

Geisinger Clinic

Annual Progress Report: 2011 Nonformula Grant

Reporting Period

July 1, 2013 – June 30, 2014

Nonformula Grant Overview

The Geisinger Clinic received \$2,909,969 in nonformula funds for the grant award period June 1, 2012 through May 31, 2015. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Utility of Genomic Data in Population Screening for Abdominal Aortic Aneurysm – Abdominal aortic aneurysm (AAA) is the 13th leading cause of death in the U.S. AAAs are frequently undiagnosed due to the absence of symptoms and lack of a simple laboratory test. Elective surgical or endovascular repair is a safe and effective treatment for AAA. Population screening to detect undiagnosed AAAs has been proposed, but current guidelines result in the screening of a large segment of the population with a low risk of AAA and exclude a significant fraction of individuals who do have an AAA. The purpose of this project is to create a novel risk stratification tool for AAA screening that combines clinical and genetic risk factor data and to test the utility of the tool in a real-world clinical setting.

Anticipated Duration of Project

6/1/2012 – 5/31/2015

Project Overview

The scientific goals of this project are to create a novel risk stratification tool for abdominal aortic aneurysm (AAA) screening that combines elements of clinical and genetic risk factor data (Aim 1) and to test the utility of the tool in a real-world clinical setting (Aim 2). Aim 1 builds on the considerable expertise in AAA pathobiology, genetics and statistics of the study team as well as an existing biorepository of DNA samples collected for genomics research that are linkable to patient electronic medical records (EMR). Retrospective clinical risk factor data obtained from the EMR and genomic risk factor data obtained by genotyping known or suspected AAA-associated variants in AAA case and control DNA samples will be used to create a novel predictive model for AAA risk. In Aim 2 the impact of the novel genomically-informed risk model will be evaluated in Geisinger primary care clinics and compared to current screening guidelines with respect to uptake and efficiency of AAA screening. Aim 2 utilizes Geisinger Clinic's resources for developing, implementing, and testing novel mechanisms to deliver actionable information to clinicians using the health system's advanced health information technology infrastructure. Because the screening tool will be created and evaluated initially in a

patient population that is predominantly of White-European ancestry, we will also validate the risk scoring tool in a more racially diverse population of patients who receive their medical care at Temple University School of Medicine in Philadelphia, PA (Aim 3). The project also includes the development of new research educational programs targeted at students from minority populations that are underrepresented in medicine and biomedical research. This will be done by enrolling minority students in an existing undergraduate summer research internship program, and by developing a two-week intensive course in translational genomics for minority students.

Principal Investigator

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Other Participating Researchers

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Daniel E. Weeks, PhD; Elizabeth Gettig, MS – employed by the University of Pittsburgh
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Expected Research Outcomes and Benefits

The research project will lead to the creation of a novel genomically-informed model for predicting risk of abdominal aortic aneurysm (AAA) and an evaluation of the impact of implementation of this novel risk model on AAA population screening in a primary care clinic setting. Improved detection of AAA will lead directly to a reduction in mortality from rupture of undiagnosed AAAs. A more highly predictive risk model that can identify patients for population screening will also have enormous public health benefits. A refined risk prediction model will focus screening resources on patients with the highest risk, increases the number of positive AAA diagnoses, and decreases the number of negative diagnoses. Early diagnosis of AAAs (prior to rupture) will allow elective repair of aneurysms, and will allow patients with small aneurysms to be treated medically, when such therapies become available. We will also learn from this study whether the inclusion of genetic information, even if it adds only a modest level of increased risk, is a more potent motivator of a positive health behavior, i.e., participation in an AAA screening referral, than non-genetic risk information.

Summary of Research Completed

AIM 1: Create a novel AAA risk scoring tool that combines genetic variant and epidemiological data, using genotype and EMR-generated data from 1,000 AAA cases and 3,000 controls. Substantial progress has been made in accomplishing Aim 1.

The initial model was developed using a cohort of 1,000 AAA cases and 3,000 controls. These research subjects had consented to provide research DNA samples and to allow information in their Geisinger electronic medical record to be used for research.

DNA samples were genotyped on the Illumina OmniExpress and exome arrays, which together assay more than 900,000 single nucleotide variants. An additional set of variants were genotyped using the Illumina open array platform. These single nucleotide polymorphisms were selected because they were reported to be associated with AAA in previous studies or were selected as candidate genes based on the known pathobiology of AAA disease, and they are not assayed on the larger arrays.

During the reporting period, an initial risk model was developed using only clinical data that was extracted from patient electronic health records. Traditional bootstrap methods were used to generate sets of controls to reflect the census age and sex demographic structure. Logistic regression was carried out with AAA as the outcome variable. Clinical risk variables were selected by bidirectional stepwise elimination to evaluate model fit. Regression estimates were aggregated by the bootstrap aggregation method using meta-analytic techniques. Variables were ranked by how often they were retained in the model, and by the *P* value, which was based on the mean *z* score weighted by the number of iterations the corresponding variable was included in the model. We considered statistically significant ($P < 0.05$, two-sided) variables that occurred in $> 65\%$ of iterations to be consistent predictors of risk.

From these analyses, smoking, peripheral artery disease, age, coronary stenosis, systolic blood pressure, taller height, pulmonary disease, hypertension, male sex, cerebrovascular disease and malignant neoplasms were significantly associated with increased risk for AAA. Type 2 diabetes, diastolic blood pressure, benign neoplasms, weight, and myelogenous neoplasms had a statistically significantly protective effect on AAA risk.

We then used a variety of approaches to evaluate the effect on the risk estimates of adding in genetic marker data. We used a penalized regression approach (e.g., the lasso) to select a subset of optimal markers from a genome-wide set for risk prediction. Markers selected via this statistically powerful way did not provide additional improvement in the 'base' risk model calculated using clinical measures. That is, the selected genetic markers added little information about risk beyond that already contained in the clinical covariates. This could be due in part to the fact that the model based on clinical variables alone has a relatively high predictive value (area under the receiver-operator curve = 0.875).

We also continued to study how the width of the confidence intervals of the risk estimates changes as the number of genetic markers included in the risk model increases. We have observed that as the model is enlarged to include more markers, the width of the confidence interval usually increases. This has important implications for the interpretation of the risk estimates, and highlights the need to present information about confidence intervals when genetic risk estimates are considered.

Although adding genetic markers had only a modest effect on the population predictive value, we also explored the utility of genomic markers to re-classify individuals from high risk to low

risk categories. The initial results of these analyses were promising. In the best models, incorporation of genomic variant data led to re-classification of up to 18% of unaffected individuals from high to low risk groups, and re-classification of up to 27% of affected individuals from low to high risk groups. Such re-classification of individuals from a low risk to a high risk category could be very useful for designing a AAA screening strategy. It would lead to inclusion of individuals that do not meet criteria used in current screening protocols and, as a consequence, increase the number of previously undetected AAAs that are detected. Conversely, reclassification of individuals identified as high risk based on conventional criteria to low risk based on inclusion of genomic information could lead to few screenings of individuals without AAAs. Additional work in this area is ongoing. Validation of these models is the primary goal of Aim 2a.

We will also be exploring other risk modeling approaches, including ones that incorporate new data on AAA-associated genomic variants.

AIM 2: Validate the genomically-informed risk model, and develop educational materials and test a clinical implementation plan for utilization of genomic risk data in Geisinger outpatient clinics. The milestone is to enroll a total of 1,550 participants by 6/30/2014.

2a Prospective test of the genomically-informed risk model

Work related to Aim 2 has been the main area of focus for the past year. The goal is to validate risk algorithm developed in Aim 1 in an independent cohort of Geisinger patients. Eligible patients are selected from pool of Geisinger patients who had previously consented to participate in the MyCode biobank project. MyCode participants consent to use of blood and DNA samples and clinical data for broad research use, and agree to be recontacted for participation in future research studies. As of July, 2014 more than 46,000 Geisinger patients had consented to participate in MyCode, and enrollment is ongoing. The main advantage of using MyCode participants is that DNA samples suitable for assaying the informative genomic variants for the risk model are already collected, and the relevant epidemiologic data is available through the Geisinger clinical data warehouse.

The protocol for patient contact and screening for Aim 2 was approved by the Geisinger IRB.

Enrollment and screening of patients is currently underway. The minimum age for eligibility in this portion of the study is 57 years; individuals with previously diagnosed AAAs are excluded. To date, 2,458 patients were contacted and invited to visit Geisinger Medical Center for a screening ultrasound to detect previously undiagnosed aneurysms.

Eligible patients are sent informational material by mail and then contacted via telephone through Survey Research Core in the Geisinger Hood Center for Health Research. Planning and training meetings were held with the call center staff prior to initiation of patient contact. The call center staff is responsible for scheduling the patient's screening ultrasound, and obtaining family history and smoking history data on each participating patient. Patients are then added to the Vascular Lab schedule and sent reminders before their upcoming appointments. Thirty ultrasound scan appointments are available each week for the study.

Patients are screened at the Department of Vascular Surgery on the Geisinger Medical Center Danville campus. Planning meetings with members of the Geisinger Department of Vascular Surgery were held to develop a logistical plan for scheduling, performing, interpreting and reporting the tests. As of July, 2014 774 patients have been scheduled for ultrasound scans; 272 scans have been completed. Enrollment of patients will continue until we reach our goal. Of the 272 completed scans three previously undiagnosed aneurysms were detected. These patients are now being followed by the Department of Vascular Surgery for clinical care.

To ensure an adequate number of study subjects within the project time frame, we are also applying the same eligibility criteria to MyCode patients who underwent a clinically ordered abdominal radiologic imaging study within the past six months, and using radiologic findings in the patients electronic medical records to determine the presence or absence of a previously undiagnosed aneurysm. This is done by chart review of the patient's record by a vascular surgeon. Patients in this portion of the study are contacted by telephone and mail to obtain informed consent and to collect information on smoking history. As of July, 2014 319 patients were enrolled via this route.

2b Genomic risk model implementation

Clinical implementation of the risk model will require completion of the risk model development and validation (Aims 1 and 2a). The initial step in the clinical implementation process is to develop patient and provider education materials that explain the risk and available treatments for AAA, and explain the role of family history and genetics in AAA risk. Educational materials for patients and providers have been prepared, based on expert input from clinicians, scientists, and genetic counselors. There is also an ongoing project to provide physician education on the role of genetic variants in disease risk, using an established on-line training platform already in wide use at Geisinger. There is also an active program to develop technical infrastructure to create genetic test reports and clinical decision support via the electronic medical record. These educational and technical resources should accelerate the implementation of the risk model when validation is complete.

AIM 3: Determine the applicability of the novel AAA risk scoring tool in minority populations recruited at Temple University School of Medicine in Philadelphia, PA. The milestone is to enroll a total of 350 cases and 700 controls by 6/30/2014.

The goal of Aim 3 is to recruit into the research study individuals through Temple University School of Medicine to enable us to determine the applicability of the genomically-informed risk scoring tool in minority populations.

Initiating Aim 3 was delayed by a longer than anticipated time to obtain Temple IRB approval. Final IRB approval was obtained in April, 2013 and enrollment of patients at that site is underway. As of July, 2014 119 Temple University patients had been enrolled into the study. This includes 47 individuals with an aneurysm and 72 controls. Seventy-three of the Temple participants are self-reported African American. Blood samples from these consented patients have been sent to Geisinger. DNA was extracted and the samples were genotyped for genetic variants that are under consideration for use in the risk model. The data have been used to

compare allele frequencies in white and African American populations. A more detailed analysis will be carried out when participant enrollment is completed.

Patient enrollment at Temple has been slower than anticipated, but several measures are being instituted to increase enrollment. A new Clinical Research Center has been formed to coordinate clinical research activities at Temple University School of Medicine. A Research Coordinator to conduct patient enrollment for the study is being hired through the Clinical Research Center. A number of eligible patients have been identified in the Vascular Surgery clinic. These will be approached for consent when the Research Coordinator is hired. Another challenge has been the comparatively low rates of enrollment of African American patients who are invited to participate in the study. Outreach to African American patients for participation in clinical research studies is a priority for the new Clinical Research Center.

AIM 4: Provide internship opportunities in translational genomics for minority students, and develop materials for an intensive educational workshop for minority students in genetics and translational genomics.

The goal of aim 4 is to provide educational opportunities in medical research and genomics for minority students. Substantial progress has been made in accomplishing this aim.

To date a total of 10 minority students have participated in a summer research intern program at the Weis Center for Research, Geisinger Clinic, including 3 students in 2014. This is a 10 week intensive, mentored, hands-on research experience. At the conclusion of the program the students present their results findings as an oral presentation to an audience of peer interns and the Geisinger Clinic research staff. They also participate in a poster presentation forum for undergraduate science students from regional colleges and universities.

In addition, in June of 2014 we conducted a 2 week didactic program on genetics and medical genomics for undergraduate students. The faculty consisted of scientists and clinicians from Geisinger and the University of Pittsburgh. Nine students completed the program in 2014; three of those students were self-reported minority students. Course evaluations were conducted and the results are being evaluated. The overall response by the students was overwhelmingly positive