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): 1/1/2011-6/30/2012**

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: 4100054849**

6. **Project Number and Title of Research Project: Project 1: Rare Genetic Variants in Patients with Abdominal Aortic Aneurysm**

7. **Start and End Date of Research Project: 1/1/2011-6/30/2012**

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:

   $40,683.28

   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
Smelser	Research Associate	16.8%	$15,300.88
Bowen	Research Assistant	7.7%	$3,294.25
Golden	Research Technician	6.7%	$1,711.68

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

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

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 _____ No ____X_____

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:
	☒NIH ☒ Other federal (specify: PA DOH) ☐ Nonfederal source (specify: _____)			
	☐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:
At this time, specific plans to apply for additional funding have not been finalized. However, as this project created a large amount of sequence variant data, future plans include applying for funding to test statistical genetic and bioinformatics approaches to establish a role for specific variants in AAA.

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

The project will continue and is expected to lead to several related projects. The project created an enormous amount of sequence variant data that will be followed up with statistical genetic and bioinformatics approaches to establish a role for specific variants in AAA. This will include for genetic variants of interest replication in other sample sets. It also includes the mapping of candidate AAA variants to specific signaling pathways, using in silico approaches such as Ingenuity Pathway software. Identification of candidate disease associated variants will also lead to studies to investigate potential biological mechanisms and pathways using model systems. In addition, some genetic variants identified through next generation DNA sequencing in this project are included in a study recently funded through a non-formulate PA-CURE grant to use genomic risk data to improve 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 research project generated preliminary data that is being used in a newly funded research project to determine the utility of genomic information for population screening for AAA. That project involves additional collaborators within and outside of Geisinger. The former include investigators with expertise in genomic medicine and predictive risk modeling. There are now formal research collaborations with investigators at the University of Pittsburgh and Temple University School of Medicine. In addition, the project gave us experience in creating and analyzing large DNA sequence data sets. This enabled us to apply this expertise to a number of other genomic studies, including a new program to use whole genome or whole exome sequence analysis for diagnosis of children with severe, undiagnosed disorders.

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:

Through this research we collaborated with two external for-profit providers of next generation DNA sequencing, Perkin Elmer Genomic Services, and Complete Genomics. These relationships are critical, because Geisinger Clinic is developing new research projects that utilize next generation sequence data but the Clinic is not investing in the creation of an internal capacity for high throughput DNA sequencing. We also collaborated with Dr. Kristin Willer at the University of Michigan. She is an expert in analysis of genetic variant data and helped develop the data analysis pipeline and variant prioritization algorithm. Follow-up studies that are ongoing involve collaborators at the University of Pittsburgh, who are assisting in statistical genetic and predictive risk modeling analyses, and with Temple University School of Medicine, where we are working with investigators to enroll additional patients for genomic studies of AAA, including patients from minority populations.

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.

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.

Patient ascertainment – Individuals for this research study come from an ongoing research study of AAA at Geisinger Clinic. A total of 1,100 validated AAA cases have been consented into that study. At the time of enrollment patients complete a questionnaire that asks questions about AAA risk factors, including family history. Family history is the second strongest risk factor for AAA, second only to smoking. A total of 206 AAA cases (19%) report a known positive family history. These individuals are eligible to participate in the family DNA sequencing study. By the end of this project period seventy of these cases have been contacted by mail and telephone; thirty-five have agreed to participate in the family study. We have obtained from these patients contact information for affected and unaffected first degree family members. Enrollment of these individuals into a genetic research study is underway, and will continue beyond the end date of this funded project. All DNA sequence analysis to date has been done using Geisinger AAA cases.

Next-generation DNA sequencing –We conducted next generation DNA sequence analysis of samples from individuals with AAA in two stages. We first applied whole exome sequence analysis to DNA samples were Geisinger patients with early onset AAA from families with multiple affected first degree relatives. The rationale was that these represent "extreme" AAA phenotypes, and so might be favorable for discovery of AAA-associated variants. Previous genome wide association studies have identified common genetic variants associated with AAA, but account for only a small portion of the estimated genetic risk. DNA sequence analysis has the advantage of enabling the discovery of low frequency or rare genetic variants, which have been suggested to account for at least some of the "missing heritability" of complex diseases. Exome sequencing targets protein-coding regions of the genome, which are more likely to harbor functional disease-associated variants.

Genomic DNA was isolated from EDTA-anticoagulated whole blood samples using a Qiagen DNA extraction robot. Agilent whole exome capture arrays were used to enrich for exomic DNA. Next generation DNA sequence analysis was carried out by Perkin-Elmer Genome Services using paired-end sequencing to an average coverage depth of >40X. An average of 58 x 10^6 sequence reads per individual sample were mapped to the human reference genome, version 37.1. Initial analysis identified 658,287 variants, mostly single nucleotide polymorphisms, when the mapped sequence reads were compared to the dbSNP database.

Table 1: Scoring scheme of variants identified by whole genome sequencing

Criterion	Score
Location relative to linkage peaks (maximum 100)	
In linkage region 19q13	100
In other linkage regions	70
Not in linkage region	0
Frequency in 1000 Genomes CEU (maximum 70)	
Novel	70
Known	50 – MAF
Predicted function (maximum 100)	
Predicted loss-of-function (frameshift insertion/deletion, essential splice)	100
Potential loss-of-function (premature stop, readthrough)	80
Probably damaging (Polyphen2 "probably damaging" or Sift "deleterious")	60
Other coding insertion/deletion (not frameshift)	20 x aa*
Other nonsynonymous change	30
Synonymous or UTR	0
Non-coding	–50
Conservation across species (maximum 30) PhyloP (range -2 to +2)	PhyloPx15
Clustering between families (maximum 50)	
Variant shared between different families	% families shared/2
Variants (with Predicted Function score ≥ 40) in same gene shared between different families (allelic heterogeneity)	30
Clustering within families (maximum 50)	% of relative pairs who share variant/2
Siblings with at least one copy of this variant	
Recessive genetic model (maximum 50)	% of carriers who are homozygotes or compound heterozygotes/2
Compound heterozygotes must have 2 alleles with function score ≥ 40 in the same gene	

*aa = number of amino acids deleted

A scoring scheme was created to prioritize variants for further analysis with the goal of focusing on variants most likely to contribute to AAA. This is necessary to filter the very large number of variants that are observed, and is a typical approach used in nearly all analyses of next generation sequence data. The scoring scheme weights variants based on the following criteria (Table 1):

1) location within a genetic loci previously shown to be linked to AAA; of particular interest here were variants within a region on chromosome 19q13 that was shown to be associated with AAA in a previous family linkage analysis (LOD score > 4).

2) novelty of the variant, based on frequency of occurrence in the 1,000 Genomes database; the rationale is that rare variants are likely to be more deleterious than common variants;

3) functional impact of the variant: predicted or potential loss of function (LOF) variants were weighted most heavily, followed by "probably damaging" variants as estimated by the Polypen2 software, then other variants, including nonsynonymous variants; non-coding variants were given a negative score to more heavily weight coding variants;

4) sequence conservation as estimated using the PhyloP software; the rationale is that functionally important variants will be subject to more stringent selection pressure and be more highly conserved across species;

5) clustering of variants within and between families;

6) an inheritance pattern that is consistent with a recessive genetic model.

Using this scoring scheme, a Mendelian recessive variant identified in the homozygous state in two relatives from several families, predicted to cause a loss of function of a protein, that is highly conserved, and not present in the 1000 Genomes variant database, the maximum score is 450.

An analysis pipeline was created to apply the scoring algorithm. The results from the first 8 AAA cases is shown in Table 2. DNA sequencing yielded an average of $58x10^6$ reads per individual genome. Ninety-six percent of these mapped in pairs using BWA and BAQ recalibration. To ensure high-quality genotype calls only those with a minimum read depth > 8, recalibrated quality score > 30, and maximum depth < 1000 were scored using the filtering algorithm. Of the 658,287 total variants identified 22,501 were non-synonymous variants. Of these potential loss of function variants 35% were novel and not in the dbSNP or 1,000 Genomes database. Application of the scoring algorithm produced 96 variants with an annotation score > 300. Variants with the highest scores had the following characteristics: 53% were in the 19q AAA linkage region, 86% were novel variants, 31% were essential splice variants, and 90% were conserved across species (PhyloP score in the top quartile).

Table 2. Summary of Exome Sequence Data

Total reads	58 x 10^6/individual
Total variants	658,287
Non-synonymous variants	22,501
Variants not in dbSNP	7,875 (35%)
Annotation score > 300	96
• in 19q13 linkage region	51 (53%)
• in other AAA linkage regions	28 (29%)
• novel variants	83 (86%)
• splice variants	30 (31%)
• conserved (PhyloP top quartile)	86 (90%

This prioritized list of variants is currently being evaluated as functional AAA variants. The strategy for accomplishing this is based in part on identifying variants with biological functions that are compatible with the known pathobiology of AAA. The variants are being mapped into functional pathways using the Ingenuity suite of software tools.

In the second phase of next generation DNA sequence analysis of AAA variants we selected additional set of 8 DNA samples that were subject to whole genome DNA sequence analysis. The rationale for whole genome vs. whole exome sequencing is based on the fact that the price of the former has been reduced to the point that it is competitive with exome sequencing, the additional data to be obtained at relatively small incremental cost (whole exome sequencing interrogates only ~2 percent of the human genome), and the possibility that the array capture technique used to enrich for exome sequences produces bias and may not adequately yield sequence data for some loci.

The samples used in this analysis included 2 affected first-degree relatives from 2 separate families, and 4 affected relatives from another family. DNA samples were sent to Complete Genomics, Inc. for whole genome sequencing. The sequencing has been completed, and the sequence data (amounting to several terabytes) has been transferred to computers at Geisinger. (The turn-around time for sequence analysis was several months, and was longer than initially anticipated). Analysis of this data will continue after the project end date, using approaches similar to those described above.

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
__X__ No

19(C) Please describe how this project involved human embryonic stem cells:
This project did not involve 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.				☐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 a manuscript that describes rare genetic variants associated with AAA. This will be drafted when the analysis of the genetic variants from this initial group of patient

samples is completed. We will determine at that time if there is sufficient evidence for association to warrant publication, or whether additional analysis and/or additional samples are required.

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.

This project provided preliminary data that were included in a PA-CURE non-formula grant on Translational Genomics that was funded and initiated in June, 2012. The goal of that three year project is to determine and validate the utility of genomic data to impact population screening for AAA. Thus, although this project did not directly impact the incidence, diagnosis or treatment of disease directly, it was a key precursor to new research in which that translational to medical care is a major goal.

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.

None

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

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person.

NAME	POSITION TITLE
David J. Carey	Associate Chief Research Officer, Director, Weis Center for Research, Geisinger Clinic

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	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

A. 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
07/01/03-	Associate Chief Research Officer, Geisinger Clinic

B. Recent 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) Chu, X., Erdman, R., Susek, M., Gerst, H., Derr, K., Al-Agha, M., Wood, C.G., Hartman, C., Yeager, S., Blosky, M.A., Krum, M., Stewart, W.F., **Carey, D.J.**, Benotti, P., Still, C.D., Gerhard, G.S. Associated of morbid obesity with FTO and INSIG2 allelic variants. *Archives of Surg.*, 143(3): 235-240, 2008.

3) Elmore, J.R., Obmann, M.A., Kuivaniemi, H., Tromp, G., Gerhard, G.S., Franklin, D.P., Boddy, A.M., **Carey, D.J.** Identification of a genetic variant associated with abdominal aortic aneurysms on chromosome 3p12.3 by genome wide association. *J Vasc Surg*, 49: 1525-31, 2009.

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C. Current grant support

NIH/National Human Genome Research Institute Carey, Ledbetter (PIs) 07/01/11-06/30/15
Geisinger eGenomic Medicine (GeM) Program UO1HG006382-01
This project supports the participation of Geisinger Clinic in the eMERGE (electronic Medical Records and Genomics) network, a consortium of institutions with biorepositories linked to electronic medical record (EMR) data for conducting genomic studies. The major aims are to use existing biospecimens and EMR-generated phenotypes to identify genetic variants with disease risk or treatment response for disorders with significant public health impact, and to develop and test approaches to incorporate genomic data into clinical care.

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.

Ben Franklin Technology Development Authority Carey (PI) 01/01/09-06/30/11
Genomic Medicine Research Support
The goal of this project is to support research fellows in genomic medicine.

Commonwealth of Pennsylvania Carey (PI) 01/01/10-12/31/12
Genetic Factors Associated with Aneurysms
The goal of this project is to identify genetic factors associated with abdominal aortic aneurysms.

University of Maryland (NIH subcontract) Gerhard (PI) 09/01/10-08/31/13
Comparative Effectiveness Trial of Personalized Anti-Platelet Therapy
The goal of this project is to determine the effect of genetic variants that affect metabolism of Plavix on its anti-platelet activity and long-term clinical outcome.
Role: Co-investigator

D. Previous experience in collaborative research

I have a broad background and experience in laboratory-based biomedical research with specific expertise in research relevant to this application. My research uses both animal/cellular models and studies of human patients, with an emphasis on molecular and genetic factors related to complex disease. This includes a strong interest and track record in the pathogenesis of abdominal aortic aneurysms. I am also Director of the Weis Center for Research and Associate Chief Research Officer, Geisinger Clinic. The Weis Center is the basic and translational laboratory research facility of Geisinger Clinic. In my dual roles as a researcher and research leader I am keenly aware of the need to bridge laboratory-based research, clinical research and patient care. I have established a number of productive collaborations with clinical investigators, and have led several successful efforts to enroll patients into genetic and genomic research studies. The Weis Center Genomics Core provides a centralized resource to process, bank, track and analyze biological samples (e.g. blood, serum, DNA) from consented Geisinger patients, and has a current inventory of more than 72,000 banked samples. Investigating the molecular and genetic basis of complex disease is a key component of the Geisinger Clinic strategic research plan.