

Pennsylvania Department of Health Final Performance Summary Report Formula Grants

Overview of the Health Research Project Performance Review Process and Criteria

An applicant that receives a health research grant under Tobacco Settlement Act / Act 77 of 2001, Chapter 9, is subject to a performance review by the Department of Health upon completion of the research project. The performance review is based on requirements specified by Act 77 and criteria developed by the Department in consultation with the Health Research Advisory Committee.

As part of the performance review process, each research project contained in a grant is reviewed by at least three experts who are physicians, scientists or researchers. Reviewers are from the same or similar discipline as the research grant/project under review and are not from Pennsylvania. Reviewers use the applicant's proposed research plan (strategic plan), the annual progress report and final progress reports to conduct the review. A grant that receives an unfavorable performance review by the Department may be subject to a reduction in funding or become ineligible for health research funding in the future. The overall grant evaluation rating is based on the ratings for the individual research projects contained in the grant.

This performance review report contains the outcome of the review for the grant as a whole (outstanding, favorable, or unfavorable), strengths and weaknesses of each research project, as well as recommendations for future improvement.

The following criteria were applied to information submitted by research grant recipients:

- **Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?**
 - Did the project meet the stated objectives?
 - Were the research design and methods adequate in light of the project objectives?
 - Consider these questions about data and empirical results: Were the data developed sufficiently to answer the research questions posed? Were the data developed in line with the original research protocol?
 - If changes were made to the research protocol, was an explanation given, and, if so, is it reasonable?
 - Consider (only for clinical research projects) the extent of laboratory and clinical activities initiated and completed and the number of subjects relative to the target goal.
 - Were sufficient data and information provided to indicate or support the fact that the project met its objectives or made acceptable progress?
 - Were the data and information provided applicable to the project objectives listed in the strategic research plan?

- **Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?**
 - What is the significance of this project for improving health?
 - Consider the value of the research completed towards eventual improvement in health outcomes.
 - Consider any changes in risk factors, services provided, incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of impact and effectiveness of the research being conducted.
 - Consider any major discoveries, new drugs and new approaches for prevention, diagnosis and treatment, which are attributable to the completed research project.
 - What are the future plans for this research project?

- **Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?**
 - If leveraging of funds were expected, did these materialize?
 - Are the researchers planning to apply for additional funding in the future to continue or expand the research?

- **Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted/filed?**
 - If any of the above listed were expected, did these materialize?
 - Are the researchers planning to submit articles to peer-reviewed publications, file for any licenses, or patents or begin any commercial development opportunities in the future?
 - Consider the number/quality of each.

- **Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?**
 - Were there improvements made to infrastructure?
 - Were any new investigators added or were any researchers brought into the institution to help carry out this research?
 - Were funds used to pay for research performed by pre- or post-doctoral students?

- **Criterion 6 - Did the project lead to collaboration with research partners outside the institution, or new involvement with the community?**
 - Are the researchers planning to begin any collaborations as a result of the research?
 - For clinical research only: consider the number of hospitals and health care professionals involved and the extent of penetration of the studies throughout the region or the Commonwealth.

Overall Evaluation Rating

An overall evaluation rating is assigned to each research project. The rating reflects the overall progress the project attained in meeting the stated goals and objectives. The rating is based on a scale of 1–3, with 1 being the highest. An average rating is obtained from all the reviews (minimum of 3) of each project and is the basis for the determination of the final overall rating for each project as follows:

1.00 – 1.33 = *Outstanding*

1.34 – 2.66 = *Favorable*

2.67 – 3.00 = *Unfavorable*

The grant level rating is an average rating from all projects as above. The numerical rating appears in parentheses for the grant and each project in the ***Overall Grant Performance Review Rating*** section of the report.

Overall Grant Performance Review Rating

Grant Rating: Favorable (1.67)

Project Rating:

Project	Title	Average Score
0989601	Genetic Factors Associated with Aneurysms	Favorable (1.67)

Project Number: 0989601
Project Title: Genetic Factors Associated with Aneurysms
Investigator: Carey, David J.

Section A. Project Evaluation Criteria

Criterion 1 - How well did the project meet its stated objectives? If objectives were not completely met, was reasonable progress made?

STRENGTHS AND WEAKNESSES

Reviewer 1:

The investigators have achieved their primary research objectives described in their original proposal:

1) Identify single nucleotide polymorphism (SNP) genetic variants associated with abdominal aortic aneurysm (AAA). During the project period 366 Vascular Clinic patients were consented to participate in the study, bringing the total number of consented AAA cases to 1,051; including controls without AAA, the total number of consented Vascular Clinic patients at the end of the project period was 1,704. They identified two SNPs using the Geisinger AAA and control samples in genome-wide association studies by deCODE Genetics. One had been previously linked to coronary artery disease and intracranial aneurysm. This variant, SNP rs10752728, is >100,000 base pairs from the nearest known protein coding genes, *CDKN2B* and *CDKN2A*, which encode cyclin-dependent kinase inhibitors 2B and 2A, proteins involved in control of cell division. They also found that the AAA-associated genomic region contains a gene for a transcribed non-coding RNA that appears to regulate expression of *CDKN2B* and *CDKN2A*. Deletion of this region also alters proliferation of aortic smooth muscle cells, which could be relevant to the biology of AAA.

They further analyzed SNP rs7025486, identified by deCODE Genetics in a genome-wide association study of AAA cases and controls. They observed that this SNP lies within an intron of the gene *DAB2IP* on chromosome 9q33. The *DAB2IP* gene encodes a member of the RAS GTPase-activating protein family, inhibits cell proliferation and induces cellular apoptosis. The genotype of this SNP was also significantly associated with AAA in the sample cohort (P = 0.044; odds ratio = 1.16).

2) Determine the utility of a panel of AAA-associated SNPs to predict AAA risk. They tested if a combination of multiple AAA genetic risk variants plus conventional risk factor data would provide a better estimate of AAA risk than individual genetic or non-genetic risk factors alone or of the feasibility of using genetic data to stratify individuals for AAA risk. They reported a surprising finding that type 2 diabetes, myelogenous neoplasms and benign neoplasms were inversely significantly associated with AAA. This seems contrary to what people have expected, and casts an uncertainty on the clinical association study.

Reviewer 2:

The project met its core objectives. The research design and methods were adequate for the project objectives. For example, candidate gene associations are only thought to be valid as a study design if they are placed within a large context where replication is an integrated part of the design. It appears that the investigators expanded their approach to incorporate this shift in the field. Their cohort was a part of a replication study, and they also did primary 'discovery' genome-wide association studies (GWAS) which fulfilled the first aim. The second aim focused on the estimate of a genetic risk score which used three SNPs from three significant replicated regions. The results of the Aim 2 analysis were good, but it was hard to tell what kind of modeling was done and how robust the inferences would be to other samples.

Reviewer 3:

Prior work in the PI's laboratory using pooled case/control samples has identified common DNA variants associated with AAA. The specific aims of the current study were to 1) validate previously identified single nucleotide polymorphisms in an existing collection of DNA samples and 2) determine the utility of a panel consisting of multiple AAA-associated SNPs to quantify AAA risk. Genotype assays were initially performed in the Genomics Core of the Weis Center for Research. Subsequent change in tactic to the 700K OmniExpress arrays was a new effort to discover novel SNPs. Existing software packages were used to determine genetic models and association with AAA.

Overall strategies to follow up on previously identified common SNPs and determine the potential utility of combining SNPs in a risk score were laudable goals at the onset of this project. However, given the maturing landscape of GWAS studies at the time, one could question the power of the study given the relatively small number of cases. As noted by the investigators, larger GWAS studies had already identified risk variants, including the cardiovascular disease variant at chromosome 9p21. This risk variant was validated in the Geisinger Clinic cohort. Moreover, a simple additive model was developed, and a positive association was found with risk increasing from zero to six risk alleles of the three genetic variants tested. Thus, while modest in effect size, this is a positive outcome based on the stated objectives of validating risk variants in the Geisinger Clinic cohort and testing the ability to produce risk models. It is, therefore, somewhat surprising that this work has not yet been published--a major stated overall goal of the proposed work.

Also important is the addition of clinical factors into the model. Thus, it will be important to see if the genetic variants add anything to already known risk factors (both positive and negative) for AAA. This is stated as one of the manuscripts in preparation, but it seems this work should be published by now.

In the middle of the study period, the strategy was adjusted to incorporate a discovery platform (Illumina OmniExpress 700K array). Little description in the summaries is given as to the rationale for the choice of this genotyping platform. Moreover, while several interesting SNP clusters appear to have come out of this effort, there is no discussion as to how these findings will be further investigated. For example, are there plans to replicate these findings in another population? Are resequencing efforts planned to discover rarer variants at these candidate loci?

Criterion 2 - What is the likely beneficial impact of this project? If the likely beneficial impact is small, is it judged reasonable in light of the dollars budgeted?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Strength: This work is of interest and clinically significant. AAA is the number 14 cause of death and often occurs suddenly. It is important to have a reliable method for early screening of risk factors and diagnosis of AAA.

Major weakness: The SNPs analyzed have largely no functional association with vascular pathobiology. In this regard, a combination of SNP analysis with functional genomics and epigenetics could be generating much needed information.

Reviewer 2:

The main beneficial impact of the project is to build the chain of evidence about genetic risk factors for AAA. Given the way in which the investigators took the 'discovery' phase of Aim 1 and moved it into a preliminary clinical utility evaluation in Aim 2, I believe there is the possibility of some additional downstream translational benefit that could come from this modest research project within the Geisinger Clinic. As clearly stated in their background materials, little can be done to prevent this outcome, but better surveillance of at-risk individuals could help to increase education of the symptoms and potentially lead to better health outcomes for individuals who have an event.

Reviewer 3:

The stated overall purpose of this proposal was to identify DNA variants associated with abdominal aortic aneurysms (AAA), a significant health problem related to aging. While several environmental factors have been associated with AAA, little insight has been derived regarding molecular mechanisms, and non-surgical treatment options are not available. Moreover, risk of disease development as well as growth monitoring is limited to imaging modalities. Heritability studies indicate a strong genetic component to AAA disease. While several studies have identified various genetic loci linked to AAA, they only account for a small fraction of the genetic risk. Thus, the potential beneficial impact of this study at the onset was very high. Some progress has been made in that 1) known common variants have been replicated in the Geisinger Clinic population; 2) the additive nature of some of these variants has been demonstrated; and, 3) clinical risk factors are also considered in risk models. However, none of the results appear to have been reported, thereby limiting impact to this point. It may be stated that the discovery of genetic risk variants in general, particularly common SNPs related to common diseases, has been underwhelming. The optimistic view is that other forms of genetic variability (rare variants, structural variants) yet to be discovered will offer more insight into AAA disease and that the studies performed in the current funding cycle were a necessary step in our understanding of the genetic underpinnings. The result of this work providing the preliminary data for Geisinger Clinic's inclusion into the eMERGE Network is a positive outcome of the studies and should add to this line of investigation.

Criterion 3 - Did the project leverage additional funds or were any additional grant applications submitted as a result of this project?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Yes, this project has become part of a large network supported in part by NIH and other funding sources.

The investigators are applying for other funding to continue and expand the research.

Reviewer 2:

It appears that they were able to leverage additional funds to complete the Illumina genotyping on their cases and controls. Also, additional grant applications were submitted, and they do appear to be committed to continuing this research.

Reviewer 3:

As noted above, this is a major positive outcome of the stated results of this project. While the impact of the data generated has been limited up to this point, the value of the Geisinger Clinic infrastructure was undoubtedly a significant strength in its ability to be one of seven members of eMERGE. The eMERGE network is directly in line with the general research direction outlined by Dr. Carey to discover novel gene-disease associations that are linkable to the electronic medical record.

Criterion 4 - Did the project result in any peer-reviewed publications, licenses, patents, or commercial development opportunities? Were any of these submitted / filed?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Per the investigator's report, there was no paper submitted, but the investigators plan to submit future papers.

Reviewer 2:

They plan to submit three publications. None has been submitted so far. Given the two-year timeline of the grant, this seems somewhat reasonable.

Reviewer 3:

This is arguably one of the great weaknesses of the proposal up to this point. While major new findings may not have come out of the studies up to this point, there are several observations that are not only worth reporting, but will be valuable to the community at large interested in AAA disease.

Criterion 5 - Did the project enhance the quality and capacity for research at the grantee's institution?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Yes, this project offers a good opportunity to promote the genetic and translation research in a remote medical center largely for patients from the countryside.

There were no new investigators or pre- and post-doctoral students joining this project.

Reviewer 2:

The project report did not really articulate ways that the quality and capacity of the grantee's institution was enhanced. There were no signature improvements made to the infrastructure. There did not appear to be any pre- or post-doctoral students on the grant. New investigators did not appear to be added. The grant was small in size, so it is not surprising that these were not key considerations of the project.

Reviewer 3:

While comprehensive data is not available, it can be stated that improvements in infrastructure were made to Geisinger Clinic due to this project. In addition to the hiring of three scientists who worked on the project, there was significant investment in both technical and intellectual infrastructure. Moreover, this investment has already resulted in further funding which should greatly expand the ability of the institution to contribute to this type of research.

Criterion 6 - Did the project lead to collaboration with research partners outside of the institution or new involvement with the community?

STRENGTHS AND WEAKNESSES

Reviewer 1:

Yes, throughout this project, the investigators have been collaborating with other investigators in the USA and other countries, including the eMERGE Network, which is supported by funding from the NIH-National Human Genome Research Institute. Collaborators included Dr. Robert Elston, Case Western Reserve University; Dr. Daniel Weeks, University of Pittsburgh deCODE Genetics; and the University of Otago in New Zealand.

Reviewer 2:

There does appear to be some additional collaboration with others through their GWAS efforts as a consequence of this grant.

Reviewer 3:

In addition to being included in the eMERGE Network, replication efforts have already been agreed upon through collaborations with investigators at deCODE Genetics and the University of Otago in New Zealand. In addition, they have also agreed to share data with international collaborators from Iceland, the UK, and Australia/New Zealand. The proposed meta-analysis

will be the largest such study of AAA disease performed to date and should greatly increase power to identify previously undetected disease-associated variants.

Section B. Recommendations

SPECIFIC WEAKNESSES AND RECOMMENDATIONS

Reviewer 1:

1. Recruit new physician-scientists into this project.
2. Have graduate and post-doctoral trainees participating.
3. Work on the combination of SNPs, functional genomics and epigenetics.

Reviewer 2:

The design of Aim 2 where the same cases and controls were used as in the primary aim of discovering variants (Aim 1) creates a kind of inflated sense of predictive capacity when the top SNPs are evaluated. A separate cohort is really needed to perform an adequate assessment.

Reviewer 3:

1. Publish the work produced up to now, as well as future findings, on a regular basis.
2. Explore other types of variants (rare, structural) that may be associated with disease. For example, resequencing efforts may be focused on current results from genotyping and linkage studies.
3. Perform more family-based studies with whole genome sequencing.

Recommendations for Geisinger Clinic

Reviewer 1:

It is recommended that Geisinger recruit vascular pathobiologists to help assess the linkage of genetic or epigenetic variances in AAA.

Reviewer 3:

The biorepository as well as the electronic medical record are rich resources for this type of investigation and should be supported as much as possible.