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, Weis Center for Research**

2. **Reporting Period (start and end date of grant award period): 01/01/2009-12/31/2010**

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees): David J. Carey, PhD**

4. **Grant Contact Person's Telephone Number: 570-271-6659**

5. **Grant SAP Number: 4100047635**

6. **Project Number and Title of Research Project: #1 - Genomics of Pregnancy-Related Complications**

7. **Start and End Date of Research Project: 01/01/2009-12/31/2010**

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:

   $ $95,593.13

   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 Tech III	24	$38,462.65

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
David J. Carey, PhD	Director, Weis Center for Research	5
Eric Bieber, MD	Chair, Obstetrics and Gynecology	2
Glenn Gerhard, MD	Director, Genomics Core	2
Helena Kiuvaniemi, MD, PhD	Staff Scientist, Weis Center for Research	10
Gerard Tromp, PhD	Staff Scientist, Weis Center for Research	5
James Betoni, DO	Maternal-Fetal Medicine Fellow	5
Corinna Muller, DO	Maternal-Fetal Medicine Fellow	5
Laura Rogers	Genetic Counselor	10
Kim Derr	Research Technician	5

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____X_____ No_____

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

The project was also supported by the Geisinger Clinical Research Fund ($43,490.42). Additional salary support for the co-investigators was provided by Geisinger Clinic.

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:_____ _____) ☐ 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:

The patient cohort and other data collected during the study will be the basis for additional applications for funding to the National Institutes of Health, March of Dimes, and other funding agencies. The anticipated application date of the first of these proposals is Fall, 2011.

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

The project will continue. Patient enrollment will continue, using funds from internal sources, including the Geisinger Clinical Research Fund. Additional miRNA analysis of placental tissue is also planned, with a short-term goal of producing sufficient data for publication in a peer-reviewed journal. After sufficient numbers of case and control DNA samples are obtained a genetic association study will be performed, initially testing candidate genetic variants from the literature. Exome sequencing of DNA samples from family trios is also planned, pending sufficient additional funding to pay for DNA sequencing.

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____X_____ No_____

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

	Undergraduate	Masters	Pre-doc	Post-doc
Male	1			1
Female				2
Unknown				
Total	**1**			**3**

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic	1			3
Unknown				
Total	**1**			**3**

	Undergraduate	Masters	Pre-doc	Post-doc
White	1			3
Black				
Asian				
Other				
Unknown				
Total	**1**			**3**

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 was used as a training vehicle for Fellows in the Maternal-Fetal Medicine Fellowship at Geisinger Medical Center. This provided a high level of training and elevated the intellectual and research environment within that program. Development and implementation of the patient recruitment strategies also promoted better collaboration and communication between investigators in the research center and clinical providers in the Department of Obstretrics and Gynecology and the genetic counselor group. These enhancements have expanded beyond and will outlive the scope and time period of this initial project.

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:

At the conclusion of his Fellowship training Dr. Betoni moved to Colorado to practice Maternal Fetal Medicine. He continues to collaborate on this project with the Geisinger investigators.

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 entire grant award period. 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.

Complications related to pregnancy are difficult to predict in advance, need better treatments, and are major causes of death or disability from pregnancy and/or delivery. Preeclampsia, which is characterized by elevated blood pressure and proteinuria in the mother during pregnancy, is a leading cause of maternal and perinatal morbidity and death worldwide and affects 5-8% of all pregnancies. The mechanisms by which preeclampsia develops are poorly understood and the only effective treatment is delivery of the child and the placenta.

Previous studies have shown that family history is a major risk factor for these complications, which indicates that they are influenced by inherited genetic factors. The goal of this study was to assemble a collection of blood and DNA samples from pregnant women and to use these in studies to identify genomic factors related to pre-eclampsia and pre-term labor. This information can be used to elucidate the biological factors associated with these conditions and to develop improved methods to diagnose and treat them.

Substantial progress was made in accomplishing each of the study aims, as summarized below.

Aim 1. Recruit a cohort of patients seen for obstetric care at Geisinger Medical Center into a genomic medicine research program; collect and bank biological specimens (blood, DNA) for genomic medicine research.

There is increasing evidence that complications of delivery have a genetic component, which has yet to be identified. In addition, novel biomarkers for these complications, especially preeclampsia and pre-term labor, are needed to improve the diagnosis and prognosis of these patients, and to guide appropriate medical care. The first aim of this project was to create a cohort of patients with associated biological samples to be used for molecular and genomic studies of the complications of pregnancy. The patients were to be recruited at Geisinger Medical Center. Geisinger Health System provides a number of advantages for clinical and genomic research, including the high degree of clinical integration, advanced electronic medical record system, and large, stable and supportive patient population. A three-pronged approach was used that incorporated prospective patient recruitment, retrospective patient recruitment, and a population recruitment approach that leveraged an existing biobanking program at Geisinger.

<u>Prospective recruitment during labor and delivery</u>: We enrolled patients who were admitted to the Labor and Delivery unit at Geisinger Medical Center including women with preeclampsia (defined as new onset hypertension and proteinuria during the second half of pregnancy) or pre-

term labor. A member of the study team met with the patient, explained the study, and obtained informed consent from willing participants. A total of 100 women were consented into the study the end of the project period. This included 59 with preeclampsia, 25 with pre-term labor, and 16 with non-complicated deliveries. EDTA whole blood (for DNA isolation) and serum blood samples were obtained from each consented patients prior to delivery; these were banked in the Geisinger Clinic Genomics Core for storage and analysis. In addition, samples of placental tissue were collected from 73 consented patients for research use. These were dissected immediately and portions preserved in RNA-later (as a source of RNA for expression studies), or paraformaldehyde (for anatomical and immunohistochemical studies), or frozen in liquid nitrogen (for proteomic studies). We also collected research blood and serum samples from 28 women with preeclamptic deliveries the day following their delivery. Thus, for these patients we have samples collected during and after the acute preeclamptic episode, which will be useful to study molecular changes associated with preeclampsia and its resolution after delivery.

In some cases we also consented and obtained DNA samples from the baby (via cord blood after the delivery) and father. The availability of DNA from mother/father/baby trios allows several novel hypotheses to be investigated. There is evidence from previous studies that babies of fathers with a history of preeclampsia are at increased risk for preeclampsia. Having DNA from the fathers provides a window to study the genetic basis of this risk. It has also been suggested that a genetic interaction between the mother and the baby influences the risk of preeclampsia. For example, this could include a genetic incompatibility between the mother and the fetus. Finally, several recent whole genome sequencing studies demonstrate the value of DNA sequence data from both parents and a child in reducing sequencing errors and in identifying trait-associated genetic variants. Of the 100 women consented into the study we have DNA samples for research use from all 100 babies and 57 fathers.

Retrospective recruitment of patients with preeclampsia: To increase the size of the study cohort patients were also recruited using a retrospective strategy. Geisinger electronic medical records were searched to identify women who had been treated for preeclampsia at Geisinger Medical Center from 2004 to 2009. These patients receive a letter inviting them to consider enrolling in the study, and informing them that unless they specifically opt-out, they will receive a follow-up phone call by a member of the study team. Initial letters are sent out in batches of 25-30. By the end of the project period 117 contact letters had been sent, which led to 60 eligible patients agreeing to participate (see Figure 1). After signing the study consent form these patients receive in the mail a saliva collection kit, which is returned and used to isolate patient DNA that is banked in the Geisinger Clinic Genomics Core for analysis. To date, saliva kits have been received from 37 consented patients. Some consented patients are also contacted to obtain a detailed family history. By the end of the project period 13 participants had completed this step.

Of particular interest are trios of mother, baby and father. These are useful to study effects of genetic interactions, as described above. Family units are also extremely useful for interpreting results of deep genomic sequencing, e.g. exome or eventually whole genome sequencing. Comparing the genomic sequences of family members reduces sequencing errors and simplifies the tracing of disease-related genetic variants. Of the consented patients, 35 represent mother-father-baby trios (separate consent forms are used for the baby and father), and 2 include mother and baby only.

Population sample of women with preeclampsia: To expand the study cohort for genomic analysis of complications of pregnancy we also enrolled women during outpatient visits to the Women's Health Clinic at Geisinger Medical Center. These women were enrolled as part of the Geisinger MyCode Project, MyCode™ project, the goal of which is to create a repository of patient samples (blood, DNA, serum and tissue) that are linkable to the rich clinical data in its EMR for genomic medicine research.

During an outpatient visit to a Geisinger clinic eligible patients meet with a research assistant who explains the study, answers questions, and invites them to consider participating in the MyCode™ program. Eligibility criteria are broad, so that any adult Geisinger patient making a non-emergent outpatient visit is eligible. Dementia or other condition that precludes informed consent is an exclusion criterion. Participating patients sign a written consent/HIPAA authorization and agree to provide blood samples for broad research use and permit access to data in their EMR for research use. In nearly all cases, research blood samples are collected at the time of a clinically ordered blood draw, which eliminates the need for an extra needle stick. The consent form states that 1) participation in the program is voluntary; 2) the patients will derive no direct benefit from participation; 3) their decision not to participate will have no impact on their medical care at Geisinger; 4) research done with their banked samples could include analysis of their genes; 5) results of research done with their sample will not be given to them or included in their medical record; and 6) researchers who have access to their samples and data will not reveal personal information about them to anyone else. The consent form also contains a check box to indicate whether the patient is willing to be re-contacted in the future regarding the biobanking program or other research projects. Ninety-five percent of consenting patients agree to be re-contacted. The enrollment rate is approximately 90% of patients who are approached.

By the end of the project period 2,973 women who were patients of the Geisinger Medical Center Women's Health Clinic had consented to participate. Of these, approximately 440 have a history of preeclampsia based on a batch query of the Geisinger electronic medical record data. Because the blood sample collection is passive (only at the time of an outpatient medically ordered blood draw), blood samples have been collected to date from approximately 60% of the consented patients. Samples from the remaining patients will accrue as they return in the future for outpatient blood draws. Thus, there are currently approximately 260 samples from patients with preeclampsia and approximately 1,500 samples from potential control patients.

Through these collective patient enrollment strategies we consented approximately 360 women with preeclampsia and more than 1,000 potential controls, with blood and serum banked for research use. These include 92 trios (mother, baby, father) from patients with preeclampsia and 41 other trios. In addition, placental tissue for research use was banked from 73 deliveries. This bank of biological samples and associated clinical data can be used for numerous studies that apply genomics technologies to these problems.

Aim 2. Conduct pilot genotyping studies to identify and/or validate candidate genes for pregnancy-related complications, such as pre-ecclampsia or pre-term labor.

The goal of aim 1 was to create a repository of biological samples from women with preeclampsia or other complications of pregnancy and suitable controls; these samples and the clinical data linked to them via Geisinger's electronic medical record database would provide the basis for molecular and genomic analyses of these diseases. By the end of the project period the sample size was not sufficient to provide ample statistical power for a case-control genetic association study. Therefore, the first genomic study to be performed with these samples was a comparison of microRNA expression in placental tissue from women with preeclampsia and controls.

MicroRNAs are small non-coding RNA molecules, which are thought to have an important role in negative, posttranscriptional regulation of protein-encoding genes. A pproximately 30% of human genes are potential targets for microRNAs. Their binding sites are often found in the 3'-untranslated regions of target mRNAs. MicroRNA binding can inhibit transcript expression through mechanisms that include targeted degradation or translational arrest. .

We hypothesized that microRNAs are important in the pathogenesis of preeclampsia. Microarray-based screening was carried out with placental tissue samples collected from preeclamptic and normal deliveries to identify differences in microRNA expression patterns between these two groups. Initial analysis was carried out with placentas from three preeclampsia cases and three controls that were age and gestational stage-matched to the controls. All deliveries were by Caesarean section. RNA was isolated from placental tissue that was stored in RNA later and processed as summarized in Figure 2. The samples were hybridized to Affymetrix miRNA arrays that contain probes for 1,839 human micro-RNAs and other small RNAs. The arrays were washed and scanned; raw data were analyzed using Affymetrix software.

Out of the 1,839 human RNAs represented on the microarray, 960 were detected in at least one of the six placental samples analyzed; 104 had significantly different expression levels between the preeclampsia and control groups. These included 19 microRNAs that showed increased expression in preeclampsia placental tissue, and 85 that showed decreased expression (Figure 3). Transcripts with increased expression in preeclampsia included mir191 and mir598. Transcripts with decreased expression included mir101 and mir223.

Analysis of an additional six samples was underway at the end of the current project period. Data from these samples had not been analyzed by the project end data, but is continuing.

These results demonstrate that differences in microRNA patterns can be found between placentas from preeclampsia cases and controls. Studies with additional patients to are needed to improve the statistical power. Statistically different microRNAs will be confirmed with quantitative PCR. A computational approach will be used to identify target genes for the differentially expressed microRNAs. The target genes will be categorized by pathways. The results will provide better understanding of the gene regulation in preeclampsia and have the potential for revealing new biomarkers for improved diagnostics or approaches for therapeutic intervention.

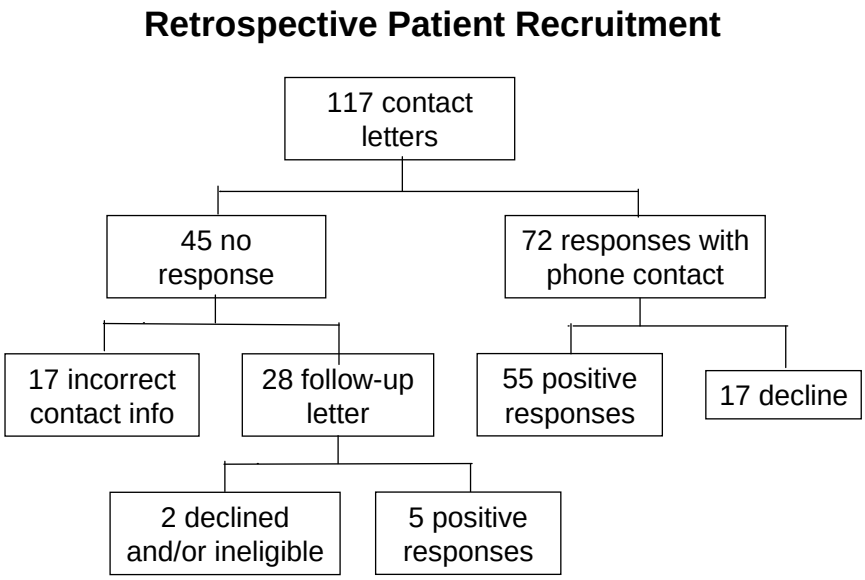

Figure 1. Strategy for retrospective recruitment of patients and family trios with preeclampsia

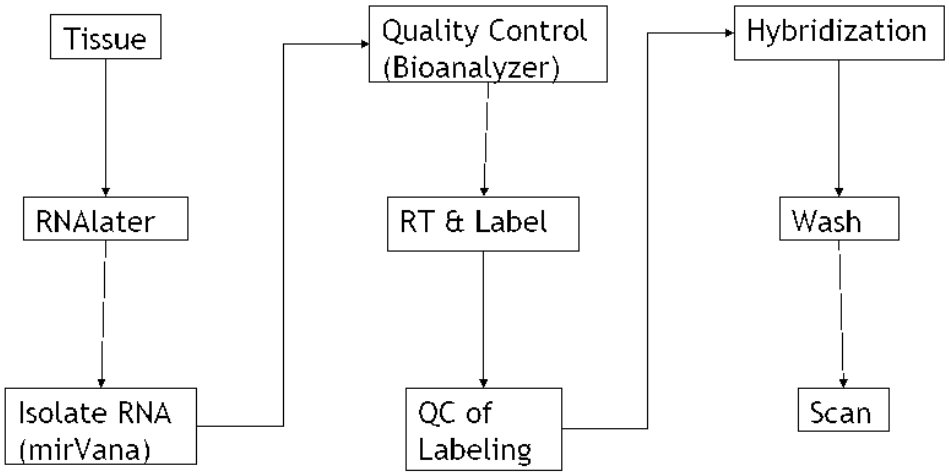

Figure 2. Flow-chart for processing RNA for microarray analysis of microRNA expression in placental tissue.

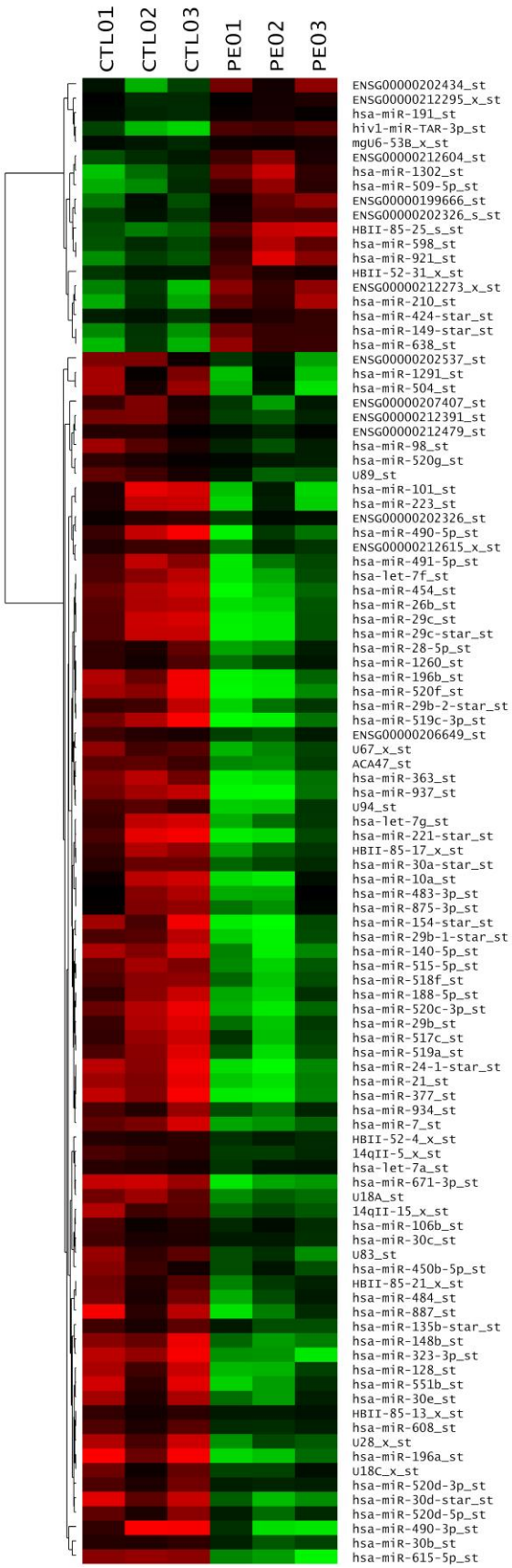

Figure 3. Heat map of microRNA expression data. Data shown are from 3 control (left columns) and 3 preeclampsia samples (right columns). Gene or transcript names are indicated on the right. Red indicates increased expression; greeen indicates decreased expression.

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

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, listed in the table, in a PDF version 5.0.5 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:

The analysis of miRNA expression in placental tissue from women with preeclampsia and controls is planned for publication in a peer-reviewed journal. This will occurs immediately after replication of some results and final analysis of the data. Other publications that utilize the valuable patient cohort that was created will also follow, based on specific research studies that are performed.

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

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. **DO NOT EXCEED FOUR PAGES.**

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

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. Personal Statement

I have a broad background in laboratory-based biomedical research with specific expertise in research relevant to this application. My research is focused on both animal models and studies of human patients, with an emphasis on molecular and genetic factors related to complex disease. I am also Director of the Weis Center for Research, a basic and translational laboratory research facility. In my dual roles as a researcher and research administrator I am keenly aware of the need to bridge laboratory-based research, clinical research and patient care. I have successfully established a number of productive collaborations with clinical investigators.

B. Positions and Honors

Positions and Employment

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

Other Experience and Professional Memberships

American Cancer Society, Personnel B Scientific Advisory Committee	1991-1996
American Heart Association, Bugher Center Awards Review Fund	1991
NIH, Pathobiochemistry Study Section	1993
American Heart Association, PA Affiliate, Research Peer Review Committee	1992-1995
Chairman, NINDS Review Panel, Surface Modification for Biocompatibility	1994
Analytical Biochemistry, Editorial Board	1993- 2005
U.S. Army Breast Cancer Research Program, Pathobiology Peer Review Committee	1995-2000
NIH, NIGMS Large Scale Collaborative Project Review Panel	2001
NIH, ICI Peer Review Panel Member	2004-2008

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

1. Lawrence, D.M., Singh, R.S., Franklin, D.P., **Carey, D.J.**, Elmore, J.R. Rapamycin Suppresses Experimental Aortic Aneurysm Growth, *J Vasc Surg.,* 40: 334-338*,* 2004.
2. Armstrong, P.J., Franklin, D.P., **Carey, D.J.**, Elmore, J.R. Suppression of Experimental Aortic Aneurysms: Comparison of Inducible Nitric Oxide Synthase and Cyclooxygenase Inhibitors, *Ann Vasc Surg.,* 19: 248-257, 2005.
3. Kalyanasundaram, A., Elmore, J.R., Manazer, J.R., Golden, A., Franklin, D.P., Galt, S.W., Zakhary, E.M.A, and **Carey, D.J.** Simvastatin Supresses Experimental Aortic Aneurysm Expansion, *J. Vasc. Surg.,* 43: 117-124*,* 2006*.*
4. 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.
5. Chernousov, M.A., Baylor, K., Stahl, R.C., Stecker, M.M., Sakai, L.Y., Arteaga, S.L., Ramirez, F., **Carey, D.J.** Fibrillin-2 is dispensable for peripheral nerve development, myelination and regeneration.*J. Matrix Biol.,* In press*,* 2010.
6. Armstrong, P.J., Johanning, J.M., Calton, W.C., Franklin, D.P., Han, D.C., **Carey, D.J**., and Elmore, J.R., Differential gene expression in human aorta: aneuysmal and occlusive disease. *J. Vasc. Surg.,* 35:346-355, 2002.
7. Erdman, R., Stahl, R.C., Rothblum, K, Chernousov, M.A., and **Carey, D.J**., Schwann cell adhesion to a novel heparan sulfate binding site in the N-terminal domain of α4 type V collagen is mediated by syndecan-3, *J. Biol. Chem*., 277:7619-1625, 2002.
8. Schworer, C.M., Masker, K.K., Wood, G.C., and **Carey, D.J.** Microarray Analysis of Gene Expression in

Proliferating Schwann Cells: Synergistic Response of a Specific Subset of Genes to the Mitogenic Action of Heregulin Plus Forskolin, *J. Neurosci. Res..* 73: 456-464, 2003.

9. Asundi, V.K., Erdman, R., Stahl, R.C., and **Carey, D.J**. Matrix Metalloproteinase-Dependent Shedding of Syndecan-3, a Transmembrane Haparan Sulfate Proteoglycan, in Schwann Cells, *J. Neurosci. Res.,* 73: 593-602, 2003.

10. Chernousov, M.A., **Carey, D.J.** αVβ8 Integrin is a Schwann Cell Receptor for Fibrin. *Exp Cell Res.,* 291:514-524, 2003.

11. Fuentealba, L., Schworer, C., Schroering, A., Rahmatullah, M., and **Carey, D.J.** Heregulin and Forskolin-induced Cyclin D3 Expression in Schwann Cells: Role of a CCAAT Promoter Element and CCAAT Enhancer Binding Protein, *Glia,* 45:238-240, 2004.

12. Rothblum, K., Stahl, R.C., **Carey, D.J.** Constitutive Release of α4 Type V Collagen N-Terminal Domain by Schwann Cells and Binding to Cell Surface and Extracellular Matrix Heparan Sulfate Proteoglycans, *J. Biol. Chem.,* 279: 51282-51288*,* 2004.

13. Chernousov, M.A., Rothblum, K., Stahl, R.C., Evans, A., Prentiss, L., and **Carey, D.J.** Glypican-1 and α (4) Collagen are Required for Schwann Cell Myelination. J. Neurosci., 26: 508-517, 2006.

14. Chernousov, M.A., Kaufman, S.J., Stahl, R.C., Rothblum, K., **Carey, D.J.** α7β1 Integrin is a Receptor for Laminin-2 on Schwann Cells, *Glia,* 55:1134-1144, 2007.

15. Chernousov, M.A., Yu, W-M., Chen, Z-Li, **Carey, D.J**., and Strickland, S. Regulation of Schwann cell function by extracellular matrix. *Glia*, 56: 1498-1507, 2008.

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Bieber, Eric J	Executive Vice President, Strategic Network Development, Geisinger Health System

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Illinois Wesleyan University	B.A.	1978-1981	Biology
Illinois State University	M.S	1981-1984	Microbiology
Loyola Stritch School of Medicine	M.D.	1982-1986	Medical
Rush-Presbyterian St. Luke's		1986-1987	Internship
Rush-Presbyterian St. Luke's		1987-1990	Residency
The University of Chicago		1990-1993	REI
Harvard University	M.S.	2004	Healthcare Management

A. Positions and Honors

Positions and Employment

1990 Instructor in Obstetrics & Gynecology, College of Medicine, Rush-Presbyterian St. Luke's
1990 – 1993 Instructor in Obstetrics & Gynecology, Pritzker School of Medicine, University of Chicago
1993 – 1999 Asst. Professor of Clinical Obstetrics & Gynecology, Pritzker School of Medicine, University of Chicago
1999 – 2001 Assoc. Professor of Clinical Obstetrics & Gynecology, Pritzker School of Medicine, University of Chicago
1999 – 2000 Acting Director of Division of Reproductive Endocrinology & Infertility, University of Chicago
2000 – 2001 Division Chief Reproductive Endocrinology and Infertility, University of Chicago

1992 – 2001 Director, Reproductive Endoscopy, University of Chicago
1999 - 2001 Executive Director of Managed Care & Clinical Operation, Dept. of Ob/Gyn, University of Chicago
2001 – 2009 Chair, Department of Obstetrics and Gynecology, Director of Women's Service Line, Program Director Ob/Gyn Residency
2005- 2008 Chief Medical Officer Geisinger Wyoming Valley & Geisinger South Wilkes Barre
2008 – Present Executive Vice President, Strategic Network Development, Geisinger Health System

Other Experience and Professional Memberships
Diplomat, National Board of Medical Examiners
Board Certified, ABOG-Reproductive Endocrinology
Board Certified, American Board of Obstetrics & Gynecology
Editorial Board, Journal of Gynecologic Surgery
Editorial Board, Current Clinical Obstetrics & Gynecology
1999 – Executive Committee, Department of Obstetrics & Gynecology, University of Chicago
2001 – Present Medical Executive Committee, Geisinger Medical Center
2001 – Present System Leadership Committee, Geisinger Medical Center
2001 – Clinical Enterprise Operations Committee – Geisinger Medical Center
1996 – Co-Chair Scientific Exhibits and Posters. AAGL Annual Meeting, Chicago, IL
2000 – Secretary, Gynecologic Surgery Society
2000 – Board of Directors, Gynecologic Surgery Society
2001 - Chair for 2001 International Society of Gynecologic Endoscopy Precongress
2001 – Fellowship Director of Reproductive Endocrinology and Infertility, University of Chicago
1996 – Charter Member, Society for Male Reproduction and Urology

B. Selected peer-reviewed publications (in chronological order).

1. Bieber EJ, Wilkinson BJ: Sodium-dependent uptake of taurine in encapsulated Staphylococcus aureus strain M. Biochemica et Biophysica Acta, 770:127, 1984.

2. Bieber EJ, Stratman T, Sanseverino M, Sangueza J, Phillippe M. Phosphatidylinositol-specific phospholipase C isoform expression in pregnant and nonpregnant rat myometrial tissue. Am J Obstet Gynecol 178:848-854, 1998.

3. Kim TT, Saunders T, Bieber E, Phillippe M. Tissue-specific protein Kinase C isoform expression in rat uterine tissue. J Soc Gynecol Investig 6: 293-300, 1999.

4. Rychlik DF, Bieber E, Phillippe M. Constitutive androstane receptor (CAR) expression in the rat cervix during gestation. J Soc Gynecol Investig 7: 355-7, 2000.

5. Bieber EJ. Erythropoietin, the biology of erythropoiesis and epoetin alpha. JRM 46:1-10:2001.

6. Kim TT, Saunders T, Bieber E, Phillippe M. Protein expression of phospholipase C (PLC) in pregnant and non-pregnant rat uterine tissue. Accepted for publication AJOG, 2001.

7. Chien EK, Sweet L, Phillippe M, Marietti S, Kim TT, Wolf DA, Thomas L, Bieber E. Protease-activated receptor isoform expression in pregnant and nonpregnant rat mymometrial tissue. J Soc Gynecol Investig. 2003 10:460-8

8. Diamond MP, El-Hammandy E, ManKarah A, Bieber EJ, Saed G. Modulation of the expression of vascular endothelial growth factor in human fibroblasts. Fertility & Sterility 2005; 83: 405-409

Selected Textbooks:

1 Bieber EJ, Loffer FD. Resettoscopia ginecologica, Antonia Delfino Editore, Roma, 1996

2. Bieber EJ, Loffer FD, eds. The gynecologic resectoscope, Blackwell Scientific Publications, Inc., Boston, MA, 1995.

3. Bieber EJ, Maclin V. The Myomectomy, Blackwell Scientific Publications, Inc, Boston, MA,1998.

4. Walker J, Bieber EJ, Richards F. Implementing an electronic medical record. Springer-Verlag, 2005.

5. Bieber EJ, Sanfillipo J, Horowitz I. Textbook of Evidence Based Gynecology. Elsievier, 2006.

6. Yuan CS, Bieber EJ, Bauer B. Textbook of Complementary and Alternative Medicine – 2nd edition. Taylor-Francis, 2006.

C. Research Support:

Ongoing Research Support

1. Tissue Bank for the Study of Postoperative Adhesion Development
2. Two Delivery Channels to Improve CRC Screening. NIH/1R01 CA102695-01 A2

Completed Research Support

1. A Multicenter, Phase III, Double-Blind, Placebo-Controlled, Parallel Study of ADL 8-2698 in Opioid-Induced Postoperative Bowel Dysfunction/ Postoperative Ileus, IND# 56,553 (PROTOCOL #: 14CL308)

2 Investigation of PI-PLC activity and expression in rat myometrium.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
GLENN S. GERHARD	**Staff Scientist**
eRA COMMONS USER NAME	**(Associate Professor)**
gsgerhard	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Penn State University, University Park, PA	**B.S.**	**1982**	**Biochemistry**
Penn State College of Medicine, Hershey, PA	**M.D.**	**1986**	**Medicine**
Wistar Institute, Philadelphia, PA	**Postdoc**	**1986-1987**	**Cell Biology of Aging**
University of Pennsylvania, Philadelphia, PA	**Postdoc**	**1990-1992**	**Human Genetics**

A. Personal Statement

I have a long-standing interest in the genetics of complex phenotypes, beginning with training in mouse models as a post-doctoral fellow at the University of Pennsylvania and extending to collaborative studies of hereditary hemochromatosis and murine QTL mapping as a faculty member at Penn State and Dartmouth. I was recruited to Geisinger because of my broad background in genetics and previous clinical training to help develop a genomic medicine program. Obesity was selected as one of the first areas to develop. Working with co-I Dr. Still, we converted his clinical program into a research-based clinic, assembling one of the largest cohorts of bariatric surgery patients available in the country, achieved with very modest internal funding. We have built an extensive clinical database and have exploited the deep electronic clinical resources available at Geisinger.

B. Positions and Honors.

Positions and Employment

1986-1987 Postdoctoral Fellow, Cell Biology of Aging, Wistar Institute, Philadelphia, PA
1987-1990 Resident Physician, Pathology, Dartmouth-Hitchcock Medical Center, Hanover, NH
1990-1992 Postdoctoral Fellow, Human Genetics, University of Pennsylvania, Philadelphia, PA
1992-1994 Research Assistant Professor, Medical College of Pennsylvania, Philadelphia, PA
1994-1995 Clinical Fellow, Transfusion Medicine, University of Wisconsin, Madison, WI
1995-1999 Assistant Professor (Clinical), Department of Pathology, Penn State-Hershey, Hershey, PA
1996-1999 Assistant Director, Molecular Diagnostics Laboratory, Penn State-Hershey, Hershey, PA
1996-1999 Member, InterCollege Graduate Program in Genetics, Penn State-Hershey, Hershey, PA
1996- Faculty Affiliate, Center for Developmental and Health Genetics, Penn State, Univ. Park, PA
1997-1999 Co-Director, ImmunoBiology Graduate Option, Penn State-Hershey, Hershey, PA
1999-2003 Assistant Professor (Research), Dept. of Pathology, Dartmouth Med. School, Hanover, NH
1999-2003 Assistant Dir., Molecular Genetics Diagnostics Lab., Dartmouth Med. School, Hanover, NH
2003- Staff Scientist, Weis Center for Research, Geisinger Clinic, Danville, PA
2004- Medical Director, Molecular Diagnostics Laboratory, Geisinger Clinic, Danville, PA

Honors

1996 American Association of Blood Banks (AABB)-Fenwal Tranfusion Medicine Fellows Scholarship Award

C. Selected peer-reviewed publications. (Selected from over 50 peer-reviewed publications)

1. Still CD, Benotti P, Petrick A, **Gerhard GS**, Hartman C, Strodel W. Gastric Bypass Surgery in High Risk Patients: Modest Pre-Operative Weight Loss Reduces the Lengths of Hospital Stay. *Archives of Surgery*, Oct;142(10):994-8; discussion 999 (2007).
2. Chu, X, Erdman, R, Susek, M, Gerst, H, Derr, K, Al-Agha, M, Wood, GC, Hartman, C, Yeager, S, Blosky, MA, Krum, W, Stewart, WF, Carey, D, Benotti, PN, Still, CD, and **Gerhard*, GS**. Morbid obesity is associated with two obesity gene variants (FTO and INSIG2). *Archives of Surgery*, Mar;143(3):235-40; discussion 241, (2008).
3. Wood, GC, Still, CD, Chu, X, Susek, M, Erdman, R, Hartman, C, Yeager, S, Blosky, MA, Krum, W, Carey, DJ, Shelding, KA, Benotti, PN, Stewart, WF, and **Gerhard*, GS**. Association of chromosome 9p21 SNPs with cardiovascular phenotypes in morbid obesity using electronic health record data. *Genomic Medicine,* Jan;2(1-2):33-43 (2008).
4. Zhang WJ, Li BH, Yang XZ, Li PD, Yuan Q, Liu XH, Xu SB, Zhang Y, Yuan J, **Gerhard GS,** Masker KK, Dong C, Koltun WA, Chorney MJ. IL-4-induced Stat6 activities affect apoptosis and gene expression in breast cancer cells. *Cytokine*. Apr;42(1):39-47, (2008).
5. Benotti PN, Still CD, Wood GC, Akmal Y, King H, El Arousy H, Dancea H, **Gerhard GS**, Petrick A, Strodel W. Preoperative weight loss before bariatric surgery. Arch Surg. Dec;144(12):1150-5 (2009).
6. Seese NK, Venditti CP, Chorney KA, **Gerhard, GS**, et al. Localization of the hemochromatosis disease gene: linkage disequilibrium analysis using an American patient collection. *Blood Cells, Molecules, and Diseases*, 22, pp. 36-46, (1996).
7. Beutler, E, Gelbart, T, West, C, Lee, P, Adams, M, Blackstone, R, Pockros, P, Kosty, M, Venditti, CP, Phatak, PD, Seese, NK, Chorney, KA, Ten Elshof, AE, **Gerhard, GS**, Chorney, M. Mutation analysis in Hereditary Hemochromatosis. *Blood Cells, Molecules, and Diseases*, 22, pp. 187-194, (1996).
8. Venditti, C, Seese, N, **Gerhard, G**, Elshof, A, Chorney, K, Mowrey, P, Lacey, P, Knoll, J, and Chorney, M. 46,XX, inv(6)(p21.1p23) in a pedigree with hereditary haemochromatosis," *J Med Genet*, vol. 34, pp. 24-27, (1997).
9. **Gerhard*, GS**. Letter: Inter-strain variation in murine models of leukemia. *Blood*, Aug 1;94(3):1142 (1999).
10. **Gerhard*, GS**, Kaufmann, EJ, Wang, X, Erikson, KM, Abraham, J, Grundy, MA, Beard, JL, and Chorney, MJ.

11. Genetic differences in hepatic lipid peroxidation potential and iron levels in mice. *Mechanisms of Aging and Development*, 123(2-3):155-66, (2002).
12. Lionikas A, Blizard DA, **Gerhard GS**, Vandenbergh DJ, Stout JT, Vogler GP, McClearn GE, Larsson L. Genetic Determinants of Weight of Fast- and Slow-Twitch Skeletal Muscle in 500-day Old Mice of the C57BL/6J and DBA/2J Lineage. *Physiol Genomics,* Apr 14;21(2):184-92, (2005).
13. Foreman, JE, Blizard, DA, **Gerhard, GS**, Mack, HA, Lang, DH, Van Nimwegen, KL, Vogler, GP, Stout, JT, Shihabi, ZK, Griffith, JW, Lakoski, JM, McClearn, GE, and Vandenbergh, DJ. Serum Alkaline Phosphatase Activity is Regulated by a Chromosomal Region Containing the Alkaline Phosphatase 2 (Akp2) Gene in C57BL/6J and DBA/2J Mice. *Physiol. Genomics.* Nov 17;23(3):295-303, (2005).
14. Blizard DA, Lionikas A, Vandenbergh DJ, Vasilopoulos T, **Gerhard GS**, Griffith JW, Klein LC, Stout JT, Mack HA, Lakoski JM, Larsson L, Spicer JM, Vogler GP, McClearn GE. Blood pressure and heart rate QTL in mice of the B6/D2 lineage: sex differences and environmental influences. Physiol Genomics. Feb 2;36(3):158-66 (2009).
*corresponding author

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
S. Helena Kuivaniemi, MD, PhD, FAHA	Staff Scientist
eRA COMMONS USER NAME (credential, e.g., agency login) aa2303	

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
University of Oulu, Oulu, Finland	MD	1984	Medicine
University of Oulu, Oulu, Finland	PhD	1985	Medical Chemistry
Rutgers-UMDNJ, Piscataway, NJ	*Postdoctoral*	1985-1986	Molecular Biology
Thomas Jefferson University	*Postdoctoral*	1986	Molecular Biology

Positions and Honors

Positions:

01/81-05/87 Teaching Assistant, Department of Medical Biochemistry, University of Oulu, Finland
07/85-03/86 Postdoc. Fellow, Biochemistry Dept., UMDNJ-Rutgers Med. School, Piscataway, NJ.
04/86-06/86 Postdoc. Fellow, Jefferson Inst. Molec. Med., Thomas Jefferson Univ., Phila., PA.
07/86-06/90 Instructor, Dept. Biochem. & Molec. Biol., Thomas Jefferson Univ., Phila., PA.
07/90-08/95 Res. Asst. Prof., Dept. Biochem. & Molec. Biol., Thomas Jefferson Univ., Phila., PA.
07/91-08/95 Res. Asst. Prof., Dept. Derm., Thomas Jefferson Univ., Phila., PA.
09/95-07/04 Assoc. Prof., Ctr. Mol. Med. & Genet., Wayne State Univ. Sch. Med., Detroit, MI.
09/95-07/04 Assoc. Prof. (Tenured 8/01), Dept. Surg., Wayne State Univ. Sch. Med., Detroit, MI.
01/00-05/09 Member, Karmanos Cancer Institute
08/04-05/09 Prof., Ctr. Mol. Med. & Genet., Wayne State Univ. Sch. Med., Detroit, MI.
08/04-05/09 Prof., Dept Surg, Wayne State Univ. Sch. Med., Detroit, MI.
06/09-prst Staff Scientist, Weis Center for Research, Geisinger Health System, Danville, PA

Honors:

2008 Fellow, American Heart Association

Selected Peer-reviewed Publications (Selected from 100 peer-reviewed original publications)

Most relevant to the current application

1) Kuivaniemi H, Shibamura H, Arthur C, Berguer R, Cole CW, Juvonen T, Kline RA, Limet R, MacKean G, Norrgård Ö, Pals G, Powell JT., Rainio P, Sakalihasan N, van Vlijmen-van Keulen C, Verloes A., Tromp G. Familial abdominal aortic aneurysms: Collection of 233 multiplex families. J Vasc Surg 37: 340-345, 2003.
2) Shibamura H, Olson JM, van Vlijmen-van Keulen C, Buxbaum SG, Dudek DM, Tromp G, Ogata T, Skunca M, Sakalihasan N, Pals G, Limet R, MacKean GL, Defawe O, Verloes A, Arthur C, Lossing AG, Burnett M, Sueda T, and Kuivaniemi, H. Genome scan for familial abdominal aortic aneurysm using sex and family history as covariates suggests genetic heterogeneity and identifies linkage to chromosome 19q13. Circulation 109: 2103-2108, 2004.
3) Tromp G, Gatalica Z, Skunca M, Berguer R, Siegel T, Kline R, Kuivaniemi, H. Elevated expression of matrix metalloproteinase-13 in abdominal aortic aneurysms. Ann Vasc Surg 18: 414-420, 2004.
4) Ogata T, Shibamura H, Tromp G, Sinha M, Goddard KAB, Sakalihasan N, Limet R, MacKean GL, Arthur C, Sueda T, Land S, Kuivaniemi H. Genetic analysis of polymorphisms in biologically relevant candidate genes in patients with abdominal aortic aneurysms. J Vasc Surg 41: 1036-1042, 2005.
5) Ogata T, MacKean GL, Cole CW, Arthur C, Andreou P, Tromp G, Kuivaniemi H. The life-time prevalence of abdominal aortic aneurysms among siblings of aneurysm patients is eight-fold higher than among siblings of spouses; an analysis of 187 aneurysm families in Nova Scotia, Canada. J Vasc Surg 42: 891-897, 2005.
6) Ogata T, Gregoire L, Goddard KAB, Skunca M, Tromp G, Lancaster WD, Parrado AR, Lu Q, Shibamura H, Sakalihasan N, Limet R, MacKean GL, Arthur C, Sueda T and Kuivaniemi H. Evidence for association between the HLA–DQA locus and abdominal aortic aneurysms in the Belgian population: a case control study. BMC Med Genet 7:67, 2006.
7) Lenk GM, Tromp G, Weinsheimer S, Gatalica Z, Berguer R, Kuivaniemi H. Whole genome expression profiling reveals a significant role for immune function in human abdominal aortic aneurysms. BMC Genomics 8:237, 2007.
8) Weinsheimer S, Lenk GM, van der Voet M, Land S, Ronkainen A, Alafuzoff I, Kuivaniemi H, Tromp G. Integration of expression profiles and genetic mapping data to identify candidate genes in intracranial aneurysm. Physiological Genomics 32:45-57, 2007.
9) Helgadottir A, Thorleifsson G, Magnusson KP, Grétarsdottir S, Steinthorsdottir V, Manolescu A, Jones GT, Rinkel GJE, Blankensteijn JD, Ronkainen A, Jääskeläinen JE, Kyo Y, Lenk GM, Sakalihasan N, Kostulas K, Gottsäter A, Flex A, Stefansson H, Hansen T, Andersen G, Weinsheimer S, Borch-Johnsen K, Jorgensen T, Shah SH, Quyyumi AA, Granger CB, Reilly MP, Austin H, Levey AI, Vaccarino V, Palsdottir E, Walters GB, Jonsdottir T, Snorradottir S, Magnusdottir D, Gudmundsson G, Ferrell RE, Sveinbjornsdottir S, Hernesniemi J, Niemelä M, Limet R, Andersen K, Sigurdsson G, Benediktsson R, Verhoeven ELG, Teijink JAW, Grobbee DE, Rader DJ, Collier DA, Pedersen O, Pola R, Hillert J, Lindblad B, Valdimarsson E, Magnadottir HB, Wijmenga C, Tromp G, Baas AF, Ruigrok YM, van Rij AM, Kuivaniemi H, Powell JT, Matthiasson SE, Gulcher JR, Thorgeirsson G, Kong A, Thorsteinsdottir U, Stefansson K. A sequence variant on chromosome 9p21 confers risk of both abdominal aortic aneurysm and intracranial aneurysm in addition to coronary artery disease. Nat Genet 40:217-224, 2008.
10) Elmore JR, Obmann MA, Kuivaniemi H, Tromp G, Gerhard GS, Franklin DP, Boddy AM, Carey DJ. Identification of a genetic variant associated with abdominal aortic aneurysms on chromosome 3p12.3 by genome wide association. J Vasc Surg 49:1525-1531, 2009.
11) Nischan J, Gatalica Z, Curtis M, Lenk GM, Tromp G, Kuivaniemi H. Binding sites for Ets family of transcription factors dominate the promoter regions of differentially expressed genes in abdominal aortic aneurysms. Circulation Cardiovasc Genet 2:565-572, 2009.
12) Haldar SM, Lu Y, Jeyaraj D, Kawanami D, Cui Y, Eapen SJ, Hao C, Li Y, Doughman Y-Q, Watanabe M, Shimizu K, Kuivaniemi H, Sadoshima J, Margulies KB, Cappola TP, Jain MK. Klf15 deficiency is a molecular link between heart failure and aortic aneurysm formation. Sci Transl Med. 2:26ra26, 2010.
13) Gretarsdottir S, Baas AF, Thorleifsson G, Holm H, den Heijer M, de Vries J-PPM, Kranendonk SE, Zeebregts CJAM, van Sterkenburg SM, Geelkerken RH, van Rij AM, Williams MJA, Boll APM, Jonasdottir A,

Jonasdottir A, Walters B, Masson G, Sulem P, Saemundsdottir J, Mouy M, Magnusson KP, Tromp G, Elmore JR, Sakalihasan N, Limet R, Ferrell RE, Ronkainen A, Ruigrok YM, Wijmenga C, Shah SH, Granger CB, Quyyumi AA, Vaccarino V, Patel RS, Zafari AM, Levey AI, Austin H, Girelli D, Pignatti PF, Martinelli N, Malerba G, Trabetti E, Becker LC, Becker DM, Reilly MP, Rader DJ, Mueller T, Dieplinger B, Haltmayer M, Urbonavicius S, Lindblad B, Gottsäter A, Gaetani E, Pola R, Wells P, Rodger M, Forgie M, Langlois N, Corral J, Vicente V, Fontcuberta J, España F, Pedersen OB, Grarup N, Jørgensen T, Witte DR, Hansen T, Aben KK, de Graaf J, Holewijn S, Collier DA, Stefansson H, Steinþorsdóttir V, Rafnar P, Valdimarsson EM, Magnadottir HB, Sveinbjornsdottir S, Olafsson I, Magnusson MK, Palmason R, Haraldsdottir V, Andersen K, Önundarsson PT, Thorgeirsson G, Kiemeney LA, Powell JT, Carey DJ, Kuivaniemi H, Lindholt JS, Jones GT, Kong A, Blankensteijn JD, Matthiasson SE, Thorsteinsdottir U, Stefansson K. A sequence variant in DAB2IP on 9q33 associates with abdominal aortic aneurysm, early-onset myocardial infarction, peripheral arterial disease and venous thromboembolism. Nat Genet 42:692-697, 2010.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Gerardus C Tromp, PhD, FAHA	Staff Scientist
eRA COMMONS USER NAME (credential, e.g., agency login)	
GerardTromp	

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
Potchefstroom Univ., Potchefstroom, R.S.A.	BSc.	1981	Biochem. & Microbiol.
Potchefstroom Univ., Potchefstroom, R.S.A.	BSc. Hon.	1982	Biochemistry
Rutgers, State Univ. of NJ/UMDNJ, NJ	Ph.D.	1989	Biochemistry
Dept. Biochem & Molec. Biol., TJU Phila. PA	Postdoctoral	1989-1990	Molecular Biology

Positions and Honors

Positions:

07/82- 12/88 Graduate work in Biochemistry, Joint Program in Biochemistry, Rutgers and UMDNJ; and Dept. Bioch. & Mol. Biol., Jefferson Medical College, Philadelphia, PA.
01/89- 06/90 Postdoc, Dept. Bioch. & Mol. Biol., Jefferson Medical College, Philadelphia, PA
07/90- 06/91 Instructor, Dept. Bioch. & Mol. Biol., Jefferson Medical College, Philadelphia, PA
07/91- 08/95 Res. Asst. Prof., Dept. Bioch. & Mol. Biol., Jefferson Med. College, Philadelphia, PA
09/95- 08/00 Asst. Prof., Cntr. Mol. Med. & Genet., Wayne State University Sch. Med., Detroit, MI
09/99- 05/09 Member, Karmanos Cancer Institute
09/00- 05/09 Assoc. Prof., Cntr. Mol. Med. & Genet., Wayne State University Sch. Med., Detroit, MI
06/09- prsnt Staff Scientist, Weis Center for Research, Geisinger Health System, Danville, PA

Honors:

03/02- 02/05 Board Member, National Bioinformatics Institute
02/08 Elected Fellow of the American Heart Association (FAHA)

Selected Peer-reviewed Publications (Selected from 108 peer-reviewed original publications and 17 reviews)

Most relevant to the current application

[1] Olson, J.M., Vongpunsawad, S., Kuivaniemi, H., Ronkainen, A., Hernesniemi, J., Ryynänen, M., Kim, L.-L., Tromp, G. Search for intracranial aneurysm susceptibility gene(s) using Finnish families. BMC Med Genet 3:7, 2002.

[2] Shibamura, H., Olson, J.M., van Vlijmen-Van Keulen, C., Buxbaum, S.G., Dudek, D.M., Tromp, G., Ogata, T., Skunca, M., Sakalihasan, N., Pals, G., Limet, R., MacKean, G.L., Defawe, O., Verloes, A., Arthur, C., Lossing, A.G., Burnett, M., Sueda, T., Kuivaniemi, H. Genome scan for familial abdominal aortic aneurysm using sex and family history as covariates suggests genetic heterogeneity and identifies linkage to chromosome 19q13. Circulation 109:2103-2108, 2004.

[3] van der Voet, M., Olson, J.M., Kuivaniemi, H., Dudek, D.M., Skunca, M., Ronkainen, A., Niemelä, M., Jääskeläinen, J., Hernesniemi, J., Helin, K., Leinonen, E., Biswas, M., Tromp, G. Intracranial aneurysms in Finnish families: confirmation of linkage and refinement of the interval to chromosome 19q13.3. Am J Hum Genet 74:564-571, 2004.

[4] Ogata, T., MacKean, G.L., Cole, C.W., Arthur, C., Andreou, P., Tromp, G., Kuivaniemi, H. The lifetime prevalence of abdominal aortic aneurysms among siblings of aneurysm patients is eightfold higher than among siblings of spouses: an analysis of 187 aneurysm families in Nova Scotia, Canada. J Vasc Surg 42:891-897, 2005.

[5] Ogata, T., Shibamura, H., Tromp, G., Sinha, M., Goddard, K.A., Sakalihasan, N., Limet, R., MacKean, G.L., Arthur, C., Sueda, T., Land, S., Kuivaniemi, H. Genetic analysis of polymorphisms in biologically relevant candidate genes in patients with abdominal aortic aneurysms. J Vasc Surg 41:1036-1042, 2005.

[6] Ogata, T., Arrington, S., Davis, P.M., Jr., Sam, A.D., 2nd, Hollier, L.H., Tromp, G., Kuivaniemi, H. Community-based, nonprofit organization-sponsored ultrasonography screening program for abdominal aortic aneurysms is effective at identifying occult aneurysms. Ann Vasc Surg 20:312-316, 2006.

[7] Ogata, T., Gregoire, L., Goddard, K.A., Skunca, M., Tromp, G., Lancaster, W.D., Parrado, A.R., Lu, Q., Shibamura, H., Sakalihasan, N., Limet, R., Mackean, G.L., Arthur, C., Sueda, T., Kuivaniemi, H. Evidence for association between the HLA-DQA locus and abdominal aortic aneurysms in the Belgian population: a case control study. BMC Med Genet 7:67, 2006.

[8] Wills, S.M., Weinsheiner, S.M., Kuivaniemi, H., Tromp, G. Smoking and family history confer greatest risk for intracranial aneurysms. Neurology 66:A27-A27, 2006.

[9] Weinsheimer, S., Goddard, K.A., Parrado, A.R., Lu, Q., Sinha, M., Lebedeva, E.R., Ronkainen, A., Niemelä, M., Khusnutdinova, E.K., Khusainova, R.I., Helin, K., Jääskeläinen, J.E., Sakovich, V.P., Land, S., Kuivaniemi, H., Tromp, G. Association of Kallikrein Gene Polymorphisms With Intracranial Aneurysms. Stroke 38:2670-2676, 2007.

[10] Weinsheimer, S., Lenk, G.M., van der voet, M., Land, S., Ronkainen, A., Alafuzoff, I., Kuivaniemi, H., Tromp, G. Integration of expression profiles and genetic mapping data to identify candidate genes in intracranial aneurysm. Physiol. Genom. 32:45-57, 2007.

[11] Helgadottir, A., Thorleifsson, G., Magnusson, K.P., Gretarsdottir, S., Steinthorsdottir, V., Manolescu, A., Jones, G.T., Rinkel, G.J., Blankensteijn, J.D., Ronkainen, A., Jaaskelainen, J.E., Kyo, Y., Lenk, G.M., Sakalihasan, N., Kostulas, K., Gottsater, A., Flex, A., Stefansson, H., Hansen, T., Andersen, G., Weinsheimer, S., Borch-Johnsen, K., Jorgensen, T., Shah, S.H., Quyyumi, A.A., Granger, C.B., Reilly, M.P., Austin, H., Levey, A.I., Vaccarino, V., Palsdottir, E., Walters, G.B., Jonsdottir, T., Snorradottir, S., Magnusdottir, D., Gudmundsson, G., Ferrell, R.E., Sveinbjornsdottir, S., Hernesniemi, J., Niemela, M., Limet, R., Andersen, K., Sigurdsson, G., Benediktsson, R., Verhoeven, E.L., Teijink, J.A., Grobbee, D.E., Rader, D.J., Collier, D.A., Pedersen, O., Pola, R., Hillert, J., Lindblad, B., Valdimarsson, E.M., Magnadottir, H.B., Wijmenga, C., Tromp, G., Baas, A.F., Ruigrok, Y.M., van Rij, A.M., Kuivaniemi, H., Powell, J.T., Matthiasson, S.E., Gulcher, J.R., Thorgeirsson, G., Kong, A., Thorsteinsdottir, U.,

Stefansson, K. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat Genet 40:217-224, 2008.
[12] 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 49:1525-1531, 2009.
[13] Nischan, J., Gatalica, Z., Curtis, M., Lenk, G.M., Tromp, G., Kuivaniemi, H. Binding sites for ETS family of transcription factors dominate the promoter regions of differentially expressed genes in abdominal aortic aneurysms. Circ Cardiovasc Genet 2:565-572, 2009.
[14] Tromp, G., Kuivaniemi, H. Developments in Genomics to Improve Understanding, Diagnosis and Management of Aneurysms and Peripheral Artery Disease. Eur J Vasc Endovasc Surg 38:676-682, 2009.
[15] Huttunen, T., von und zu Fraunberg, M., Frösen, J., Lehecka, M., Tromp, G., Helin, K., Koivisto, T., Rinne, J., Ronkainen, A., Hernesniemi, J., Jääskeläinen, J.E. Saccular intracranial aneurysm disease: distribution of site, size, and age suggests different etiologies for aneurysm formation and rupture in 316 familial and 1454 sporadic eastern Finnish patients. Neurosurgery 66:631-638, 2010.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
James S Betoni D.O.	MFM Fellow

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Muhlenberg College	BS	1984	Biology
Philadelphia College of Osteopathic Medicine	D.O.	1991	Medicine

NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.

A. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

Currently Maternal Fetal Medicine fellow at Geisinger Medical Center.
Previous history: 2001-2007 :Director of Women's Health,Peak Vista Community Health Center .Colorado Springs,CO

2000-2001: Private Practice,Pueblo Women's Clinic,Pueblo ,CO
1997-2000: Staff OBGYN, Mt Sinai Medical Center,Chicago ,IL
1992-1996: OBGYN Resident,Midwestern University, Chicago,IL
1991-1191:General medical rotating internship,Philadelphia College of Osteopathic Medicine,Phila,PA

B. Selected peer-reviewed publications (in chronological order). Do not include publications submitted or in preparation.

C. Research Support. List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.