Geisinger Clinic - Weis Center for Research

Annual Progress Report: 2010 Formula Grant

Reporting Period

January 1, 2011 – June 30, 2011

Formula Grant Overview

The Geisinger Clinic - Weis Center for Research received $80,673 in formula funds for the grant award period January 1, 2011 through June 30, 2012. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Rare Genetic Variants in Patients with Abdominal Aortic Aneurysm - The goal of this study is to carry out whole exome DNA sequencing of individuals with abdominal aortic aneurysm (AAA). While AAA is known to have a strong genetic basis, functional genetic variants that cause AAA have yet to be identified. An emerging concept in human genetics research is that a substantial portion of the genetic basis of complex diseases results from rare sequence or structural variants in the genome. Recent advances in genomic technology, including next generation DNA sequencing, make it feasible to identify such variants in individuals with diseases of interest. Identifying functional genomic variants that cause AAA would pave the way for novel approaches to diagnose and treat this often fatal disease. Currently, AAA is often undiagnosed; when diagnosed surgical or endovascular repair are the only available treatment options.

Anticipated Duration of Project

1/1/2011 – 6/30/2012

Project Overview

The goal of this study is to identify genes that cause abdominal aortic aneurysms (AAA). This will be done by whole exome DNA sequence of individuals with confirmed diagnosis of AAA. Identifying functional genetic variants associated with AAA provides the best way to gain insight into the underlying disease mechanisms as a means to develop new diagnostic tests and medical therapies.

In previous studies genetic variants on chromosomes 1, 3, and 9 and genomic regions on chromosomes 4 and 19 were shown to be associated with AAA. However, these account for only a portion of the genetic risk of AAA; moreover, in none of these regions has the functional genetic variant that is associated with AAA been identified.

Recent studies demonstrate the value of large scale DNA sequencing to identify functional

genetic variants associated with an inherited disease. As part of an ongoing research project we enrolled >900 Geisinger patients with AAA into a research study. The goal of this study is to carry out whole exome DNA sequence analysis of 8 selected AAA patients. The genomic variants identified in AAA patients will be compared to those in control human genomes, to identify candidate AAA-causal variants. The variants found in AAA genomes will also be mapped to known physiological pathways to reveal potential underlying mechanisms.

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Expected Research Outcomes and Benefits

Abdominal aortic aneurysm (AAA) rupture is a major cause of death in the elderly, accounting for more than 15,000 deaths annually. With the aging of the U.S. population the prevalence of AAA is predicted to increase. Research is needed to address two major gaps in the treatment of this potentially fatal disease. Improved diagnosis of AAA would allow more affected individuals to receive available live-saving treatments; in addition, non-surgical therapeutic alternatives are needed to make treatment available to more patients and to reduce the dependence on expensive, invasive procedures. AAA is highly heritable. Knowledge of functional genetic variants associated with AAA would provide a unique window into the cellular and molecular basis of the disease and lead to novel diagnostic and therapeutic approaches.

Summary of Research Completed

This project has 3 aims: 1) to carry out whole exome sequence analysis of individuals with abdominal aortic aneurysms (AAA); 2) to categorize variants by type and potential functional consequences; and 3) to compare variants in individuals with AAA with normal controls.

The AAA cases for the study come from an ongoing research study of AAA at Geisinger Clinic. As of the date of this report, 997 AAA cases have been consented into the research study. Cases for whole exome sequencing were selected using the following criteria, based on the assumption that these individuals might have more potent genetic factors influencing their disease risk. The criteria were: individuals with a family history of AAA, young age of onset, limited smoking history, with oversampling of females.

Twelve individual samples (6 females, 6 males) were selected for whole exome sequence analysis (Aim 1). Genomic DNA isolated from EDTA-anticoagulated whole blood was used for exome capture using Agilent arrays. Next generation DNA sequencing was performed by an external service company. Exome sequencing has been completed on all samples. The sequence reads were mapped to the human reference genome, with more than 40X coverage of at least 80 percent of predicted exons. The sequence data are being analyzed to generate list of variants as compared to the reference genome (Aim 2, in progress).

Research Project 2: Project Title and Purpose

The Natural History and Comparative Effectiveness of Electronic Alerts in Geisinger Health System's Electronic Health Record - The purpose of this project is to build a dataset of all electronic alerts that have been triggered in Geisinger's Electronic Health Record from 1/1/2002 through 11/30/2010. Data will include the type of alert (e.g., drug-drug interaction, best practice alert, etc.) as well as details regarding when/why the alert was triggered and the action taken by the provider in response to the alert. This information will be used to describe the "natural history" of the use of alerts within Geisinger's primary care practices, and will also lead to analyses focused on identifying the types of alerts that are most successful in improving the quality and safety of care. This project will create a valuable source of evidence on the "real-world" comparative effectiveness of various forms of alerts that are used in clinical practice.

Anticipated Duration of Project

1/1/2011 – 6/30/2012

Project Overview

Electronic alerts can be used to prompt preventive care processes, to inform physicians of evidence-based treatment options at the time of ordering, and to prompt a diversity of other actions that require physician decision-making at the point of care. Given the proliferation of electronic health records (EHRs) in clinical practice, effective alerts have the potential to significantly improve health care quality and safety and to lower medical care costs. However, while it is technically straightforward to trigger an alert during a clinical encounter, this does not ensure that such alerts will be utilized as intended at the point of care. Moreover, there is evidence that "alert fatigue" can result from too many low-value alerts being triggered, minimizing the impact of all alerts. For example, it is estimated that millions of alerts fire within the Geisinger Health System's EHR each year, yet preliminary evidence suggests that only a portion of such alerts are opened and acted upon by providers.

The main objective of this project is to identify the various types of alerts that have been deployed in clinical practice, describe the frequency with which they are used, and characterize their effectiveness in achieving the desired clinical outcome. The results of this study will be helpful in rapidly advancing our understanding of what forms of alerts do and do not work, with the ultimate goal of translating this knowledge into forms of decision support that lead to improvements in meaningful outcomes (safety, quality, etc.). The first aim of this project is to establish a comprehensive database that will enable the quantitative and qualitative analysis of

the effectiveness of EHR alerts. Aims two and three are to characterize the "natural history" of alerts and alerting protocols implemented in the Geisinger EHR., as well as to identify characteristics (e.g., physician, technical, clinical) associated with effective (i.e., lead to the intended behavior on the part of the provider) alerts.

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Expected Research Outcomes and Benefits

Little is known regarding the effectiveness of various forms of electronic health record (EHR)-based alerts used in clinical practice, and research is lacking with respect to evidence supporting the specific forms and types of alerts that are successful (i.e., result in a provider taking a suggested action). There are very few institutions in the country that have as extensive a history of EHR-based alert use as does Geisinger. As such, the primary goal of this project is to mine the underlying data that characterize Geisinger's experience implementing alerts. We expect to generate evidence that will guide the development of future alerting protocols and decision support rules that can be adopted at both Geisinger and at other institutions that have or will adopt EHRs. This evidence is critical in this era of "meaningful use" of electronic health records, in which it is imperative to increase health care quality and safety and to concomitantly hold steady or decrease medical expenses.

Summary of Research Completed

This project has three aims. The first aim of this project is to establish a comprehensive database that will enable the quantitative and qualitative analysis of the effectiveness of EHR alerts. Aims two and three are to characterize the "natural history" of alerts and alerting protocols implemented in the Geisinger EHR., as well as to identify characteristics (e.g., physician, technical, clinical) associated with effective (i.e., lead to the intended behavior on the part of the provider) alerts. To date, aims one and two have been completed.

<u>Aim 1:</u>
Alert triggers are typically based on clinical status (e.g. out-of-range lab value), safety (e.g., drug-drug interactions), or quality (e.g., eligible for screening) criteria. After an alert is fired for a specific patient, there is a corresponding set of actions (e.g., order a lab) that the provider can take to close the alert. If the conditions are not met, alerts can be set to refire until the intended

action is taken. Geisinger's EHR, EpicCare®, tracks and stores data related to each alert. We queried these data and created a database of more than 27 million alerts deployed in Geisinger's 40 community practice sites over a 7-year period (2002-2009).

Aim 2:
To describe the "natural history" of alerting protocols deployed in Geisinger's primary care population since the EHR's inception, we limited our analysis to Best Practice Alerts (BPAs), as these types of alerts are customizable, point-of-care reminders intended to improve care when used. We manually subdivided BPAs into 10 different categories based on the alert descriptors, including: Medication, Preventive/Process, Preventive/Exam, Preventive/Vaccination, Preventive/Lab, Preventive/Medication, Risk, ePrescribing (eRx), Process, and Research.

Methods: We identified all BPAs fired in the primary care practice from June 2002 – December 2009. Alert-level information was used to determine the type of provider (i.e., physician, nurse) receiving the alert. Each alert's unique identifier (was used to determine the total number of times the alert fired, as well as the number of times each alert was refired before it was closed.

Results:
Growth in Alerts: The use of BPAs within Geisinger Clinic's primary care population has increased exponentially since 2002; nearly two million alerts were fired in 2009 alone (Figure 1). For patients who have had an alert fire, the average number of alerts that fire per patient has increased steadily over time (Figure 2).

Evolution of alert types and frequency of use by type of alert: From 2002-2004, the majority of alerts directed at nurses were preventive/ vaccination reminders (Figure 3). This began to shift in 2005 as preventive/lab alerts were increasingly fired, and later in 2007 when preventive/exam alerts were introduced into clinic workflows (Figure 4).

Figure 1: Best Practice Alerts (BPAs) fired from 2002-2009

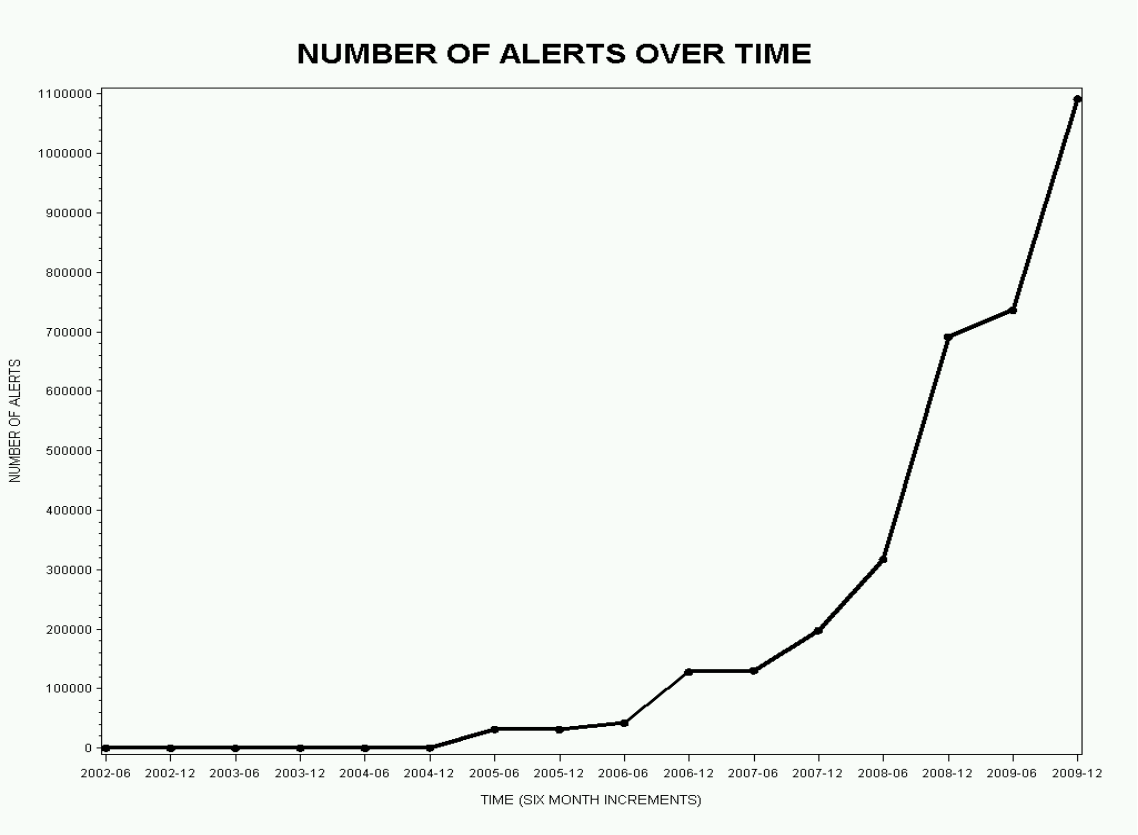

Figure 2: Average number of BPAs fired per patient from 2002-2009

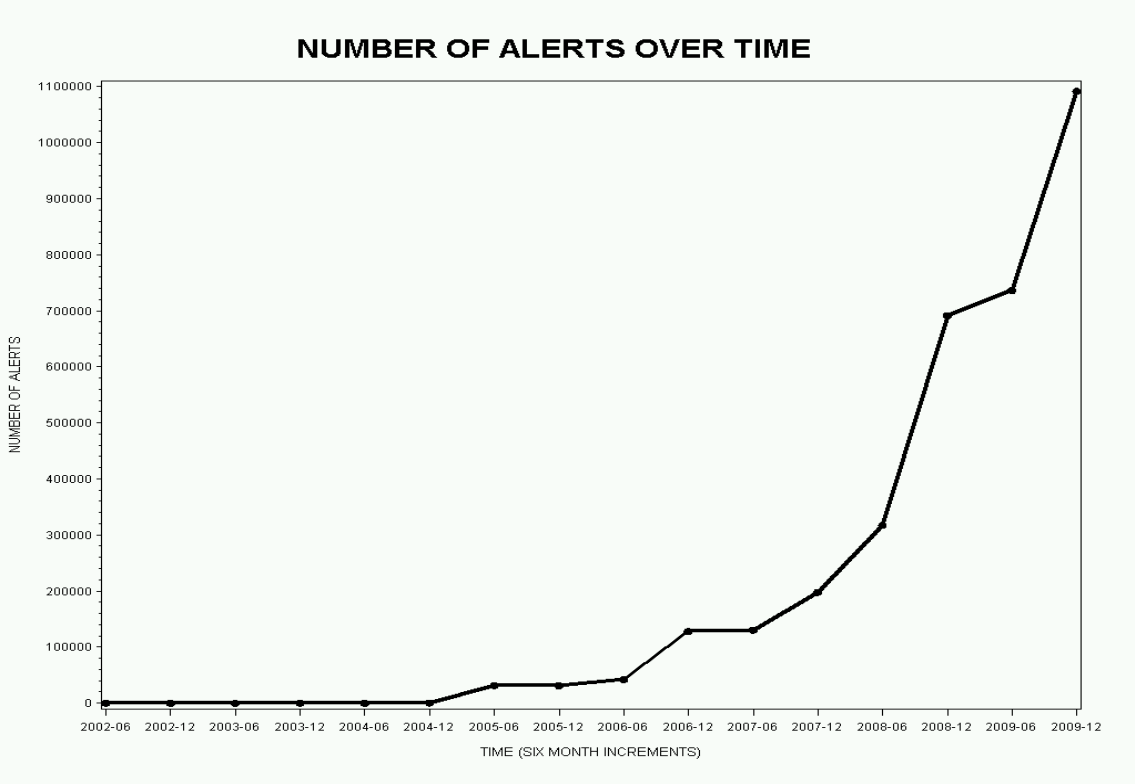

Figure 3: Categorical alerts by provider type, 2002-2004

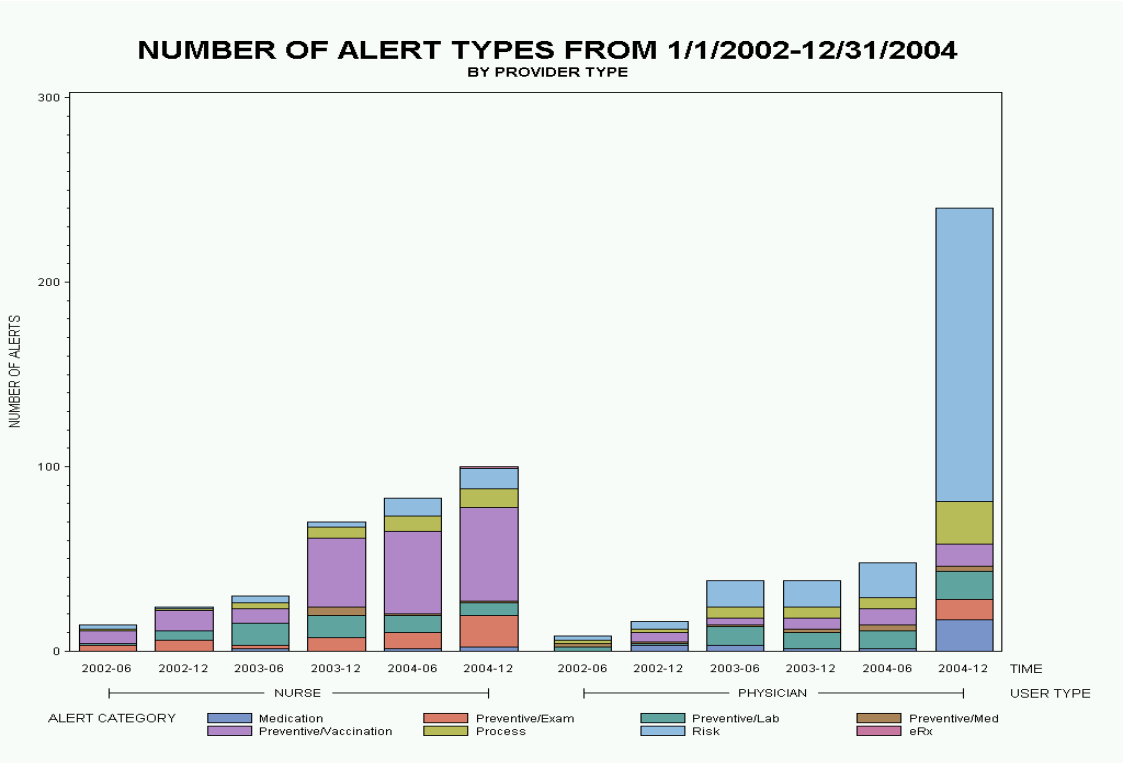

Figure 4: Categorical alerts by Provider type, 2005-2009