Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution: Geisinger Clinic**

2. **Reporting Period (start and end date of grant award period): 1/01/2010–12/31/2011**

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees): Samantha Fetterolf**

4. **Grant Contact Person's Telephone Number: 570-214-5230**

5. **Grant SAP Number: 4100050896**

6. **Project Number and Title of Research Project: 1- Genetic Factors Associated with Aneurysms**

7. **Start and End Date of Research Project: 1/01/2010-12/31/2011**

8. **Name of Principal Investigator for the Research Project: David J. Carey, PhD**

9. **Research Project Expenses**.

   9(A) Please provide the amount of health research grant funds spent on this project for the entire duration of the grant, including any interest earned that was spent:

   $ 102,403.61

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project	Cost

Masker	Research Technician	14% Yr 1; 32% Yr 2	$20,838.65
Schworer	Research Scientist	0% Yr 1; 28% Yr 2	$21,712.05
Golden	Research Technician	0% Yr 1; 29% Yr 2	$13,270.56

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name	Position Title	% of Effort on Project
None		

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No__X____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes ___X____ No_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
Geisinger eGenomic Medicine (GeM) Program	☑NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)	11/2010	$3,282,594	$3,279,226
	☐NIH ☐Other federal (specify:) ☐ Nonfederal source (specify:)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes ___X_____ No_____

If yes, please describe your plans:

A grant to the PA-CURE non-formula fund is pending. If approved, this grant would support the creation of a hybrid risk scoring tool that combines genomic variants studied during this project with non-genetic risk factor data.

Future plans also include a AAA genome wide association meta-analysis that combines our genotype data with other studies from Iceland, Europe, and Australia/New Zealand. Funding to support this meta-analysis will be sought from various sources.

12. Future of Research Project. What are the future plans for this research project?

The project will be continued along several lines.

Some of the future work will be done through funding obtained as a result of our participation in the eMERGE (electronic MEdical Records and Genomics) Network. The eMERGE Network is a National Human Genome Institute (NHGRI)-funded consortium of seven US medical research institutions. The main goals of the eMERGE Network are to discover new gene-disease associations using existing DNA biorepositories that are linkable to electronic medical record data for electronic phenotyping, and to translate the use of genomic data in clinical practice. AAA is a primary phenotype to be studied by Geisinger through the eMERGE Network

The genome wide association data will be analyzed in more detail to identify new SNP variants that are associated with AAA. This will include imputation of SNP genotypes using variant data from the 1,000 Genomes Project. Imputation is being carried out by the eMERGE Network Coordinating Center. This will allow genotype data on AAA patients at other eMERGE sites to be combined with the Geisinger genotype data to increase sample size and statistical power to detect statistically significant associations. The imputed data set will also be analyzed to discern the genetic structure of the AAA-associated loci to develop hypotheses regarding the potential functional variants. The final step in establishing a genome-disease association will be replication of the genetic association in one or more independent populations. Samples for replication will be obtained from other eMERGE sites, and from agreed-upon collaborations with investigators at DeCode Genetics and the University of Otago in New Zealand who have existing AAA case-control cohorts.

We have also agreed to share our genome wide association data with an international group of collaborators from Iceland, the United Kingdom, and Australia/New Zealand to perform a

large meta-analysis of AAA genetic association. The proposed meta-analysis will contain more than 5,000 AAA cases and 30,000 controls. This will be the largest such study of this disease ever conducted, and should have sufficient power to identify previously undetected AAA-associated genetic variants.

We also plan to incorporate additional AAA-associated genomic variants and non-genetic data into a hybrid AAA risk scoring model and to retrospectively test and refine the model using the existing Geisinger DNA biorepository and electronic medical record data. We then plan to test the risk model prospectively in Geisinger outpatient clinics to determine its utility in stratifying patients for population screening for AAA.

13. **New Investigator Training and Development**. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____ No___X_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. **Recruitment of Out-of–State Researchers**. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No ___X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes ___X____ No_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

The project allowed us to generate preliminary data and approaches that were incorporated into new grant applications, especially the eMERGE Network grant, which was recently funded by the NIH-National Human Genome Research Institute. This grant enabled us to recruit investigators, data analysts, and programmers that are part of the growing translational research infrastructure at Geisinger. The project also generated key data and hypotheses that were the basis of a grant application to the PA-CURE non-formula (competitive) program. That grant is pending final review and, if funded, would also support salaries for investigators, research assistants, data analysts, and programmers that will further augment the research infrastructure at Geisinger.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes ___X____ No_____

If yes, please describe the collaborations:

Efforts related to the health research fund project led to several fruitful external collaborations.

One of these is related to our participation in the eMERGE Network, which is supported by funding from the NIH-National Human Genome Research Institute. This gives us access to six other eMERGE sites, who through the Network have the goal to collaborate on projects to identify genomic variants associated with important clinical phenotypes, and to translate use of genomic data into clinical care. AAA is a primary phenotype proposed by Geisinger, and all other eMERGE sites have agreed to collaborate with us on studying this phenotype.

We have also initiated collaborations with Dr. Robert Elston, Case Western Reserve University, and Dr. Daniel Weeks, University of Pittsburgh, to participate in the analysis of genomic data and risk modeling.

We have also agreed to participate in an international AAA genome wide association meta-analysis, to be led by Dr. Matt Bown, United Kingdom.

16(B) Did the research project result in commercial development of any research products?

Yes_____ No ____X____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No ____X____

If yes, please describe involvement with community groups that resulted from the research project:

17. Progress in Achieving Research Goals, Objectives and Aims.

List the project goals, objectives and specific aims (as contained in the grant application's strategic plan). Summarize the progress made in achieving these goals, objectives and aims for the period that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

The project had two specific aims: 1) Identify single nucleotide polymorphism (SNP) genetic variants associated with abdominal aortic aneurysm (AAA), and 2) Determine the utility of a panel of AAA-associated SNPs to predict AAA risk.

Substantial progress was made in achieving both Aims.

Study population and samples: Genetic association and risk modeling studies require large sets of well-annotated patient samples. Effort was made to identify and enroll additional AAA cases through the Geisinger Clinic Department of Vascular Surgery. 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. .

An important source of control subjects is the Geisinger MyCode project. For the MyCode Project adult Geisinger Clinic outpatients are consented to provide blood and serum samples for broad research use and authorization for Geisinger investigators to access data in their medical records for research. (Note: the MyCode Project was not funded through this Formula Fund grant; MyCode samples were made available for this project through application to the MyCode Governing Board per MyCode protocols). By the end of the project period more than 23,000 Geisinger patients had consented to participate in the MyCode project. The demographic profile of this cohort approximates that of the Geisinger adult primary care population. For this study, a subset of 1,231 matched controls were randomly selected from the MyCode cohort to be used in the genetic association studies.

Aim 1. Identify AAA-associated single nucleotide polymorphisms: Two approaches were used to identify SNP variants that were associated with AAA. The first was to genotype SNPs in the Geisinger AAA case and control samples that were previously identified in other populations. Such replication of genetic associations is an essential step in establishing gene variant-disease links.

Two SNPs for which the Geisinger AAA and control samples were used for replication were first identified in genome wide association studies by DeCode Genetics. One of these 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. 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.

We determined SNP rs10757278 genotype using a TaqMan assay on an Applied Biosystems 7500 Fast Real-Time PCR instrument in 1,384 AAA cases (additional cases were obtained from a collaborator to supplement the Geisinger cases) and 858 controls. The SNP genotype was significantly associated with AAA by chi-squared analysis (P = 0.0019; odds ratio = 1.21).

In a second case we analyzed SNP rs7025486 that was identified by DeCode Genetics in a genome wide association study of AAA cases and controls. 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, and inhibits cell proliferation and induces cellular apoptosis. The genotype of this SNP was also significantly associated with AAA in our sample cohort (P = 0.044; odds ratio = 1.16).

DeCode Genetics had also observed association of this SNP with other forms of vascular disease, specifically early onset myocardial infarction and peripheral artery disease, similar to what had been observed for SNP rs10757288 on chromosome 9p21. To determine whether these associations with other forms of vascular disease could be replicated in the Geisinger population both SNPs were genotyped in Geisinger Vascular Clinic patients who were diagnosed with peripheral artery disease but not AAA. In both cases a significant association with peripheral artery disease was observed. For SNP rs10757288 on chromosome 9p21: p = 0.0078, odds ratio = 1.34; for SNP rs7025486 on chromosome 9q33: p = 0.038, odds ratio = 1.15.

In other genetic association studies using AAA samples as cases and peripheral artery disease samples as controls we identified genetic variants on chromosomes 3p12.3 and 1q41 that were significantly associated with AAA. Together, these results suggest there are at least 2 classes of genetic variants that affect AAA: some (e.g. rs10757288 and rs7025486) influence biological features common to multiple forms of vascular disease, and some (e.g. the variants on chromosomes 3p12.3 and 1q41) influence features specific to AAA pathophysiology. Further study of these genetic variants and their biological functions should lead to new insights into the pathobiology of these important diseases. It is also noteworthy that the two known variants that affect AAA and other forms of vascular disease both have functions related to control of cell division and cell survival. This probably reflects a common biological feature of these diseases, and uncovers specific molecular pathways that were not previously implicated in vascular disease.

To identify additional new genomic variants for AAA we carried out a genome wide association study of 940 Geisinger AAA cases and 1,240 MyCode controls using Illumina Human-OmniExpress arrays, which interrogate more than 731,000 common variants (genotyping costs were paid by Geisinger Clinic research funds). The genotyping data was subjected to quality control analysis. Variants were excluded that showed a minor allele frequency < 0.1% and an assay call rate <95%. A total of 594,034 variants passed quality control.

Genetic association analysis using an allelic association genetic model was carried out using logistic regression to control for age and sex (major risk factors for AAA). The preliminary analysis identified three clusters of SNPs that were in strong linkage disequilibrium and had P

values for genetic association < 10^{-6}. These SNPs were located on chromosomes 12q24.21, 15q25.3, and 16q22.1.

These data identify potential new AAA-associated genetic loci, and will be followed up by replication studies in other sample cohorts. These are available via collaborations with DeCode Genetics and other participating eMERGE Network sites.

Aim 2. Investigate the utility of a panel of AAA-associated SNPs to quantify AAA risk: The AAA-associated genetic variants that have been identified so far each have only a moderate effect on disease risk. This is typical of common genetic variants that have been shown to be associated with a specific disorder and discovered by genome wide association studies. We hypothesized that 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 alsone. This section summarizes our preliminary work to determine the impact of using multiple AAA-associated common variants on estimating AAA risk.

DNA samples from Geisinger Clinic patients (938 AAA cases and 1,126 age-matched MyCode controls) were genotyped for three AAA-associated SNPs on chromosome 9p21, 3p12.3, and 1q41, each with a small individual effect on AAA risk (ORs 1.2 – 1.3). A simple genetic model that assumed additive effects of risk alleles and no genetic interaction was used. The distribution of total risk alleles for the 3 genetic variants (from 0 to 6 risk alleles per genome) was different in the AAA case and control groups, with the case group shifted toward more total risk alleles ($P < 0.0001$). Consistent with this finding, the odds ratio for AAA increased as a function of the number of risk alleles. For individuals with 3 or more risk alleles the odds ratio for AAA disease was increased 2.4-fold compared to individuals with 0-2 alleles ($P < 0.0001$). For individuals with 6 risk alleles the odds ratio was increased 3.5-fold ($P < 0.01$). The association of allele burden with AAA was also examined by linear regression analysis. The linear regression line had a positive non-zero slope ($P < 0.01$, $R^2 = 0.8$). The AAA disease odds varied by 3.7-fold from 0 to 6 risk alleles. These data support the feasibility of using genetic data to stratify individuals for AAA risk.

We also wanted to refine the risk model by incorporating non-genetic risk factor data. As a first step in this process we determined the feasibility of using data mined from the Geisinger electronic health record (EHR) to determine AAA risk based on known risk factors identified in previous epidemiologic studies.

The study was based on 964 AAA cases (752 males and 212 females) identified by ICD-9 codes (441.3, 441.4, or 441.9), CPT procedure code associated uniquely with AAA, or referral to the Geisinger Department of Vascular Surgery and an ultrasound, CT scan, or other imaging study that confirms an infrarenal aortic diameter >3.0 cm. Controls (5,063 males, 9,492 females) were ascertained from the Geisinger MyCode cohort of Geisinger primary care patients described above.

Clinical and diagnostic data pertaining to these patients from January 2004 to December 2009 were extracted from the Geisinger EMR via the Geisinger clinical data warehouse. Clinical risk factors were selected from the literature or were of biological interest based on the pathobiology of AAA. Data were obtained for all diagnoses, laboratory measures and clinical values from

primary care and specialty clinic visits. A total of 565 ICD-9 diagnostic codes were collapsed into 17 categories based on similar physiologies. Bootstrap replication procedures on the dataset (with and without replacement) confirmed the reproducibility of the results. Odds ratios for the potential risk factors were calculated using multivariate logistic regression with AAA as the dichotomous outcome variable.

Statistically significant risk factors included pulse pressure, peripheral artery disease, coronary stenosis, cranial artery stenosis, and pulmonary disease. These results are consistent with the magnitude and direction of risk factors for AAA reported previously. Type 2 diabetes, myologenous neoplasms and benign neoplasms were inversely significantly associated with AAA. The inverse association of AAA with type 2 diabetes was previously known, whereas the inverse association of AAA with benign neoplasms is a novel finding.

This study demonstrates the feasibility of utilizing retrospective EHR data to identify risk factors for a complex disease. This is a key step in the ultimate creation of a robust risk model for AAA that incorporates genetic and non-genetic data.

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X_ No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
___X_ No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics
_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
___X_ No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
_____ No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include the number of the research project, the last name of the PI, the number of the publication and an abbreviated research project title. For example, if you submit two publications for PI Smith for the "Cognition and MRI in Older Adults" research project (Project 1), and two publications for PI Zhang for the "Lung Cancer" research project (Project 3), the filenames should be:

Project 1 – Smith – Publication 1 – Cognition and MRI
Project 1 – Smith – Publication 2 – Cognition and MRI
Project 3 – Zhang – Publication 1 – Lung Cancer
Project 3 – Zhang – Publication 2 – Lung Cancer

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. None				☐Submitted ☐Accepted ☐Published
2.				☐Submitted ☐Accepted ☐Published
3.				☐Submitted ☐Accepted

				☐Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes ____X____ No_____

If yes, please describe your plans:

We plan to submit three articles for peer-reviewed publications. One of these will summarize our AAA genome wide association study. Another will focus on using multiple AAA-associated genomic variants to model disease risk. The third will discuss use of electronic medical record data to identify disease risk factors.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None. This was basic research that lays groundwork for future studies that will test the utility of genomic data in reducing deaths from AAA by improving population screening strategies.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The research led to the identification of novel genomic variants associated with AAA, which is a major cause of death in the US.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No____X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No____X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. *For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

BIOGRAPHICAL SKETCH	
NAME **David J. Carey**	POSITION TITLE **Director and Senior Scientist**
eRA COMMONS USER NAME (credential, e.g., agency login) **djcarey**	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	MM/YY	FIELD OF STUDY
St. Louis University, St. Louis, MO	**B.A.**	**1974**	**Biology/Chemistry**
St. Louis University, St. Louis, MO	**Ph.D.**	**1980**	**Biochemistry**
Washington University, St. Louis, MO	**Postdoc**	**1980-1982**	**Neurobiology**

B. Positions and Honors

11/01/82-06/30/84	Assistant Professor of Biochemistry, Louisiana State University Medical Center in Shreveport, Shreveport, LA
07/01/84-06/30/87	Assistant Professor of Physiology, The Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey, PA
07/01/87-06/30/96	Staff Scientist, Weis Center for Research, Geisinger Clinic, Danville, PA
07/01/96-06/30/97	Senior Scientist, Weis Center for Research, Geisinger Clinic, Danville, PA
07/01/97-06/30/00	Professor of Cellular and Molecular Physiology, Pennsylvania State University, College of Medicine, Hershey, PA
07/01/00-	Senior Scientist and Director, Weis Center for Research/Geisinger Clinic, Danville, PA

C. Selected Peer-reviewed Publications (Selected from more than 100 peer-reviewed publications)

1. Wood, G.C., Still, C.D., Chu, X., Susek, M., Erdman, R., Hartman, C., Yeager, S. Blosky, M.A., Krum, W., **Carey, D.J**., Skelding, K.A., Benotti, P., Stewart, W.F., and Gerhard, G.S. Association of chromosome 9p21 SNPs with cardiovascular phenotypes in morbid obesity using electronic health record data. *Genomic Medicine*. 2:, 2008
2. Gerhard, G.S., Langer, R.D., **Carey, D.J**., and Stewart, W.F. Electronic Medical Records in Genomic Medicine Practice and Research. In *Genomic and Personalized Medicine*, H. Willard and G. Ginsburg, eds., 2008.
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D. Research Support

NIH Carey, Williams (Co-PI's) 7/1/2011 - 6/30/2015
GEISINGER EGENOMIC MEDICINE (GEM) PROGRAM
The goal is to use existing biospecimens and EMR-generated phenotypes to identify genetic variants associated with increased disease risk or altered treatment response and to develop and test approaches to provide clinically relevant genetic research results to patients and clinical providers. Also the project will study sociocultural concerns of patients residing in rural areas regarding Genomic Medicine research.
Role: Co-Principal Investigator

Center for Disease Control and Prevention Carey (PI) 09/18/09-09/17/12
Myeloproliferative Neoplasms – JAK2 Prevalence Study
The goal of this project is to investigate the prevalence of an acquired mutation that causes the myeloproliferative neoplasm polycythemia vera and an inherited genetic variant that is associated with the acquired mutation.
Role: co-investigator