aggressive triple negative breast cancer (TNBC) and identifying clinically useful markers of this disease. They have identified a protein known as EZH2 as a novel regulator of stem cells in breast tissue. In TNBC, high EZH2 results in increasing the breast cancer stem cell population, which is associated with more aggressive disease. The investigators developed a large database of breast cancer samples obtained from Ghanaian patients and are examining the biological significance of high EZH2 levels in Caucasian, African American and Ghanaian women with TNBC.

The list of grant awards, affiliations, and funding information are in Appendix 4.

Appendix 2. Insight Awards to Stamp Out Breast Cancer Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2000	ALBANY MEDICAL COLLEGE OF UNIONUNIVERSITY	BENNETT, JAMES A	$116,250
2000	BAYLOR COLLEGE OF MEDICINE	ROSEN, JEFFREY	$78,488
2000	BETH ISRAEL DEACONESS MEDICALCENTER	JUNGHANS, RICHARD P	$130,500
2000	CALIFORNIA UNIVERSITY, IRVINE	BLUMBERG, BRUCE	$105,946
2000	CALIFORNIA UNIVERSITY, SANFRANCISCO	COLLINS, COLIN C	$110,625
2000	CENTER FOR MOLECUCULAR MEDICINE AND IMMUNOLOGY/GARDEN STATE	BLUMENTHA, ROSALYN D	$142,500
2000	CLEMSON UNIVERSITY	CHEN, WEN Y	$105,000
2000	COLUMBIA UNIVERSITY HEALTH SCIENCES	SWERGOLD, GARY D	$127,875
2000	DANA-FARBER CANCER INSTITUTE	KUFE, DONALD W.	$126,138
2000	FOX CHASE CANCER CENTER	RUSSO, JOSE	$126,866
2000	GEORGETOWN UNIVERSITY	WONG, LEE-JUN C	$116,950
2000	HADASSAH UNIVERSITY HOSPITAL	VLODAVSKY, ISRAEL	$61,000
2000	HAWAII UNIVERSITY	GOTAY, CAROLYN C	$101,000
2000	ILLINOIS UNIVERSITY	WESTBROOK, CAROL A	$116,475
2000	INSTITUTE FOR CANCER RESEARCH	YEUNG, ANTHONY T	$126,866
2000	HENRY M. JACKSON FOUNDATION	LECHLEIDER, ROBERT J	$74,000
2000	JEFFERSON THOMAS UNIVERSITY	SAUTER, EDWARD R	$117,851
2000	LONG ISLAND JEWISH MEDICAL CENTER	SHI, Y ERIC	$116,616
2000	VIRGINIA MASON RESEARCH CENTER	NELSON, BRAD H	$47,250
2000	MASSACHUSETTS GENERAL HOSPITAL	HABER, DANIEL A.	$129,500
2000	MASSACHUSETTS UNIVERSITY, AMHERST	JERRY, D JOSEPH	$115,125
2000	MELBOURNE UNIVERSITY	THOMPSON, ERIK W	$75,000
2000	MOUNT SINAI SCHOOL OF MEDICINE	KRETZSCHMAR, MARCUS D	$125,387
2000	NEW YORK STATE UNVERSITY	MUTI, PAOLA C	$68,950

2000	PENNSYLVANIA UNIVERSITY	LEMMON, MARK A.	$118,875
2000	PENNSYLVANIA UNIVERSITY	RADICE, GLENN L	$118,875
2000	PITTSBURGH UNIVERSITY	NICHOLS, MARK D	$112,500
2000	SCHEPENS EYE RESEARCH INSTITUTE	D'AMORE, PATRICIA A	$121,500
2000	UTAH UNIVERSITY	GRISSOM, CHARLES B	$112,125
2000	VERMONT UNIVERSITY	KRAG, DAVID N	$113,250
2000	WAKE FOREST UNIVERSITY	SHELNESS, GREGORY S	$108,750
2000	YALE UNIVERSITY	ZHANG, HUI	$122,625
2001	ALBANY MEDICAL COLLEGE OF UNION UNIVERSITY	BENNETT, JAMES A	$116,250
2001	BAYLOR COLLEGE OF MEDICINE	ROSEN, JEFFREY	$109,322
2001	BETH ISRAEL DEACONESS MEDICAL CENTER	JUNGHANS, RICHARD P	$128,509
2001	CALIFORNIA UNIVERSITY, IRVINE	BLUMBERG, BRUCE	$112,800
2001	CALIFORNIA UNIVERSITY, SAN FRANCISCO	COLLINS, COLIN C	$110,625
2001	CALIFORNIA UNIVERSITY, IRVINE	RADANY, ERIC H	$112,800
2001	GARDEN STATE CANCER CENTER	BLUMENTHAL, ROSALYN D	$142,500
2001	CLEMSON UNIVERSITY	CHEN, WEN Y	$105,000
2001	COLUMBIA UNIVERSITY HEALTH SCIENCES	FISHER, PAUL B	$127,875
2001	COLUMBIA UNIVERSITY HEALTH SCIENCES	SWERGOLD, GARY D	$127,875
2001	DANA-FARBER CANCER INSTITUTE	GARBER, JUDY E	$128,750
2001	DANA-FARBER CANCER INSTITUTE	KUFE, DONALD W.	$99,298
2001	FOX CHASE CANCER CENTER	RUSSO, JOSE	$126,133
2001	GEORGETOWN UNIVERSITY	BYERS, STEPHEN W	$116,550
2001	GEORGETOWN UNIVERSITY	DICKSON, ROBERT B.	$116,600
2001	GEORGETOWN UNIVERSITY	WONG, LEE-JUN C	$116,400
2001	HADASSAH UNIVERSITY HOSPITAL	VLODAVSKY, ISRAEL	$61,000
2001	HAWAII UNIVERSITY, MANOA	GOTAY, CAROLYN C	$99,411
2001	JOHNS HOPKINS UNIVERSITY	FEDARKO, NEAL S	$122,750

2001	ILLINOIS UNIVERSITY	WESTBROOK, CAROL A	$115,959
2001	INSTITUTE FOR CANCER RESEARCH	YEUNG, ANTHONY T	$126,133
2001	HENRY M. JACKSON FOUNDATION FOR THE ADVANCEMENT OF MILITARY MEDICINE	LECHLEIDER, ROBERT J	$74,000
2001	JEFFERSON THOMAS UNIVERSITY	SAUTER, EDWARD R	$82,386
2001	LONG ISLAND JEWISH MEDICAL CENTER	SHI, Y ERIC	$103,844
2001	VIRGINIA MASON RESEARCH CENTER	NELSON, BRAD H	$47,250
2001	MASSACHUSETTS GENERAL HOSPITAL	HABER, DANIEL A.	$127,500
2001	MASSACHUSETTS UNIVERSITY, AMHERST	JERRY, D JOSEPH	$112,323
2001	MEDICAL DIAGNOSTIC RESEARCH FOUNDATION	CHANCE, BRITTON	$92,500
2001	MELBOURNE UNIVERSITY	THOMPSON, ERIK W	$75,000
2001	MINNESOTA UNIVERSITY, TWIN CITIES	SHEAFF, ROBERT J	$111,375
2001	MOUNT SINAI SCHOOL OF MEDICINE OF NEW YORK UNIVERSITY	KRETZSCHMAR, MARCUS D	$127,125
2001	NORTHWESTERN UNIVERSITY	JORDAN, VIRGIL C	$110,250
2001	PENNSYLVANIA UNIVERSITY	LEMMON, MARK A.	$118,875
2001	PENNSYLVANIA UNIVERSITY	RADICE, GLENN L	$118,875
2001	PITTSBURGH UNIVERSITY	NICHOLS, MARK D	$112,323
2001	SCHEPENS EYE RESEARCH INSTITUTE	D'AMORE, PATRICIA A	$121,499
2001	STANFORD UNIVERSITY	CONTAG, CHRISTOPHER H	$119,597
2001	UTAH UNIVERSITY	GRISSOM, CHARLES B	$112,500
2001	UNIVERSITY OF VERMONT AND STATE AGRICLTURAL COLLEGE	KRAG, DAVID N	$112,302
2001	WAKE FOREST UNIVERSITY	SHELNESS, GREGORY S	$108,375
2001	WAYNE STATE UNIVERSITY	FERNANDEZ-MADRID, FELIX R	$111,750
2001	WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH	WEINBERG, ROBERT A	$116,250
2001	YALE UNIVERSITY	ZHANG, HUI	$122,625
2002	CALIFORNIA UNIVERSITY, IRVINE	RADANY, ERIC H	$112,800
2002	COLUMBIA UNIVERSITY HEALTH SCIENCES	FISHER, PAUL B	$122,799
2002	DANA-FARBER CANCER INSTITUTE	GARBER, JUDY E	$128,374

2002	FOX CHASE CANCER CENTER	RUSSO, JOSE	$4,300
2002	GEORGETOWN UNIVERSITY	BYERS, STEPHEN W	$116,400
2002	GEORGETOWN UNIVERSITY	DICKSON, ROBERT B.	$116,400
2002	JOHNS HOPKINS UNIVERSITY	FEDARKO, NEAL S	$114,274
2002	MEDICAL DIAGNOSTIC RESEARCH FOUNDATION	CHANCE, BRITTON	$103,350
2002	MINNESOTA UNIVERSITY, TWIN CITIES	SHEAFF, ROBERT J	$111,375
2002	WAYNE STATE UNIVERSITY	FERNANDEZ-MADRID, FELIX R	$111,750
2002	WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH	WEINBERG, ROBERT A	$116,238
Total	**Insight Awards to Stamp-Out Breast Cancer**		**$9,409,783**

*Some amounts displayed in this table may be different than amounts displayed in reports from prior years. The primary reason for such differences relates to funding balances that were not fully expended on project activities and were reclaimed through the grant accounting process.

Appendix 3. Exceptional Opportunities in Breast Cancer Research Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2003	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L.	$545,271
2003	COLUMBIA UNIVERSITY	HARLAP, SUSAN	$616,010
2003	HOPKINS JOHNS UNIVERSITY	OUWERKERK, RONALD	$154,852
2003	MISSOURI UNIVERSITY	SAUTER, EDWARD R	$33,055
2003	NORTHWESTERN UNIVERSITY	HUANG, SUI	$389,482
2003	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$198,759
2003	PITTSBURGH UNIVERSITY	WIENER, ERIK C	$405,009
2003	ST VINCENT'S INSTITUTE	PRICE, JOHN T	$108,000
2003	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$532,409
2003	TORONTO UNIVERSITY	VOGEL, WOLFGANG F	$81,000
2003	WISCONSIN UNIVERSITY	SCHULER, LINDA A.	$268,791
2004	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L.	$545,576
2004	COLUMBIA UNIVERSITY	HARLAP, SUSAN	$604,299
2004	HOPKINS JOHNS UNIVERSITY	OUWERKERK, RONALD	$157,176
2004	NORTHWESTERN UNIVERSITY	HUANG, SUI	$389,522
2004	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$198,759
2004	PITTSBURGH UNIVERSITY	WIENER, ERIK C	$410,688
2004	ST VINCENT'S INSTITUTE	PRICE, JOHN T	$108,000
2004	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$566,037
2004	TORONTO UNIVERSITY	VOGEL, WOLFGANG F	$81,000
2004	WISCONSIN UNIVERSITY	SCHULER, LINDA A.	$254,625
2005	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L.	$561,474

2005	COLUMBIA UNIVERSITY	HARLAP, SUSAN	$600,585
2005	NORTHWESTERN UNIVERSITY	HUANG, SUI	$400,140
2005	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$198,759
2005	PITTSBURGH UNIVERSITY	WIENER, ERIK C	$423,007
2005	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$550,147
2005	WISCONSIN UNIVERSITY	SCHULER, LINDA A.	$254,625
2006	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L.	$561,838
2006	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$194,088
2006	PITTSBURGH UNIVERSITY	WIENER, ERIK C	$404,520
2006	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$24,291
2007	CALIFORNIA UNIVERSITY	NEUHAUSEN, SUSAN L.	$250,078
2007	TEXAS UNIVERSITY GALVESTON	LU, LEE-JANE W	$468,507
2007	PENNSYLVANIA UNIVERSITY	LEE, WILLIAM M	$188,457
2008	MASSACHUSETTS GENERAL HOSPITAL	MOORE, ANNA	$616,625
Total	**Exceptional Opportunities Awards**		**$12,345,462**

*Some amounts displayed in this table may be different than amounts displayed in reports from prior years. The primary reason for such differences relates to funding balances that were not fully expended on project activities and were reclaimed through the grant accounting process.

Appendix 4. Breast Cancer Pre-Malignancy Program Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2006	BAYLOR COLLEGE OF MEDICINE	OSBORNE, C KENT	$249,838
2006	DARTMOUTH COLLEGE	CARNEY, PATRICIA A	$101,546
2006	GROUP HEALTH COOPERATIVE	BUIST, DIANA SM	$114,226
2006	GROUP HEALTH COOPERATIVE	MIGLIORETTI, DIANA L	$217,296
2006	NCI INTRAMURAL PROGRAM	VARIOUS	$369,794
2006	NORTH CAROLINA UNIVERSITY	YANKASKAS, BONNIE C	$90,514
2007	UNIVERSITY OF VERMONT	GELLER, BERTA	$115,047
2007	NCI INTRAMURAL PROGRAM	VARIOUS	$419,818
2008	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	TLSTY, THEA	$666,024
2008	NSABP FOUNDATION, INC.	WOLMARK, NORMAN	$119,226
2008	UNIVERSITY OF VERMONT	GELLER, BERTA	$230,312
2008	NCI INTRAMURAL PROGRAM	VARIOUS	$490,754
2009	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	TLSTY, THEA	$640,750
2009	MASSACHUSETTS GENERAL HOSPITAL	MOORE, ANNE	$598,918
2009	NSABP FOUNDATION	WOLMARK, NORMAN	$123,992
2009	NCI INTRAMURAL PROGRAM	VARIOUS	$508,939
2010	BECKMAN RESEARCH INSTITUTE		$174,792
2010	FRONTIER SCI & TECHNOLOGY RSCH FDN, INC	COMIS, ROBERT L	$200,000
2010	NSABP FOUNDATION, INC.	WOLMARK, NORMAN	$97,000
2010	UNIVERSITY OF CALIFORNIA SAN FRANCISCO	TLSTY, THEA D	$634,250
2010	MASSACHUSETTS GENERAL HOSPITAL	MOORE, ANNA	$94,933
2010	OHIO STATE UNIVERSITY	HUEBNER, KAY	$548,311
2010	STANFORD UNIVERSITY	CLARKE, MICHAEL	$553,639
2010	UNIVERSITY OF MICHIGAN AT ANN ARBOR	KLEER, CELINA G	$353,718

2010	NCI INTRAMURAL PROGRAM	VARIOUS	$108,313
2011	MASSACHUSETTS GENERAL HOSPITAL	MOORE, ANNA	$488,276
2011	OHIO STATE UNIVERSITY	HUEBNER, KAY	$465,130
2011	UNIVERSITY OF MICHIGAN AT ANN ARBOR	KLEER, CELINA G	$341,695
2011	STANFORD UNIVERSITY	CLARKE, MICHAEL	$520,754
2011	NCI INTRAMURAL PROGRAM	VARIOUS	$160,895
2012	OHIO STATE UNIVERSITY	SHAPIRO, CHARLES L	$443,720
2012	STANFORD UNIVERSITY	CLARKE, MICHAEL	$505,636
2012	UNIVERSITY OF MICHIGAN AT ANN ARBOR	KLEER, CELINA G	$340,325
2012	NCI INTRAMURAL PROGRAM	VARIOUS	$364,718
2013	OHIO STATE UNIVERSITY	SHAPIRO, CHARLES L	$411,074
2013	STANFORD UNIVERSITY	CLARKE, MICHAEL	$449,650
2013	UNIVERSITY OF MICHIGAN AT ANN ARBOR	KLEER, CELINA G	$318,654
2013	NCI INTRAMURAL PROGRAM	VARIOUS	$157,408
2014	OHIO STATE UNIVERSITY	HUEBNER, KAY	$394,509
2014	UNIVERSITY OF MICHIGAN AT ANN ARBOR	KLEER, CELINA G	$327,572
2014	STANFORD UNIVERSITY	CLARKE, MICHAEL	$455,316
2014	NCI INTRAMURAL PROGRAM	VARIOUS	$299,749
Total	**Breast Pre-Malignancy Awards**		**$14,267,031**

*Some amounts displayed in this table may be different than amounts displayed in reports from prior years. The primary reason for such differences relates to funding balances that were not fully expended on project activities and were reclaimed through the grant accounting process.

Appendix 5. Molecular and Cellular Characterization of Screen-Detected Lesions Consortium Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2015	Dartmouth College	Amos, Christopher I.	$120,910
2015	University of California San Francisco	Esserman, Laura J.	$796,788
2015	University of Vermont and State Agricultural College	Stein, Janet L.	$717,240
2016	Dartmouth College	Amos, Christopher I.	$118,438
2016	University of California San Francisco	Esserman, Laura J.	$786,457
2016	University of Vermont and State Agricultural College	Stein, Janet L.	$749,256
2017	Baylor College of Medicine	Amos, Christopher I.	$99,440
2017	Dartmouth College	Amos, Christopher I.	$16,345
2017	University of California San Francisco	Esserman, Laura J.	$782,497
2017	University of Vermont and State Agricultural College	Stein, Janet L.	$741,335
2018	University of Vermont and State Agricultural College	Stein, Janet L.	$741,429
2018	Baylor College of Medicine	Amos, Christopher I.	$113,545
2018	University of California San Francisco	Esserman, Laura J.	$784,304
2019	University of Vermont and State Agricultural College	Stein, Janet L.	$705,072
2019	Baylor College of Medicine	Amos, Christopher I.	$111,054
2019	University of California San Francisco	Esserman, Laura J.	$701,540
Total	**Screen-Detected Lesions Awards**		**$8,085,650**

*Because the principal investigator on this award, Christopher Amos, changed institutions in 2017, the award for the CDMG has moved to Baylor College of Medicine from Dartmouth College. The award's history is available at https://projectreporter.nih.gov/project_info_history.cfm?aid=9334552&icde=0.

Appendix 6. Breast Cancer Weight Loss (BWEL) Trial Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2018	Brigham and Women's Hospital	Mooney, Margaret M.	$1,000,000
2019	Brigham and Women's Hospital	Mooney, Margaret M.	$1,000,000
Total	**BWEL Awards**		**$2,000,000**

Appendix 7. Tomosynthesis Mammographic Imaging Screening (TMIST) Trial Funded with Proceeds from the Breast Cancer Research Stamp

Fiscal Year	Institution	Principal Investigator	Total
2018	ECOG-ACRIN Cancer Research Group	Lee, Cecilia H.	$2,709,686
Total	**TMIST Awards**		**$2,709,686**