

University of Pennsylvania

Annual Progress Report: 2011 Nonformula Grant

Reporting Period

July 1, 2013 – June 30, 2014

Nonformula Grant Overview

The University of Pennsylvania received \$2,818,505 in nonformula funds for the grant award period June 1, 2012 through May 31, 2016. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Translation of Genomics into Improvements in Cancer Prevention and Treatment – The overarching goal of the project is to improve the translation of genomic testing into reductions in the clinical, economic and societal burden of the three most common cancers affecting Pennsylvanians: breast, colon, and lung cancer. The project uses a highly integrated series of studies to assess clinical utility and/or population utility for the testing scenarios, and integrates data from administrative claims, cancer registry, clinical records, patient surveys, and genetic studies. The proposed research focuses on the potential for use of genomic information to reduce racial cancer disparities. This initiative includes a training and community advisory core to ensure its relevance to the communities in question and to support the training and career development of underrepresented minorities within the Commonwealth of Pennsylvania.

Anticipated Duration of Project

6/1/2012 – 5/31/2016

Project Overview

We propose an innovative, transdisciplinary research initiative that generates critically needed evidence about the effects of currently available genomic markers on cancer-related outcomes and lays the foundation for an ongoing, comprehensive approach to the evaluation of future genomic tests. This initiative spans half the continuum of the translational research in genomics – moving from research assessing the population impact of the use of clinically available genomic tests in cancer treatment, to research assessing the optimal strategy for the dissemination of the genetic risk information from a family history pedigree. The research is using a series of rigorous methods including observational study using propensity score and instrumental variable techniques, and a randomized controlled trial of communication strategies.

Aim 1 (Population utility): To determine the effect of clinically available genomic tests for cancer prognosis and treatment on treatment regimen, disease-free survival, direct medical costs

and racial disparities in these outcomes among patients with breast, colon and lung cancer in the Commonwealth of Pennsylvania.

Aim 2 (Clinical utility): To evaluate the effects of two alternative strategies for conveying the genetic risk information from family history on risk reducing behaviors among 1st and 2nd degree relatives of newly diagnosed breast or colorectal cancer patients.

Aim 3: To develop and implement a successful minority training and community engagement core to advance the careers of minority scientists and ensure that the research is relevant to the communities in question.

The proposed initiative has five key characteristics that will greatly increase its impact including: (1) Focus on major cancer burden; (2) Focus on racial disparities; (3) Multidisciplinary science; (4) Partnerships with key stakeholders including community-based, minority-serving organizations and private insurers; and (5) Leveraging existing resources.

Principal Investigator

Peter W. Groeneveld, MD, MS,
Associate Professor of Medicine
Division of General Internal Medicine
University of Pennsylvania Perelman School of Medicine
1229 Blockley Hall, 423 Guardian Drive
Philadelphia, PA 19104

Other Participating Researchers

Angela Bradbury, MD; Susan Domchek, MD; Andrew Epstein, PhD; Monica Ferguson, MD; Joanne Levy, MBA; Nandita Mitra, PhD; Anil Vachani, MD – employed by the University of Pennsylvania
Mary Daly, MD, PhD; Michael Hall, MD, MS; Eric Ross, PhD; Yu-Ning Wong, MD, MSCE – employed by the Fox Chase Cancer Center
Hendrik Vermeulen, MS; Aaron Smith-McLallen, PhD – employed by Independence Blue Cross
Linda Patrick-Miller, PhD – employed by MacLean Center for Clinical Medical Ethics
Katrina Armstrong, MD, MS – employed at the Massachusetts General Hospital

Expected Research Outcomes and Benefits

The project will have two major outcomes and benefits. First, the research will provide critically needed evidence about the effect of currently available cancer genetic tests on patient and population outcomes, including cancer treatment, treatment complications, cancer mortality, economic costs and cancer racial disparities. Information about the outcomes of these tests is critically needed to enable patients and providers to make informed decisions about if and when the tests should be used and for payers and policy makers to make decisions about coverage, recommendations and other strategies to guide the use of the tests. In addition, this research will also identify key determinants of appropriate and inappropriate testing use, thereby enabling

interventions to improve the quality of care around cancer genomics.

Second, the research will develop and test a novel strategy for conveying the genomic risk information captured in a family history pedigree. Increasingly, pedigree information is recognized as a potentially effective clinical and public health tool for increasing risk reduction behaviors and for identifying appropriate individuals for genetic testing. The development of an effective communication strategy will facilitate the use of this information and reduce the burden of cancer among individuals at increased genetic risk. Together, these three highly integrated projects will improve the use of genomic information surrounding cancer prevention and treatment, thereby addressing one of the major clinical and public health problems facing Pennsylvania today.

Summary of Research Completed

Aim 1 (Population utility): To determine the effect of clinically available genomic tests for cancer prognosis and treatment on treatment regimen, disease-free survival, direct medical costs and racial disparities in these outcomes among patients with breast, colon and lung cancer in the Commonwealth of Pennsylvania.

Work in Year 2 focused heavily on finishing construction of an analytic cohort that began in Year 1. We have completed a number of necessary tasks, including:

- 1) Developing clinical selection criteria for each of the three cancer types using Pennsylvania Cancer Registry (PCR) data covering 2004-2011. In lung cancer: there are 83,282 patients initially; after excluding those with non-invasive cancer, those without sufficient diagnosis confirmation, those with post-mortem diagnoses, those with irrelevant lung histology, those without non-small cell lung cancer, those without adenocarcinoma, and those without Stage IV cancers, there are 17,719 unique patients. In colon cancer: there are 53,704 patients initially; after excluding those with non-invasive cancer, those lacking diagnosis confirmation, those with post-mortem diagnoses, and those with irrelevant cancer histology, there were 8,054 patients with Stage IV colon cancer and 34,334 patients with non-metastatic colon cancer. In breast cancer: there are 100,595 patients initially; after excluding those with non-invasive cancer, those without diagnosis confirmation, those with post-mortem diagnoses, those with irrelevant breast histology, those without metastatic node-negative disease, and those with ER/PR positive status, there are 39,791 unique patients.
- 2) Linking the breast cancer cohort from PCR to health insurance claims data from Independence Blue Cross (IBC), fee-for-service Medicare, and Pennsylvania Medicaid covering 2007-2011. A substantial amount of effort has been devoted to standardizing the information across these three claims data sources, which are each unique. We further excluded patients with HER2 positive status, patients missing race/ethnicity information, and male patients, leaving us with 27,199 breast cancer patients diagnosed during 2007-2011. Table 1 provides descriptive information about the sample derived from matching each health insurer's claims to the PCR breast cancer cohort. Independence Blue Cross: here were 2,871 women with breast cancer who had coverage from IBC for a year after diagnosis, of whom 845 (29%) had a claim for genomic testing (OncoType DX). Fee-for-service Medicare: there were 8,003 women with breast cancer who had coverage via fee-for-service Medicare for at least a year from diagnosis, of whom 1,390 (17%) had an OncoType DX claim. Pennsylvania Medicaid: there were 1,177 women with breast cancer who had at least

a year of coverage from Medicaid following diagnosis. Of these, only 16 (1%) had an OncoType DX claims. As this is substantially lower than the other two insurers, we investigated and determined that Pennsylvania Medicaid did not cover OncoType DX testing during this period.

- 3) We have started preliminary analyses of the use of OncoType DX and its impact on use of chemotherapy among the breast cancer cohort. Because of the lack of Medicaid coverage for genomic testing, we are currently focusing on the subset of women with either IBC or Medicare coverage. Of the 10,874 women in this subsample, 2,235 (21%) received OncoType DX within a year of diagnosis. Table 2 shows the characteristics of this subsample stratified by OncoType DX receipt. Although this table indicates that chemotherapy receipt was actually higher among those receiving OncoType DX (23.0% vs. 15.0%, $p < 0.001$), it is important to note that patient characteristics were very different between patients who received or did not receive OncoType DX. This work specifically addresses our goals in Aim 1a.
- 4) Because older women were markedly less likely to receive OncoType DX testing, we have explored the impact of OncoType DX testing on chemotherapy receipt within a year of diagnosis stratified by age group. Table 3 shows preliminary results of this analysis. Chemotherapy use was lower among younger women who received OncoType DX than those who did not, but not among older women. Specifically, among women age 50-64, receipt of OncoType DX was associated with about a 5-percentage-point significantly lower use of chemotherapy.

Aim 2 (Clinical utility) To evaluate two alternative strategies for conveying the genetic risk information from family history on risk reducing behaviors among 1st and 2nd degree relatives of newly diagnosed breast or colorectal cancer patients.

Progress has been made since the start of recruitment at Fox Chase Cancer Center (FCCC) in May of 2013. In order to ensure enrollment targets for the study are met, a recruitment team has been established at the University of Pennsylvania (Penn) where the Penn IRB is permitting eligible family members referred by patients to be contacted directly by the staff. We expect that direct contact with family members will enhance our ability to meet recruitment goals at Penn. The Penn team has obtained IRB approval to utilize multiple strategies for recruitment including approaching patients in clinic, contacting patients via introductory mailing and follow-up phone call, approved study advertisements emailed to the broader patient community. We continue to work with the FCCC HIPAA office to implement a strategy for directly contacting patients' relatives. We have expanded the participant surveys by adding a cancer belief section along with a program evaluation to aid planning future research in cancer risk education for patients' relatives.

We've been successful in scheduling both FCCC and Penn patients for education with the FCCC counselors. We will evaluate the effects of 2 alternative strategies for conveying genetic risk information which includes randomizing study subjects to either family history risk education or family history risk education plus an additional numeric risk estimate. Health educators will provide a pedigree and risk-reduction recommendations in both the family history and family history + numeric risk estimate groups, but in the latter group, subjects will also receive a numeric risk estimate of breast or colon cancer, calculated by the health educators using the

BRCAPRO program. As of June 30, 2014, we have recruited 58 breast cancer patients and 12 patients at risk of colon cancer. Please see Table 4 for recruitment details.

Aim 3: To develop/implement a successful Community Engagement and Minority Training Core.

Aim 3a: Community Engagement Core

In the last year, we convened a Community Advisory Board (CAB) consisting of African American women and men who are cancer survivors and/or represent community organizations with a cancer focus. Specifically, individuals who are survivors of breast, colorectal, and lung cancers were invited to participate. Additionally, members of the National Black Leadership Initiative on Cancer–Philadelphia chapter, and Women of Faith and Hope, Inc. (for survivors of breast cancer), as well as the outreach coordinator of the American Cancer Society, Philadelphia branch were among those invited to participate. A total of twenty individuals were invited to participate of which thirteen attended the CAB meetings on October 15, 2013 and March 18, 2014. During the meetings, the principal investigator addressed the group with a presentation on Genomics and Disparities. We also requested input from the CAB regarding our first annual personalized medicine and cancer screening/prevention educational event for fall of 2014.

Aim 3b: Minority Training Core

During the summer of 2013, we had two Summer Undergraduate Minority Research (SUMR) Scholars working with us. Christina Nguyen is a member of the class of 2015 at Harvard University, where she is majoring in Sociology, with a secondary major in Global Health and Health Policy while simultaneously fulfilling pre-medical requirements. During SUMR, Christina worked with the Aim 1 team on a study to validate genetic concordance between medical and administrative records within a subset of PCR data. Julio Albarracin is a rising senior at the University of Pennsylvania from Corpus Christi, TX. He is pursuing a BA in Biology with a minor in Chemistry. During SUMR, Julio worked with Dr. Angela Bradbury on Aim 2 on an analysis of the delivery and dissemination of genetic testing in cancer prevention.

Table 1. Breast Cancer Cohort Construction, 2007-2011

Year	Initial Sample	Any Coverage Ever	Coverage at Dx	1-Year Continuous Coverage	Surgery Claim	OncoType Claim	Chemo Claim
Independence Blue Cross							
2007	5,215	914	715	663	612	146	221
2008	5,464	962	705	641	599	191	194
2009	5,615	971	686	592	553	184	187
2010	5,645	990	605	549	493	170	137
2011	5,260	834	478	426	393	154	86
	27,199	4,671	3,189	2,871	2,650	845	825
Fee-For-Service Medicare							
2007	5,215	2,026	1,719	1,647	1,417	179	214
2008	5,464	1,939	1,699	1,641	1,417	254	210
2009	5,615	1,862	1,705	1,641	1,442	280	223
2010	5,645	1,750	1,664	1,601	1,425	354	219
2011	5,260	1,536	1,506	1,473	1,242	323	120
	27,199	9,113	8,293	8,003	6,943	1,390	986
Pennsylvania Medicaid							
2007	5,215	311	245	208	128	2	47
2008	5,464	347	274	234	160	2	49
2009	5,615	359	272	239	157	2	54
2010	5,645	395	306	268	203	6	66
2011	5,260	332	261	228	171	4	47
	27,199	1,744	1,358	1,177	819	16	263

Table 2. Descriptive Characteristics of Women with Breast Cancer and ≥ 1 Year of IBC or Medicare Coverage by Receipt of OncoType DX

Variable Name	OncoType Dx Receipt		P-Value
	No	Yes	
Age at Diagnosis, Mean (SD)	73.11 (11.39)	65.14 (10.58)	<0.001
Age at Diagnosis, Median (IQR)	74.00 (14.00)	67.00 (14.00)	<0.001
Age at Diagnosis Category, % (N)			<0.001
<50	4.9% (421)	10.3% (230)	
50-64	10.9% (944)	25.7% (574)	
65-74	34.7% (3,000)	46.2% (1,032)	
75-84	35.1% (3,035)	17.2% (384)	
≥ 85	14.3% (1,239)	0.7% (15)	
Year of Diagnosis, % (N)			<0.001
2007	23.0% (1,985)	14.5% (325)	
2008	21.3% (1,837)	19.9% (445)	
2009	20.5% (1,769)	20.8% (464)	
2010	18.8% (1,626)	23.4% (524)	
2011	16.5% (1,422)	21.3% (477)	
Patient is a Minority, % (N)	10.1% (869)	9.1% (203)	0.17
Cancer Stage, % (N)			<0.001
1	74.4% (6,431)	78.8% (1,761)	
2	21.9% (1,890)	20.0% (447)	
3	1.7% (145)	0.2% (5)	
Missing	2.0% (173)	1.0% (22)	
Patient Received Chemotherapy, % (N)	15.0% (1,296)	23.0% (515)	<0.001
Medical Spending in Year Prior to Dx, Mean (SD)	9,275.12 (25,613.33)	9,184.91 (23,159.32)	0.88
Medical Spending in Year Prior to Dx, Median (IQR)	2,508.16 (6,503.07)	2,996.62 (6,487.61)	<0.001
Prior Year Medical Spending Quintile, % (N)			<0.001
1	22.1% (1,913)	11.7% (262)	
2	19.4% (1,676)	22.3% (499)	
3	19.5% (1,683)	22.0% (492)	
4	19.0% (1,643)	23.8% (532)	
5	20.0% (1,724)	20.1% (450)	

Table 3. Preliminary Comparison of Chemotherapy Use by OncoType DX Receipt

Age Category	Receipt of Chemotherapy		Unadjusted	Difference		P-value
	No OncoType	Yes OncoType		P-value	Adjusted	
<50	49.8%	45.2%	-4.7%	0.11	-2.3%	0.42
50-64	34.7%	30.0%	-4.8%	0.01	-4.9%	0.007
65-74	16.8%	18.9%	2.0%	0.11	1.5%	0.22
75-84	7.1%	11.5%	4.3%	0.024	4.2%	0.023
>= 85	2.8%	0.0%	-2.8%	0.76	-2.8%	0.75

Table 4. Recruitment at Fox Chase Cancer Center and University of Pennsylvania

July 2013 to June 2014	FCCC	Penn	Total	Colon	Breast
Eligible patients	755	713	1468		
Approached patients	531	840	1371	122*	635*
• number of flyers mailed	278	654	929	*since	*since
• number of flyers given out in the clinic	200	69	269	Jan 2014	Jan 2014
Drop-outs					
• not interested	80	46	126		
• no eligible relatives	70	47	117		
Patient with eligible relatives	381	747	1128		
Relatives consented	25	45	70	12	58
Opted out	3	1	4		
Completed education session	21	37	58		
Completed 3-day follow up survey	23	20	43		
Completed 12-month follow up survey	1				