PI: **Marchant, Gary E.**	Title: Liability in the delivery of personalized medicine: driver, impediment, or both?	
Received: 06/29/2011	FOA: PA10-067	Council: 01/2012
Competition ID: ADOBE-FORMS-B1	FOA Title: RESEARCH PROJECT GRANT (PARENT R01)	
1 **R01 HG006145-01A1**	Dual:	Accession Number: 3406158
IPF: 488301	Organization: ARIZONA STATE UNIVERSITY-TEMPE CAMPUS	
Former Number:	Department: Ctr for Law, Science & Innovat	
IRG/SRG: SEIR	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 175,000 Year 2: 200,000 Year 3: 200,000	Animals: N Humans: N Clinical Trial: N Current HS Code: 10 HESC: N	New Investigator: N Early Stage Investigator: N

Senior/Key Personnel:	*Organization:*	*Role Category:*
Gary Marchant	AZ Board of Regents for Arizona State University	PD/PI
Amalia Issa	University of the Sciences in Philadelphia	Other (Specify)-Co-Investigator
Doug Campos-Outcalt	Arizona Board of Regents for the University of Arizona	Other (Specify)-Co-Investigator
Scott Ramsey	Fred Hutchinson Cancer Research Center	Consultant
Paul Wicks	PatientsLikeMe	Consultant
Rachel Lindor	Mayo Medical School	Consultant

424 R&R and PHS-398 Specific
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LIABILITY IN THE DELIVERY OF PERSONALIZED MEDICINE: DRIVER, IMPEDIMENT, OR BOTH?

PROJECT SUMMARY

Personalized medicine (PM) has the potential to transform medicine and the health care system over the next decade. An overlooked variable that will play an important role in the implementation of PM is the potential for legal liability. Physicians, a key gatekeeper in the uptake of PM, are at the greatest risk of liability. Currently, there is great uncertainty, disagreement and rapid change with regard to the use of PM tests in clinical care. It is during this period of uncertainty and change where the potential for liability is at its greatest and thus the need for comprehensive legal research and analysis of the intersection of these issues is most pressing. This proposed project seeks to fill the gap in the understanding of PM liability risks by providing legal doctrinal, empirical, and policy research on the risks, impacts and possible policy approaches with regard to PM liability. The results of this project can help to better understand and predict the future course of PM and to identify the key legal and policy levers that may be available to ensure that liability plays a beneficial rather than detrimental role in the implementation of PM. This project has five primary objectives. This project will provide a comprehensive investigation and analysis of potential liability to physicians, first by examining the applicable claims, defenses and doctrines that will, provide the legal framework for liability, and which themselves are currently undergoing important changes. Second, we will evaluate the potential risks of liability to physicians by integrating the doctrinal analysis with the fact patterns and evidence in four likely PM case studies, as well as by evaluating liability lessons from the uptake of previous medical technologies and practices. Third, we will examine the likely impact liability will have on physicians, patients, and the broader adoption, availability and implementation of PM. Fourth, we will identify and evaluate policy tools that can be used to better manage risks and uncertainties in the PM arena. Finally, we will communicate the findings and implications of our project through an outreach program targeting three key stakeholder groups: (i) physicians and medical educators; (ii) patient groups and advocates; and (iii) legal practitioners (including judges). At this critical juncture in the rollout of PM, *before* widespread liability has taken hold, it is very important and useful to comprehensively study and make widely available the best information and projections of the risks and relevant factors for physician liability relating to PM.

PUBLIC HEALTH RELEVANCE: The advent of personalized medicine (PM) has the potential to greatly impact and improve patient care by providing the opportunity for better tests, better drugs, and overall better health outcomes. The increased risk of legal liability for physicians will ultimately influence which technologies will be adopted and rejected in the PM space, shape the relevant standard of care, dictate public health outcomes, affect access to PM technologies and the care that the ultimate beneficiary, the patient, receives. Better understanding, communication and policy interventions relating to PM liability risks can help to ensure that liability has a beneficial rather than detrimental impact on PM uptake and implementation.

FACILITIES AND OTHER RESOURCES

ARIZONA STATE UNIVERSITY – PRIME

Laboratory:
N/A

Animal:
N/A

Clinical:
N/A

Computer:
Computers, both desktop and laptop, for Gary Marchant are provided by Arizona State University.

Office:
Office space for Gary Marchant is provided by Arizona State University.

OTHER RESOURCES:
The Sandra Day O'Connor College of Law at Arizona State University will provide secretarial services and administrative support to Gary Marchant for all of his work related to this project.

SCIENTIFIC ENVIRONMENT:
The scientific environment created by the collaboration of the Investigators and Consultants, led by Professor Gary Marchant of the Center for Law, Science & Innovation (CLSI), is ideal for the execution of this project. A geneticist and a lawyer, Professor Marchant has been interested in the intersection of genetics and pharmacogenomic testing and liability for over a decade. He has written numerous articles and made numerous presentations on the topic, and recently served on a National Academy of Sciences committee that examined the implementation and implications of toxicogenomics and pharmacogenomics. He directs the CLSI at ASU, which has 25 law faculty and over 80 students specializing in the law and science field, many focusing on the biosciences and the law. The Center's Genetics and the Law program has organized seven conferences and workshops on legal aspects of genetics over the past decade, including a large conference last year co-sponsored with AAAS and the Mayo Clinic looking at emerging legal issues in the clinical application of personalized medicine that was attended by over 250 people. One of the panels was focused on what role liability would play in the rollout of personalized medicine, particularly relating to physicians and the standard of care. The CLSI has close connections and ongoing collaborations with various other institutions interested in this project, including TGen, the Biodesign Institute at ASU, the Mayo Clinic Scottsdale and Mayo Medical School. The other members of the team add to the depth and breadth of expertise. Dr. Campos-Outcalt is a physician and medical school professor who specializes in analyzing genetic tests, and has served for the past couple years on the CDC's EGAPP group evaluating the clinical readiness of genetic tests. Dr. Issa is an expert in personalized medicine and public health who has extensive experience and contacts in the personalized medicine field. Working under Dr. Issa are Nelson Atehortua, a post-doc with extensive experience in policy-relevant research related to genomics, and Mo Yang, a graduate student, and both have worked with Dr. Issa in the past. The consultants add extremely valuable expertise as well. Paul Wicks of PatientsLikeMe represents the patients' perspective and Scott Ramsey, a health economist and physician, will contribute an economic perspective. Rachel Lindor, a JD and highly accomplished medical student, will be able to contribute to case law and data analysis from both a legal and medical perspective. Lastly, the graduate students selected to assist in legal research and data collection are trained for those tasks and eager to contribute to the proposed project.

UNIVERSITY OF THE SCIENCES – SUBCONTRACT

Laboratory:
N/A

Clinical:
N/A

Animal:
N/A

Computer:
Computers, both desktop and laptop, for Amalia Issa are provided by University of the Sciences.

Office:
Office space for Amalia Issa is provided by University of the Sciences.

Other:
The Department of Health Policy and Public Health at the University of the Sciences will provide secretarial services and administrative support to Amalia Issa for all of her work related to this project.

UNIVERSITY OF ARIZONA – SUBCONTRACT

Laboratory:
N/A

Clinical:
N/A

Animal:
N/A

Computer:
Computers, both desktop and laptop, for Doug Campos-Outcalt are provided by University of Arizona.

Office:
Office space for Doug Campos-Outcalt is provided by University of Arizona.

Other:
The College of Medicine at the University of Arizona will provide secretarial services and administrative support to Doug Campos-Outcalt for all of his work related to this project.

CAPITAL EQUIPMENT

This project requires no capital equipment.

PHS 398 Modular Budget, Periods 1 and 2

OMB Number: 0925-0001

Budget Period: 1

Start Date: 04/01/2012 End Date: 03/31/2013

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	175,000.00
Consortium F&A	43,739.00
* Total Direct Costs	218,739.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Modified Total Direct Costs (MTDC)	52.5	77,536.00	66,956.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, Cora Coleman, 415-437-7821

Indirect Cost Rate Agreement Date 06/16/2009

Total Indirect Costs 66,956.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) 285,695.00

Budget Period: 2

Start Date: 04/01/2013 End Date: 03/31/2014

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	200,000.00
Consortium F&A	46,763.00
* Total Direct Costs	246,763.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Modified Total Direct Costs (MTDC)	52.5	95,932.00	50,391.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, Cora Coleman, 415-437-7821

Indirect Cost Rate Agreement Date 06/19/2009

Total Indirect Costs 50,391.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) 297,154.00

PHS 398 Modular Budget, Periods 3 and 4

Budget Period: 3

Start Date: 04/01/2014 End Date: 03/31/2015

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	200,000.00
Consortium F&A	46,355.00
* Total Direct Costs	246,355.00

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	Modified Total Direct Costs (MTDC)	52.5	96,712.00	50,774.00
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number) DHHS, Cora Coleman, 415-437-7821

Indirect Cost Rate Agreement Date 06/16/2009

Total Indirect Costs 50,774.00

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($) 297,129.00

Budget Period: 4

Start Date: End Date:

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date

Total Indirect Costs

C. Total Direct and Indirect Costs (A + B)

Funds Requested ($)

PHS 398 Modular Budget, Periods 5 and Cumulative

Budget Period: 5

Start Date: | End Date:

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	
Consortium F&A	
* Total Direct Costs	

B. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.				
2.				
3.				
4.				

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date | Total Indirect Costs

C. Total Direct and Indirect Costs (A + B) Funds Requested ($)

Cumulative Budget Information

1. Total Costs, Entire Project Period

*Section A, Total Direct Cost less Consortium F&A for Entire Project Period	$	575,300.00
Section A, Total Consortium F&A for Entire Project Period	$	136,857.00
*Section A, Total Direct Costs for Entire Project Period	$	711,857.00
*Section B, Total Indirect Costs for Entire Project Period	$	168,121.00
*Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period	$	879,978.00

2. Budget Justifications

Personnel Justification	1246-11111205_Marchant_NIH_Per		Delete Attachment	View Attachment
Consortium Justification	1247-11111205 Marchant NIH Cor		Delete Attachment	View Attachment
Additional Narrative Justification	1248 11111205_Marchant_NIH_Add		Delete Attachment	View Attachment

PERSONNEL JUSTIFICATION

This proposal requests $575,000 in total direct costs over three years (year 1: $175,000, year 2: $200,000, year 3: $200,000) beginning April 1, 2012 and ending March 31, 2015.

Principal Investigator

Gary E. Marchant, Ph.D., J.D., M.P.P., Lincoln Professor of Emerging Technologies, Law and Ethics and Executive Director of the Center for Law, Science and Innovation at ASU, EFFORT months per year.

The PI will provide overall direction of the project. He will also supervise and provide the lead role in all the legal research and analysis in the first and second years of the project and work closely with the two primary co-investigators in undertaking the four case studies in year 2. He will then work closely with all the investigators and consultants who will evaluate the impacts and policy approaches to personalized medicine liability, and he will take the lead in the outreach initiative in year 3. The PI will also be responsible for timely submission of reports and submission of manuscripts for publication.

Consultants

Paul Wicks, Ph.D., Director of Research and Development at PatientsLikeMe, "as needed."

Dr. Wicks's work with patients began early in his career. For his PhD, Paul travelled the UK testing patients with rare forms of ALS/MND. Dr. Wicks is now a research neuropsychologist specializing in the emotional and cognitive effects neurological conditions can have; particularly ALS/MND and Parkinson's disease. Dr. Wick joined PatientsLikeMe in 2006, and as the company has grown, the R&D team has grown with it to include 5 PhDs and 2 RNs working full-time on improving patient outcomes, the only team of its kind in the world. In regards to the proposed project, Dr. Wicks is going to contribute an evaluation of patient outcomes as it relates to the personalized medicine technologies studied in the course of the grant, attend two meetings with the investigators, and assist in preparation of manuscripts.

Scott Ramsey, M.D., Ph.D. Full Member of the Fred Hutchinson Cancer Research Center, "as needed."

Dr. Ramsey is a physician, cancer researcher, and health economist. He currently leads projects funded by the National Cancer Institute, National Human Genome Research Institute, Centers for Disease Control and Prevention, and several pharmaceutical manufacturers. Dr. Ramsey also works with health insurers throughout the United States, including Medicare, to help them decide what procedures and medication to cover or not cover. In regards to the proposed project, Dr. Ramsey is going to contribute an economic perspective to the research analysis, attend two meetings with the Investigators, and assist in the preparation of manuscripts.

Rachel Lindor, J.D., M.D. candidate, Prescription Assistance Program Coordinator at Mayo Medical School, "as needed."

Rachel spent four summers as a research assistant in the Department of Medical Genetics at the Mayo Clinic where she contributed to the NIH-funded Colon Cancer Family Registry (UO1-CA75800). Prior to entering medical school, she worked for Mayo Clinic's Familial Cancer Program, where her research compared the clinical validity of predictive risk models for hereditary breast cancer (Lindor et al., 2007). In law school, she was involved in various projects related to medical liability, especially in the context of genetic testing and personalized medicine. She is currently a fellow at the Department of Health and Human Services where her work addresses government policies related to the regulation of personalized medicine technologies. In regards to the proposed project, Rachel will be the lead researcher in the year 2 legal analysis of liability trends and lessons from previous medical technologies and practices and will also work collaboratively with the other team members in year three to evaluate the impacts and policy approaches to liability risks, including assistance in preparation of the manuscripts in year 3.

Graduate Research Assistants

Blake Atkinson, Edith Cseke, Rebecca Janssen, Patricia Lepkowski, Athanasios Papailiou, and Khanrat Piensook, Graduate Research Assistants, 0.9 academic months each per year.

Each of these students applied to participate in the proposed project and was selected after an interview with Dr. Marchant. The Graduate Research Assistants will be responsible for data collection, review of relevant literature, and case study research. The PI will oversee the six Graduate Research Assistants.

CONSORTIUM JUSTIFICATION

UNIVERSITY OF THE SCIENCES (DOMESTIC INSTITUTION)

	Year 1	Year 2	Year 3	All Years
Direct + F&A Costs (nearest $1,000)	$102,000	$108,000	$108,000	$318,000

Personnel

Dr. Amalia Issa, Co-Investigator, EFFORT months per year. Dr. Issa will conduct research and prepare work product (draft memos, working papers and manuscripts for publication) on how the potential for liability, and various scenarios for liability developed by the research team, will affect patient and physician uptake of personalized medicine. In particular, given her experience and expertise with respect to patient decision making and personalized medicine (she developed an instrument to quantitatively measure patient preferences and the trade-offs they make in deciding for specific personalized genomic services), Dr. Issa will be the investigator responsible for collaboration with consultant Paul Wick in analyzing the effect of liability on patients, and how liability may affect the physician-patient relationship, and the availability and uptake of personalized medicine technologies. Dr. Issa also has experience in analyzing the economic implications of personalized medicine and consequently she will be the investigator responsible for collaboration with health economist consultant Scott Ramsey, on identifying the way economic factors are going to affect the uptake of various PM technologies, for both public and private payors, and how those economic decisions will ultimately affect the patient. Finally, Dr. Issa will be a core member of the project team responsible for planning and coordinating the grant activities.

Nelson Atehortua, MD/PhD, Postdoctoral Associate, EFFORT months per year. Dr. Atehortua will assist Dr. Issa with research and analysis. Dr. Atehortua has extensive experience in policy-relevant research, including in genomics, and has previously worked with PAHO. Dr. Atehortua will be responsible for organizing the research and particularly the case studies and ensuring that the policy analysis is up-to-date.

Mo Yang, MS, Graduate Student, 6 calendar months per year. Ms. Yang is a PhD student who is currently supervised by Dr. Issa. Funds are budgeted for her to assist Dr. Issa as a EFFORT research assistant on this grant. Her responsibilities will include data collection and analysis of research findings.

Travel

$1,800 per year is budgeted for Dr. Issa to travel to ASU to work on the project. $1,800 is budgeted in year 2 for Dr. Issa to attend a conference related to the project topic.

THE UNIVERSITY OF ARIZONA (DOMESTIC INSTITUTION)

	Year 1	Year 2	Year 3	All Years
Direct + F&A Costs (nearest $1,000)	$39,000	$43,000	$41,000	$123,000

Personnel

Dr. Doug Campos-Outcalt, Co-Investigator, EFFORT months per year. Dr. Campos-Outcalt will conduct research and prepare work product (draft memos, working papers and manuscripts for publication) evaluating the scientific and medical criteria that are, should and might be applied by courts in adjudicating personalized medicine liability claims. This evaluation will be critical in assessing the potential benefits and/or detriments that liability may play with regard to personalized medicine, both with respect to overall societal well-being and

the interests of specific stakeholders such as physicians, payors and testing companies. Dr. Campos-Outcalt has significant expertise is evaluating the clinical utility and validity of genetic tests through his membership on EGAPP and other activities. Consequently, he will be responsible for evaluating the role that scientific and clinical evidence plays in liability claims relating to pharmacogenomic testing and specifically how those claims align with the clinical utility and validity of the tests. This research will be integrated with the work product of the other investigators to produce published manuscripts and briefing documents for stakeholders such as physicians, lawyers and judges, patients, and payors. Finally, Dr. Campos-Outcalt will be a core member of the project team responsible for planning and coordinating the grant activities.

Travel

$1,885 is budgeted in year 2 for Dr. Campos-Outcalt to attend a conference related to the project topic.

ADDITIONAL NARRATIVE JUSTIFICATION

	Year 1	Year 2	Year 3	All Years
Total Direct Costs	$175,000	$200,000	$200,000	$575,000

The budget for this project requires an increased number of modules in years 2 and 3 for the following reasons:

- Another consultant will be added in years 2 and 3. While this consultant is not necessary for the proceedings in year 1, she will provide a key service in the following years.
- Additional travel funds were budgeted in years 2 and 3 for the consultants.
- Additional travel funds were budgeted in years 2 and 3 for the principal investigator so that he can meet with stakeholders to get feedback on the project's progress and direction.
- Additional travels funds were budgeted in year 2 for the co-investigators to attend conferences related to this project topic.
- A 3% inflationary increase was added to salaries in years 2 and 3.

OMB Number: 0925-0001

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

☐ New ☒ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application (for RESUBMISSION or REVISION only)	1249 11111205_Marchant_NIH_		Delete Attachment	View Attachment
2. Specific Aims	1250-11111205_Marchant_NIH_		Delete Attachment	View Attachment
3. *Research Strategy	1251-11111205_Marchant_NIH_R		Delete Attachment	View Attachment
4. Inclusion Enrollment Report		Add Attachment		
5. Progress Report Publication List		Add Attachment		

Human Subjects Sections

6. Protection of Human Subjects		Add Attachment		
7. Inclusion of Women and Minorities		Add Attachment		
8. Targeted/Planned Enrollment Table		Add Attachment		
9. Inclusion of Children		Add Attachment		

Other Research Plan Sections

10. Vertebrate Animals		Add Attachment		
11. Select Agent Research		Add Attachment		
12. Multiple PD/PI Leadership Plan		Add Attachment		
13. Consortium/Contractual Arrangements	1252-11111205_Marchant_NIH_C		Delete Attachment	View Attachment
14. Letters of Support	1253-11111205_Marchant_NIH_L		Delete Attachment	View Attachment
15. Resource Sharing Plan(s)		Add Attachment		

16. Appendix Add Attachments

LIABILITY IN THE DELIVERY OF PERSONALIZED MEDICINE: DRIVER, IMPEDIMENT, OR BOTH?

INTRODUCTION

reviewers' comments

LIABILITY IN THE DELIVERY OF PERSONALIZED MEDICINE: DRIVER, IMPEDIMENT, OR BOTH?

SPECIFIC AIMS

Personalized medicine (PM) is widely expected to transform medicine and the health care system over the next decade. Yet, the emergence and implementation of PM has been slower than many anticipated. Scientific complexity and uncertainties, the need for validation of biomarkers, commercial unavailability of relevant diagnostic tests, economic costs, lack of reimbursement for diagnostic testing, regulatory approval barriers, structural problems in the existing health care delivery system, inadequate business models, physician educational gaps and resistance, and intellectual property issues have all been identified as potential factors impeding the implementation of PM. One factor that has not been subject to much attention to date, but is likely to play an increasingly significant role in the future, is the potential for liability. In particular, physicians, a key gatekeeper in the uptake in PM, are most at risk of liability relating to PM due to their lack of available defenses, limited training in genetics, and legal doctrinal trends that will be further evaluated in this project.

Indeed, the first PM lawsuits are already being pursued in the courts, and a rapid ramp-up of such litigation can be expected over the next few years, particularly if some of the initial lawsuits are successful. Uncertainties about the benefits, costs and standards for applying PM technologies and tests will further clinical adoption of some PM technologies and practices, while potentially deterring others, affecting the availability, safety and benefits of PM innovations for patients. Notwithstanding the major role that liability risks and uncertainties are likely to play in the implementation and direction of PM, relatively little doctrinal, empirical or policy research has been conducted on this issue to date.

This project proposes to examine the nature and risks of potential PM-related liability for physicians, the key doctrinal and evidentiary issues that will determine the potential likelihood and success of such lawsuits, the likely impacts of liability risks on the development and direction of PM, and potential policy tools to better manage liability risks and uncertainties. It will then seek to communicate the findings and implications of our research to key stakeholder groups. Specifically, this project aims to:

1. Identify the legal claims, defenses and doctrines, including current trends and changes in these key legal criteria, that will affect liability for physicians relating to PM;

2. Evaluate the risks of PM-related liability to physicians by integrating the doctrinal analysis with the fact patterns in four likely PM case studies, as well as by analyzing lessons from previous examples of physician liability relating to new medical technologies and procedures;

3. Explore the potential impacts of physician liability on the development and direction of PM, including physician practices and patient access to and benefit from PM;

4. Identify and evaluate potential policy options for better management of physician liability risks and uncertainties relating to PM; and

5. Conduct outreach on the findings and implications of our research to key stakeholder groups (including physicians, physician educators, patient groups, and legal practitioners (including judges)) to help them better prepare for and anticipate future liability trends and impacts.

LIABILITY IN THE DELIVERY OF PERSONALIZED MEDICINE: DRIVER, IMPEDIMENT, OR BOTH?

RESEARCH STRATEGY

I. Significance

There are many obstacles affecting the implementation of personalized medicine (PM), including scientific complexity and uncertainty, the need for validation of biomarkers, economic costs, lack of reimbursement for diagnostic testing, regulatory approval barriers, structural problems in the existing health care delivery system, lack of physician training and motivation, inadequate business models, and intellectual property issues. One potentially important factor that has received less attention to date, but which could be enormously influential in the uptake and future direction of PM, is liability. While liability could potentially affect all actors in the PM lifecycle -- including drug and device manufacturers, test providers and testing labs, health care providers, third-party payors, and pharmacists – physicians are at the greatest risk of liability and their behavior is most likely to be influenced by potential liability relating to PM (Marchant et al. 2011; Marchant et al 2006). This proposal will therefore focus on physicians and their patients, and the impact that liability may have on them in the context of PM.

Liability can be a powerful incentive for actors to take appropriate measures to protect public health and safety, or it can skew priorities and practices in socially disadvantageous ways. Thus, liability has the potential to have both beneficial and detrimental influences on whether and how physicians uptake PM. Liability may speed up the development and clinical use of some PM technologies and practices, while deterring others. Notwithstanding the potential importance of liability in influencing the future direction and uptake of PM, relatively little is known about, and very little research has been conducted on, the liability risks associated with PM and their likely impacts. This proposed project seeks to fill that gap by providing legal doctrinal, empirical, and policy research on the risks, impacts and possible policy approaches with regard to PM liability for physicians. The results of this project can help to better understand and predict the future course of PM, to identify the key legal and policy levers that may be available to ensure that liability plays a beneficial rather than detrimental role in the implementation of PM, and to provide guidance to physicians, patients, attorneys and judges on PM liability issues .

In this section, we first provide a brief description of PM and its current status, followed by a more extensive discussion of potential liability risks to physicians and why the potential liability in the burgeoning field of PM is unique and pressing issue that needs to be comprehensively analyzed and addressed.

1. Brief Description and Status of Personalized Medicine

The practice of medicine in the United States is on the verge of a profound paradigm shift from the "one size fits all" approach of the past to individualized care in which a new generation of molecular diagnostics will be used to target treatments to the unique genetic and molecular profile of individual patients and their diseases. As NIH Director Francis Collins recently noted, "[t]he power of the molecular approach to health and disease has steadily gained momentum over the past several decades and is now poised to catalyze a revolution in medicine" (Collins, 2010). Notwithstanding the enormous potential and excitement about the dawning era of PM, the implementation of PM has turned out to be slower and more complex than many experts originally anticipated (SACGHS, 2008; The Royal Society, 2005).

Today, there is substantial uncertainty and disagreement about the appropriate use of genetics and other personalized medicine data in clinical care, giving rise to the types of disagreements and disputes that can spawn litigation. On one hand, some experts claim certain PM techniques are ready for clinical application today, and several leading medical institutions have begun to deploy such techniques (Personalized Medicine Coalition, 2009; Flockhart et al., 2009; Lesko, 2007). Experts with this perspective have expressed frustration that physicians and other stakeholders in the health care system have been too slow to uptake PM methods and tools (Lesko & Woodcock, 2004; Evans, 2006). Other experts, however, are more skeptical about the near-term deployment of PM, contending that such methods are not likely to benefit patient care and are not yet ready for widespread adoption (The Royal Society, 2005; Nebert & Vesell, 2004).

We are currently at a critical and unsettled juncture in the implementation of PM, where much uncertainty and disagreement exists about which PM technologies and approaches are ready for use, what outcomes they will provide, and who will pay for them. In such a period of uncertainty, the potential for liability is at its greatest.

2. Liability Doctrines Affecting Personalized Medicine

One factor that may accelerate (appropriately or inappropriately) the widespread clinical use of personalized medicine is liability (Marchant et al., 2011; SACGHS, 2008; Roth 2007; Marchant et al., 2006; Evans, 2006; Ossorio, 2001). A patient who suffers a serious adverse effect from a pharmaceutical for which he or she carries a genetic susceptibility or a patient whose treatment was adversely affected by the failure to use new genetic diagnostic techniques in a timely manner may bring a lawsuit against any number of entities across the PM lifecycle, including the physician who prescribed the drug, the drug manufacturer who produced the drug, the manufacturer who developed the diagnostic test, the testing lab that conducted the test, the insurer which may not have been willing to pay for a more appropriate genetic test, or the pharmacist that dispensed the drug. If and when one or more lawsuits are successful, the dynamics of litigation generally are such that news of the successful litigation will spread quickly among the legal community, and the number of such cases brought by trial attorneys will quickly skyrocket. If such a dynamic were to be unleashed in the context of PM, the impacts would be enormous. Even a relatively low number of lawsuits would have pervasive effects on how PM is delivered and implemented, since the economic and psychological consequences of liability for any individual at-risk party could be substantial.

Physicians are likely to be the most at risk for liability relating to PM, mostly because other parties will be protected by various statutory and common law defenses such as the learned intermediary doctrine (Marchant et al., 2011; Marchant et al., 2006). This is not just a hypothetical issue. There has already been a smattering of PM-related lawsuits filed against physicians, including: (1) failing to recommend a genetic test before prescribing a drug or treatment; (e.g. *Downey v. Dunnington*, 2008 – physician performed prophylactic mastectomy on woman based on her family history of breast cancer, but was sued for failing to test her for a BRCA mutation first); (2) failing to timely diagnose genetic condition, thereby leading to loss of chance to treat (e.g. *Cardone v. Gunsberger*, 2005 – physician liable for taking 3 weeks to diagnose a genetic disorder in an infant); (3) failing to recognize that family history indicates need for a given diagnostic or screening test (e.g. *Bointy-Tsotigh v. U.S.,* 1996 – physician liable for not recommending early colonoscopy in patient with family history of cancer); (4) for providing an inaccurate diagnosis or prognosis based on genetic tests (e.g., *Gallagher v. Duke University*, 1988 – hospital erred in inaccurately reporting results of genetic tests to parents); (5) failure to warn family members about heritable conditions (e.g., *Pate v. Threlkel*, 1995 – doctor had duty to warn daughter of his patient of genetic risk for cancer);

These initial cases are likely to be just the tip of the iceberg. As the scientific knowledge, regulatory approval, and commercial availability of pharmacogenomic tests continues to expand, the potential and likelihood for liability will likewise continue to grow, especially if physicians are resistant to the uptake of these new technologies and procedures. Yet, there is considerable uncertainty about the prospects of a medical malpractice or other lawsuit brought by patients or other injured persons against their physician alleging that their injury was caused or exacerbated by the use or failure to employ PM technologies. The applicable legal scenarios, doctrines and evidentiary requirements relevant for PM liability for physicians are relatively uncharted, and are not fixed but rather are evolving due to shifting legal and policy trends. The *first objective* of this project will therefore be to identify and evaluate the relevant legal claims, defenses, and doctrines that will be applicable for potential liability lawsuits against physicians relating to PM, including recent doctrinal changes and trends that will significantly affect the liability exposure of physicians.

For example, to bring a successful medical malpractice case against a physician, a plaintiff must show that (i) the physician had a duty of care to the plaintiff, (ii) the physician breached that duty, (iii) the plaintiff incurred an injury, and (iv) the physician's breach caused the plaintiff's injury. The key element of liability exposure is the standard of care, which is undergoing rapid and significant doctrinal changes (Gostin & Jacobson, 2006). In some jurisdictions the standard of care is determined by local custom, and if few local physicians are currently using PM tests, a physician who is sued for failing to use adequate methods will not be held to have violated the applicable standard of care. However, some jurisdictions apply a more objective "risk based" test to

determine the standard of care, where instead of looking to the common practices of the medical profession, the court looks to whether the physician's conduct was "reasonable" as determined by a judge or jury (Helling, 1974; Peters, 2000). Under this standard, a physician may be held liable even if the medical community at large has not yet adopted the PM test that a patient claims should have been used. Additionally, some jurisdictions are now applying a national standard of care rather than a standard based on local practice and custom (Lewis et al., 2007). These shifting definitions of the standard of care, along with new claims (e.g., informed consent) brought against physicians to skirt medical malpractice defenses, are likely to create uncertainty and substantially affect liability risks for physicians relating to PM (Marchant et al. 2006).

There are a number of other legal doctrinal trends and changes that will affect PM liability for physicians. New causes of action beyond medical malpractice are emerging in the context of genetics and PM. For example, physicians have been held liable in their handling of genetics by failing to obtain fully informed consent related to diagnostic and treatment procedures (*Granata v. Fruiterman*, 668 S.E.2d 127 (2008). These informed consent claims are increasingly powerful tools for patients, especially as courts transition to a patient-centered approach to this doctrine, which requires physicians to disclose all information that reasonable *patients* would consider material to their decision making (rather than the information that reasonable physicians would consider material, as the traditional doctrine required). Physicians have also been sued for failure to disclose genetic risks to family members of their patients who refuse to communicate the risk to their relatives, with mixed results (Pate v. Threlkel, 1995; Safer v. Pack, 1996; Molloy v. Meier, 2004). Other important doctrinal changes, such as those adopted by courts or legislatures affecting "loss of chance" (King, 1981; Renehan, 2009), the learned intermediary doctrine (Calabro, 2004), and standards and procedures for medical malpractice cases (Kachalia & Mello, 2011) will also impact significantly the liability potential for physicians in the PM context.

3. *Liability Risks in Personalized Medicine*

While the number of lawsuits filed to date against physicians directly involving PM is limited, the number of cases will likely rise significantly in the next few years. However, little or no empirical analysis or in-depth research has been undertaken to date to try to evaluate the likelihood and magnitude of PM lawsuits being filed, the likely outcome of those lawsuits, and the impact that such outcomes will have on physician practice and the implementation of PM. Some important lessons can likely be learned from previous litigation episodes and experiences involving previous medical technologies. A general trend has been that new technologies, even if they improve overall health care, lead to a significant bump up in liability as expectations are increased and the gap in performance widens between early and slow adopters (Sage, 2003; De Ville, 1998). Such a dynamic can be expected with PM.

Yet, there are reasons to believe that personalized medicine may present unique liability issues for physicians compared to past medical technologies, although the project will seek to test this hypothesis. Reasons that PM may present unique liability dynamics include: (i) unlike other areas of medical practice where specialists with training and experience in the relevant specialty are applying a new technology or procedure, PM will involve the application of genetic information by physicians in virtually every type of practice, most of whom have no training or expertise in genetics; (ii) there are major uncertainties and disagreements within the medical and scientific communities about the appropriate use of personalized medicine tests at this time (Burke et al., 2010), and such uncertainty is known to be a major factor increasing liability risks (Craswell & Calfee, 1986); and (iii) the rapid pace of technology change in the personalized medicine results in constantly changing expectations and standards of care that can again greatly increase liability risk (SACGHS, 2008; Marchant et al., 2011).

In this present and unique environment, where much uncertainty exists about both the appropriate implementation of PM and the risks associated with implementing or not implementing specific PM methods, there is an important need for greater information and guidance on liability risks. Physicians, hospitals, malpractice insurers, and other PM stakeholders will be making important decision that are currently based on incomplete or inaccurate impressions of their liability risks. Moreover, once liability has been established and starts to snowball, it will be too late to take appropriate measures and safeguards to protect against liability. At this critical juncture in the rollout of PM, *before* widespread liability has taken hold, it would therefore be very

important and useful to comprehensively study and make widely available the best information and projections of the risks and relevant factors for liability relating to PM. Because both the likelihood and outcome of PM lawsuits will be highly fact- and evidence-dependent, it will be necessary to evaluate liability risks in the context of specific examples in which the applicable legal and evidentiary information is assessed and integrated. This attempt to predict the risks of PM liability, integrating both legal doctrine and factual evidence, will be the *second objective* of this proposal.

4. *Is Liability A Problem?*

The *third objective* of this project will be to anticipate the potential impacts, both beneficial and detrimental, of physician liability in the PM arena Personal injury liability, including liability for health care professionals, can serve an important social purpose to the extent that it induces actors to take appropriate actions to minimize unreasonable health risks (Gostin, 2000; Mello, 2006). If individuals are being harmed or denied the best health care because of the unreasonable failure of physicians to take full advantage of PM knowledge and technologies, the threat of liability can be an important driver for implementing sooner and more widely such beneficial personalized medicine technologies at the clinical level.

On the other hand, problems are created by the enormous, and inevitably growing, uncertainties about the liability risks relating to personalized medicine. This uncertainty is caused by a number of factors including the lack of existing legal precedents in this specific area, the diverse state laws for determining the applicable standard of care, the lack of authoritative standards for practicing personalized medicine, the divergent expert opinions about the feasibility and effectiveness of existing PM tests, and the uncertainty about how lay jurors will evaluate claims relating to genetic testing. These pervasive uncertainties about PM liability risks present several potential policy problems. First, physicians may engage in defensive medicine and over-utilize genetic testing in order to protect against liability. Defensive medicine is defined generally as a deviation from sound medical practice induced primarily by a threat of liability (OTA, 1994).

A physician may practice defensive medicine by performing extra tests or procedures to minimize potential liability, hoping that the additional testing will reduce adverse medical outcomes, deter patients from filing malpractice claims, and persuade the legal system that the appropriate standard of care was met. A number of studies have suggested that many physicians practice defensive medicine by ordering more diagnostic tests that would be warranted based on medical considerations alone (Studdert et al., 2005; Birbeck et al, 2004). Uncertainty about applicable legal standards tends to increase the practice of defensive medicine (Studdert et al., 2005; Fenn et al., 2004). The resulting unnecessary diagnostic tests impose a significant cost on the medical system. The practice of defensive medicine has already been observed in the context of prenatal genetic testing, for which some commentators have argued that legal standards have over-ridden medical judgment in determining when prenatal genetic tests are appropriate (Young, 2003; Howlett et al., 2002; Annas, 1985). In addition, the potential is there for some tests to do more harm than good. FVL is an example. Patients and physicians may be compelled to take action (anticoagulation) that will result in more overall harm (bleeding complications) than benefit (clots prevented) because of not understanding the nature of absolute risk versus relative risk.

In addition to creating pressures for practicing defensive medicine, the uncertainty about applicable liability standards relating to PM will have other adverse effects. For example, the lack of any agreed standards for ordering personalized medicine tests will results in different standards of care, with some physicians being more proactive on ordering such tests and others being slower to adopt these new tools. Patients may thus be provided with inconsistent care if decisions are being influenced by legal concerns on an ad hoc basis.

Given these potential counter-productive consequences from the uncertainties and risks of PM liability, it is not too early to begin considering policy options – at either the private or public levels – to address these problems. Even less work has been done on solutions to the liability problem for PM than has been devoted to identifying the risks of liability. The *fourth objective* of this project will be to identify potential policy initiatives to provide greater certainty to PM actors and thus to reduce liability risks and uncertainties. Almost no work has been done on liability prevention in the PM context to date, but some of the ideas that will be explored include better business models to integrate drugs and companion diagnostic tests, clinical guidelines that recommend best practices, better training of physicians and other health professionals, regulatory changes and other

possible solutions (Evans, 2007; Roth, 2007; Evans, 2006; Marchant et al., 2006).

Finally, there is an important need to educate affected stakeholders and policymakers about the potential risks and impacts of liability for PM. For example, physicians, PM policymakers, medical guidelines writers, regulators, and medical educators need to have realistic expectations about the potential for liability in this sphere as PM emerges as the dominant medical model of this century. Patients, the group who will potentially bring such lawsuits, and the stakeholders who could be most affected by both the beneficial and detrimental potential impacts of liability, need to be aware of liability issues and become proactive in the inevitable policy and legal battles relating to liability. Finally, the practitioners in the legal liability field, including lawyers, expert witnesses and judges, also would benefit from clear and informative information about liability. Thus, the *fifth objective* of the proposal will be to conduct outreach on the findings of this project to key stakeholder groups including physicians, patient groups and legal practitioners.

II. Innovation

Much research has been done on the scientific, medical, regulatory, economic, educational, intellectual property, ethical and public policy aspects of personalized medicine. In contrast, very little doctrinal, empirical or theoretical work has been done on the issue of liability in the PM field, notwithstanding frequent references to the importance of the issue for PM (e.g., SACGHS, 2008, p. 47; Sorrel, 2008, NRC, 2007). Only a handful of short, preliminary analyses emphasizing the potential importance of this subject have been published to date (Marchant, 2011; Roth, 2007; Marchant et al., 2006; Evans, 2007; Rothstein, 2005; Ossorio, 2001). The risks, relevant key factors, impacts, and possible solutions relating to potential PM liability are largely unknown and have been under-studied to date. There is much that could be done to provide beneficial further information, trends, predictions, and proposed policy interventions to address this largely uncharted subjected that is likely to play a critical role in the implementation of PM over the next decade. The knowledge generated by research on these issues would likely prove very useful in helping physicians, patient groups, legal practitioners and other various stakeholders in PM to make informed decisions relating to the risks and prevention of liability.

The present proposal therefore addresses a conspicuous gap in the knowledge base and available literature on PM. To fill this gap, it is important to not only have a good knowledge of law and legal research, but also of the scientific, medical, economic, and policy dimensions of PM, because these integrate with the law in understanding, predicting and preventing liability. In this proposal, we have attempted to address the need for such an integrated and inter-disciplinary approach in two innovative ways. First, the research team incorporates a broad range of relevant training, experience and expertise necessary to address the multi-dimensional and complex issues of PM liability. The PI (Gary Marchant) is trained as both a geneticist and lawyer, and has worked on liability issues relating to genetics for the past decade, including publishing numerous articles on such issues and serving as lead organizer of three previous conferences and workshops on genetics liability issues. Co-Investigator Doug Campos-Outcalt is a medical school professor involved in training future physicians and who has worked and written on physician uptake of PM genetic tests, and has served on the CDC's EGAPP (Evidence based Genomics Applied in Practice and Prevention) group evaluating the clinical readiness of PM tests. Co-Investigator Amalia Issa is a scientist whose work focuses on how PM applications will be translated and integrated into clinical practice, health care delivery and health systems, including studying physician and patient perspectives on PM uptake. Consultant Scott Ramsey is a physician and health economist whose work examines economic factors affecting clinical uptake of new medical technologies and procedures. Consultant Paul Wicks is Director of Research and Development at PatientsLikeMe and works on new approaches and models for patient participation and engagement in their own healthcare. Consultant Rachel Lindor is a lawyer currently completing her MD training at Mayo Medical School who has conducted research on medical liability and reimbursement issues relating to PM, including a poster presentation on liability issues relating to PM at this year's American Society for Clinical Oncology annual conference.

Second, we plan to directly engage key stakeholders in the project through our consultants and supporters on the project and using our extensive existing network of contacts in the PM field. The stakeholder engagement is discussed further in the Research Approach section (below).

III. Research Approach

This project will proceed in three steps, roughly segmented by the three years of the proposal. The first year will be devoted to identifying relevant legal doctrine, including potential claims, criteria, and defenses for the wide variety of liability lawsuits that might be anticipated against physicians related to PM lifecycle.. In the second year, we will assess the risk of liability for physicians relating to PM, by integrating the doctrinal analysis with the specific factual and evidentiary data for four PM case studies. We will also look to previous examples of physician liability relating to new medical technologies for relevant lessons and projections for PM. Finally, in the third year, we will address two objectives. First, we will investigate impacts of liability on physicians, patients and society more generally as well explore possible policy options for addressing the potential liability risks and uncertainties relating to PM. Second, we will adapt and customize our findings for relevant stakeholders groups and undertake outreach on our findings to those sectors, including physicians, patient groups, medical educators, and malpractice insurers.

Year One: Identifying Liability Claims and Doctrine

The first year will involve identifying and assessing the applicable legal claims and doctrines that may be applicable to PM lawsuits against physicians. As discussed above, the legal landscape applicable to such lawsuits has been undergoing significant change in recent years, with major potential implications for the chances of PM lawsuits against physicians being filed and succeeding. The first year of the project will be devoted to a comprehensive scoping of the legal landscape for PM liability of physicians. This work will include two lines of research.

The first line of research will be to identify, analyze and catalogue every reported case in the United States in which a physician was sued relating to PM or genetic testing in other medical contexts (e.g., prenatal genetic testing). We anticipate finding 100-200 relevant judicial decisions. For each case, we will identify the relevant legal claims brought against the physician, as well as the outcome of the case and the key factual evidence, expert opinions, reliance on authoritative statements or professional guidelines, defenses, or other factors that led to the outcome. In addition to looking at the reported decision, we will also review court filings and briefs and expert opinions filed in significant cases when accessible. From this data set, we will distill some overall findings as to the range and dimensions of possible legal claims that could be brought against physicians in the PM context and the key factors likely to determine the outcome of those claims based on the historical legal precedents. The list and characterization of cases will be posted on a public website created to communicate the results of this project.

The second line of research in year one will be to evaluate some of the key legal doctrinal issues that are likely to affect liability relating to PM. PM liability risks will be dependent on some key legal doctrines that are currently evolving and are in flux, including:

a. *Standard of care for medical malpractice:* Medical malpractice is based on whether a physician breached the applicable standard for care. As discussed in more detail above, the standard of care for physicians is currently undergoing significant change. The standard of care has traditionally been defined by custom in the locality in which the physician practices, but in many jurisdictions the standard has been evolving from a local to a national standard, and from a duty based on custom to a more objective standard. These and other changes in how the standard of care is defined are likely to have significant impacts on PM liability risks for physicians (Lewis et al., 2007; Marchant et al., 2006; Peters, 2000). Moreover, important legislative and policy initiatives relating to medical malpractice are being implemented or considered across the nation (Kachalia & Mello, 2011), and these too could significantly affect the prospects for PM physician liability.

b. *Learned intermediary doctrine* - The learned intermediary doctrine shifts responsibility (and associated liability) for failure to warn a patient from a drug or device manufacturer to the prescribing physician if the manufacturer included an appropriate warning in the product materials received by the physician (i.e., patient package insert for a pharmaceutical). The applicability and scope of this doctrine is currently being challenged, with two states (New Jersey and W. Virginia) recently deciding to no longer recognize the defense, a trend which if it continues could have major implications for PM liability

(Perez, 1999; Calabro, 2004).

c. *Role of clinical guidelines* – Various organizations have produced clinical guidelines to attempt to guide health care professionals to make appropriate clinical decisions. The role that such clinical guidelines should play in defining the standard of care in a medical malpractice case is still evolving. The role and weight that judges and juries extend to clinical guidelines in medical malpractice cases will potentially play an important role in determining PM liability risks (SCGHS, 2008; Evans, 2006).

d. *Loss of chance* – In most PM liability cases, a physician's negligence will not "cause" the plaintiff's injury, which will often be pre-existing to the doctor's treatment (e.g., cancer or cancer predisposition). Rather than causing the plaintiff's illness, the physician's actions may have reduced the probability that the plaintiff might have been successfully treated. Notwithstanding the lack of causation per se, courts have gradually permitted recovery for the "loss of a chance" of survival under certain circumstances (King 1981). The recognition and criteria for allowing a plaintiff to receive compensation for loss of chance have been evolving in recent years (Renehan, 2009), and the availability and scope of this cause of action will be critical to the viability of many potential PM lawsuits.

The shifting status, application and criteria for these important legal doctrines affecting potential PM lawsuits will be analyzed through a review of key court decisions and secondary materials. The results of this doctrinal analysis will be integrated with the case law analysis and will be published in one or more journal manuscripts prepared at the end of year one of the project.

Year Two: Evaluating PM Liability Risks

As discussed above, there has been no in-depth research or analysis on the level of risk that physicians are likely to face in the PM context – in terms of both the likelihood of facing a lawsuit and the probable outcome of such lawsuits. In the second year of the project, we will undertake two projects to help elucidate the risks of liability and the key factors influencing such risks. The first task will analyze previous lawsuits against physicians relating to their failure to use, premature use, or faulty use of new medical technologies. We will examine the results and important factors in individual lawsuits, as well as the dynamics of the litigation relating to that technology as a class. In reviewing individual cases, we will evaluate why physicians were held liable in some cases and not in others, discerning the key factors, evidence and legal rules that influenced the outcome. In looking at classes at cases, we will seek to understand the dynamics of the litigation, investigating such questions as; What was the time line of the cases? How did a positive or negative outcome for the plaintiff affect the rate of new cases against that same technology? Were the cases brought by the same plaintiffs' lawyers, or were there a variety of lawyers? These types of trends can help provide insights on the dynamics of litigation – for example, is there likely to be a steady trickle of such cases, or will the cases come in clusters or bursts of lawsuits?

In choosing and undertaking this analysis of other litigation against physicians for their utilization (or lack thereof) of new medical technologies, we will start our research with some major secondary sources on the issue of technology and medical malpractice litigation (e.g., Sage, 2003; De Ville, 1998) to help us identify the most promising and informative technology precedents to analyze in depth. We will then pick 3-5 medical technologies that have been the subject of significant litigation against physicians and collect and analyze the primary cases involving those technologies. The objective will be to draw lessons from these previous examples (recognizing and addressing the various ways that PM litigation may differ because of its uniqueness) about the risks and dynamics of such litigation. In addition to this broader question, this comparative and historical analysis will enable us to focus in on specific factors that might affect liability. For example, one question that will be pursued is what impact does decisions by CMS and private insurers to cover or not cover a specific technology or procedure affect the potential liability of physicians with respect to their use (or non-use) of that technology or procedure (the difficulty in obtaining reimbursement for many genetic tests currently is an important impediment to the uptake of PM by physicians). We will publish our findings on the more general trends as well as specific factors that can affect liability (e.g., insurance coverage) in an academic journal.

The second task will be to look at four case studies involving different uses of PM technologies to evaluate the

potential risks of physician liability. The risk of liability will depend in significant part on the factual and scientific evidence about the effectiveness, safety, clinical utility and cost of the specific tests that the plaintiff alleges the physician failed to use, used prematurely, or used incorrectly, combined with the applicable legal doctrines discussed above. Because liability risks will be fact- and context-specific, the risks can best be evaluated by using case studies to assess the potential for liability in specific contexts. We have identified the following four case studies to evaluate, each involving a different type of PM test:

a. *Warfarin (Coumadin)*: Warfarin is one of the most discussed drugs with respect to whether physicians should require a genetic test before prescribing the drug (Wadelius & Pirmohamed, 2007). Warfarin has a very narrow therapeutic index and the safe dose for an individual patient can vary based on a number of factors including polymorphisms in two genes (*CYP2C9* and *VKORC)*. If the initial dose is too high for the individual patient, a serious bleeding event can result. The FDA revised the label for warfarin in 2007 (and again in 2009) to give greater emphasis to the potential benefits of genetic testing for initial dose determination, and a number of experts and organizations (e.g., CMS, Mayo/Medco) have offered inconsistent opinions on whether genetic testing is warranted (Epstein et al., 2010; Lenzini et al. 2010; Kamali & Wynne, 2010; CMS, 2009; Roth, 2009). A number of other studies are underway, including randomized clinical trials, so the evidentiary support for genetic testing may change over time. The case for genetic testing prior to prescribing warfarin therefore remains uncertain and contested. This case study will evaluate whether a physician who fails to genetically test a patient prior to prescribing warfarin might be held liable if that patient suffers a serious or fatal reaction as a result of the failure to recommend genetic testing prior to initial dosing.

b. *Gene expression diagnostic tests* – A variety of diagnostic products using gene expression assays are available or being developed to profile tumors or infectious disease agents to predict prognosis or risk of recurrence. For example, the Oncotype Dx® diagnostic test used gene expression analysis to predict the risk of recurrence of breast cancer, which can then be used to make decisions about whether procedures such as chemotherapy are necessary (Snoo et al., 2009; EGAPP, 2009; Sotiriou & Pusztai, 2009). It is possible that a physician could be sued either for using the test prematurely (before its use had been validated) or for not using the test at all.

c. *BRCA testing* - Among the strongest and best validated disease predisposition genes are the *BRCA*1/2 genes for breast cancer, as women carrying a mutation in either of these genes have a 50-85 percent risk of breast or ovarian cancer (Robson & Offit, 2007). Interventions such as prophylactic bilateral radical mastectomies and oophorectomies have been shown to substantially reduce the risk of cancer in asymptomatic women carrying a *BRCA*1/2 mutation (Robson & Offit, 2007). Various expert evidentiary reviews have recommended genetic testing of women who have certain risk factors for carrying one of these mutations, such as having two first-degree female relatives who have developed breast cancer. A physician could potentially be sued if he or she sees an asymptomatic patient with a strong family history of breast cancer, but does not recommend the patient undergo genetic counseling or *BRCA* testing. If that patient subsequently develops breast cancer, she or her surviving family members could bring a lawsuit alleging that the physician breached a duty to warn her of her potential genetic risk, and the failure to recommend genetic testing resulted in the patient's "loss of chance" to have prevented or successfully treated the disease.

d. Whole Genome Sequencing: The final case study involves a very recent type of genetic testing that is only in early research stages at this time but could become part of clinical care relatively quickly in at least some practices. The potential for rapid adoption of whole genome sequencing may fuel a discrepancy in care that could leave slower adopter physicians and provider institutions at risk of liability. This technique is already being used in the research context, for example, to sequence the entire genome of a cancer patient's tumor and compare it to that same patient's inherited genome (Bonetta, 2010; Ormend, et al., 2007). Genetic changes revealed in tumors using this comparative approach could be used to identify otherwise unexpected treatment regimes that target the particular molecular identity of the tumor. Although this method has only been used in research studies on a relatively small number of patients to date, the results today are promising and have generated significant interest in the method. While the technique is too expensive and experimental to be used in routine cancer care now, leading institutions and physicians may adopt the technology on selected

patients in the relatively near future. As will be the case for any new, expensive, and highly technical new medical procedure, a gap is likely to quickly grow between those providers at the leading edge of technology and care, and those that lack the resources, expertise, and wherewithal to keep up with the leaders in the field or those physicians who are more cautious about adopting new technologies until they have a proven track record. Especially as more and more jurisdictions migrate to a national rather than local standard of care, this growing discrepancy between the leaders and the slow adopters creates an opening for litigation and liability (Lewis, et al., 2007).

Slow adopters of whole-genome sequencing and related genetic technologies may face liability risk in a number of different scenarios. For example, tissue from the tumor of a patient who succumbed to cancer at a local hospital may be sent to a leading laboratory conducting a cancer genetics research project, where it might be discovered that the tumor had a specific mutation that had been successfully targeted by therapies given to cancer patients at a different hospital, where their tumors had been analyzed using whole genome sequencing. In this situation, the family of the deceased patient may be able to bring a lawsuit alleging that the treating physician and hospital had failed to apply the appropriate standard of care in not conducting whole genome sequencing of their family member. Another possibility is that a family member of the deceased patient whose genome was sequenced may subsequently develop a cancer and allege that the physician should have identified a cancer-predisposing mutation in the deceased patient and warned other family members that they may carry the same risky mutation (Pate v. Threlkel, 1995; Safer v. Pack, 1996; Molloy v. Meier, 2004).

In evaluating these four case studies, we will seek to identify those legal or factual variables that increase or decrease the likelihood of liability, recognizing that the ultimate resolution of any individual case will likely be affected by the vagaries of the individual attorneys, experts, jury members and judge involved in that case. Thus, any absolute or certain prediction of risk is not possible. What will be possible, however, and will be the output of this project will be to identify fact patterns and variable that will make a physician's employment of a particular PM test or procedure more or less prone to liability, as well as some qualitative observations and predictions about the frequency and outcomes of such liability generally. We will summarize this analyze in a published manuscript. We will also post the four case studies and supporting materials on the public project website.

Year Three: Impacts, Solutions and Outreach

In the third year, we will wrap up the project by exploring the likely impacts on physicians and patients of the liabilities and liability risks identified and characterized in the first two years of the project as well as the broader societal implications of such liability, and also seek to identify possible policy interventions and other solutions that can help reduce uncertainties about the risks of liability relating to PM. We will also use the third year of our project to communicate the findings of our project to relevant stakeholders and other interested parties.

The potential impacts of liabilities and liability risks imposed on physicians will necessarily be conjectural during the course of this study, since we are anticipating liability trends for the next decade or so that will only be starting to occur during the course of this study. Nevertheless, examining previous legal precedents and economic studies of physician response to other sources of liability (e.g., defensive medicine), we will develop some possible projections of how physicians will be impacted by different liability scenarios and risks relating to PM. The other major stakeholder group we will examine the impact on is patients. As discussed above, physician liability relating to PM could have both positive and negative impacts (or both) on patients, potentially affecting the safety, availability and cost of PM tests. Again, this analysis will be somewhat conjectural, but will draw on extrapolations from legal and economic analyses of medical liability as they apply to patient well-being as well as the liability risk analyses from year two, to project potential outcomes both in terms of the health and welfare of individual patients as well as broader population and distributional justice impacts (Issa et al., 2009). We will publish our overall findings on the impacts of PM liability for physicians in a wrap-up paper co-authored by all the investigators and consultants that provides our best informed assessment based on the various study results about how such liability is expected to impact the uptake and development of PM, while also examining other broader questions such as the social justice implications relating to effects on access and availability of

PM by various affected sub-populations and longer-term impacts on innovation by manufacturers and test providers. This wrap-up paper will also summarize the lessons we can draw from PM liability for liability relating to other emerging medical technologies such as regenerative medicine, nanomedicine and human genetic engineering.

This liability impact analysis will then set up and feed into a study of potential policy solutions to address any negative impacts predicted from PM liability on physicians, patients or other stakeholders. Some of the policy solutions we will evaluate include greater use of and protection provided by clinical guidelines, better training of physicians and other health professionals, increased patient awareness and participation, regulatory and doctrinal change to malpractice standards or other applicable legal provisions, judicial and other courtroom reforms, and other possible solutions. There is almost no existing analysis of such policy responses to reduce liability relating to PM, so this analysis will be breaking new ground. The goals will be to identify and assess options that increase informed decision-making by participants in the medical and liability communities, including physicians, patients, judges and lawyers, as well as mechanisms for reducing uncertainties and providing greater predictability of expectations.

Relating to this emphasis, the final objective of our project will be to communicate the findings of our analysis and to provide guidance to relevant stakeholders, including particularly physicians and patients, and legal practitioners on how they might use our analysis to better understand how PM liability may affect them and how they might mitigate or prevent such impacts. We will communicate our results through three primary channels. First, our research, analysis and recommendations will be published in a series of academic articles as discussed above, with many of our detailed analyses and data sets posted on a publicly available project website to be hosted by the Sandra Day O'Connor College of Law. Second, we will produce and make available electronically 4-page briefing papers that summarize our analyses and distill the key findings, implications and recommendations of the project that are specifically adapted and focused on a key stakeholder for each briefing paper. We will produce one briefing paper for physicians, one for patients, and one for lawyers and judges.

Finally, we will conduct an outreach campaign with affected stakeholders to communicate our findings and recommendations to key stakeholders, including physician groups, patient groups, medical educators, and malpractice insurers. We have attached a letter of support from a representative organization from each of these stakeholder groups (see attached letters from Maricopa County Medical Society (physicians), PatientsLikeMe (patients), Mayo Medical School (medical educators), and the Mutual Insurance Company of Arizona (physician malpractice insurers)). Each of these organizations is interested in having us communicate the findings of our research to their organizations and members, and to assist us in our outreach to similar organizations across the country.

In conclusion, many studies and analyses have referred to the potential importance of liability to the roll-out and uptake of PM (e.g., SACGHS, 2008, p. 92; NRC, 2007). Yet, very little empirical, doctrinal or theoretic research has been conducted to date to explore the nature and likelihood of liability affecting PM. By focusing here on the liability of the physician, the most legally vulnerable player in the PM lifecycle and a key gatekeeper for the use of PM, we hope and expect to make an important contribution for policymakers, stakeholders and other interested parties concerned with the near-future development of PM.

Leadership Plan

PI Gary Marchant will have overall responsibility for the project. He and Co-Investigators Amalia Issa and Doug Campos-Outcalt will divide responsibility for the genetic case law and doctrinal analysis in year one (with research assistance from student workers), and the four PM case studies in year two. J.D./M.D. graduate student Rachel Lindor will undertake the historical analysis of physician liability from other technologies under the supervision of PI Marchant and in collaboration with Co-Investigator Issa and her research team. Co-Investigator Campos-Outcalt will focus his efforts in year two on the four case studies. All three primary investigators, along with consultants Ramsey and Wicks, will work together in year three for the impact analysis, development of potential policy solutions, and stakeholder outreach. All members of the research team will participate in periodic conference calls to discuss recent findings and their implications.

REFERENCES

Annas, G.J. (1985). Is a Genetic Screening Test Ready When the Lawyers Say It Is? *Hastings Center Report*, Dec. 1985, 16-18.

Birbeck, G. L., D. R. Gifford, J. Song, T. R. Belin, B. S. Mittman, and B. G. Vickrey. (2004). Do Malpractice Concerns, Payment Mechanisms, and Attitudes Influence Test-ordering Decisions? *Neurology* 62: 119-121.

Bointy-Tsotigh v. U.S., 953 F.Supp. 358 (1996).

Bonetta, L: (2010). Whole-genome sequencing breaks the cost barrier. *Cell* 141:917-919.

Burke, W., Laberge, AM, & Press N. (2010). Debating Clinical Utility. *Public Health Genomics* 13: 215-223.

Calabro S. (2004). Breaking the Shield of the Learned Intermediary Doctrine: Placing Blame Where It Belongs. *Cardozo Law Rev.* 25:2241-2316.

Cardone v. Gunsberger, Nassau Cty Supreme Ct., New York (2005).

Centers for Medicare & Medicaid Services (CMS) (2009). Decision Memo for Pharmacogenomic Testing for Warfarin Response (CAG-00400N).

Collins, F.C. (2010). Opportunities for Research and NIH. *Science* 327:36-37.

Craswell, R. & Calfee, J. (1986). Deterrence and Uncertain Legal Standards. *J. Law, Econ. & Org.* 2:279-303.

De Ville, K. (1998). Medical Malpractice in Twentieth Century United States: The Interaction of Technology, Law, and Culture. *Int. J. Technol. Assessment in Health Care* 14: 197-211.

Downey v. Dunnington, 895 N.E.2d 271 (2008).

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2009). Recommendations from the EGAPP Working Group: Can Tumor Gene Expression Profiling Improve Outcomes in Patients with Breast Cancer? *Genetics In Medicine* 11:66-73.

In Press

Evans, B.J. (2007). Finding a Liability-Free Space in which Personalized Medicine Can Bloom. *Clin. Pharmacol. Ther.* 82:461- 467.

Evans, B.J. (2006). What Will It Take to Reap the Clinical Benefits of Pharmacogenomics?, *Food & Drug Law J.* 61:753-794.

Fenn, P., Gray, A. & Rickman, N. (2004). *Liability, Insurance, and Defensive Medicine: New Evidence.* Department of Economics, University of Surrey: Discussion Papers in Economics. 0304: 1-40.

Flockhart D.A., Skaar T., Berlin D.S., Klein T.E., Nguyen A.T. (2009). Clinically Available Pharmacogenomics Tests. *Clin. Pharmacol. Ther.* 86:109-113.

Gallagher v. Duke University, 852 F.2d 773 (4th Cir. 1998).

Gostin, L. (2000) A Public Health Approach to Reducing Error: Medical Malpractice as a Barrier. *JAMA* 283: 1742-1743.

Gostin, L.O. & Jacobson, P.D. (2006). *Law and the Health System.* Foundation Press, NY, NY.

Granata v. Fruiterman, 668 S.E.2d 127 (2008).

Helling v. Carey, 83 Wash.2d 514 (Sup.Ct., 1974).

Howlett, M.J., Avard, D. & Knoppers, B.M. (2002). Physicians and Genetic Malpractice. *Med. Law* 21:661-680.

Issa, A.M. et al. (2009). Assessing Patient Readiness for the Clinical Adoption of Personalized Medicine. *Public Health Genomics* 12:163-169.

Kachalia, A. & Mello, M.M. (2011). New Directions in Medical Liability Reform. *New Engl. J. Med.* 364:1564-1572.

Kamali, F. & Wynne, H. (2010). Pharmacogenetics of Warfarin. *Annu. Rev. Med.* 61:63–75.

King, J. H. (1981). Causation, Valuation and Chance in Personal Injury Torts Involving Preexisting Injuries and Future Consequences, *Yale L.J.* 90:1353-1397.

Lenzini, P., et al. (2010). Integration of Genetic, Clinical, and INR Data to Refine Warfarin Dosing. *Clin. Pharm. & Therap.*87:572-578.

Lesko, L.J. (2007). Personalized Medicine: Elusive Dream or Imminent Reality? *Clin. Pharmacol. Ther.* 81:807-816.

Lesko LJ , Woodcock J. (2004). Translation of Pharmacogenomics and Pharmacogenetics: a Regulatory Perspective. *Nat Rev Drug Discov.* 3:763–769.

Lewis, MH, Gohagan, JK, Merenstein, DJ. (2007). The Locality Rule and the Physician's Dilemma: Local Medical Practices vs the National Standard of Care. *JAMA* 297:2633-2637.

Marchant GE, Milligan R.J., Wilhelmi B (2006). Legal Pressures and Incentives for Personalized Medicine. *Personalized Medicine* 3:391-397.

Marchant, G.E., Lindor, R.A., Campos-Outcalt, D.E. Physician Liability: The Next Big Thing for Personalized Medicine?, *Personalized Medicine* 8(5) (in press) (July 2011).

Mello, M. M. (2006). *Understanding Medical Malpractice Insurance: A Primer.* The Robert Wood Johnson Foundation Synthesis Project: New Insights from Research Results. Report No. 8, available at: http://www.rwjf.org/pr/synthesis/reports_and_briefs/pdf/no10_primer.pdf.

Molloy v. Meier,

National Research Council (2007). Application of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment. Washington, D.C.: National Academy Press.

Nebert, D.W., Vesell, E.S. (2004). Advances in Pharmacogenomics and Individualized Drug Therapy: Exciting Challenges that Lie Ahead. *Eur. J. Pharmacol.* 500:267-280.

Office of Technology Assessment (OTA) (1994). *Defensive Medicine and Medical Malpractice.* Washington, DC: U.S. Government Printing Office.

Ormond, K.E., *et al,* (2010). Challenges in the Clinical Application of Whole-Genome Sequencing. *Lancet* 375:1749-1751.

Ossorio, P.N. (2001). Product Liability for Predictive Genetic Tests. *Jurimetrics* 41:239-60.

Pate v. Threlkel, 661 So.2d 278 (1995).

Perez v. Wyeth Laboratories, Inc., 734 A.2d 1245 (N.J. 1999).

Personalized Medicine Coalition (2009). *The Case for Personalized Medicine*, available at http://www.personalizedmedicinecoalition.org/communications/TheCaseforPersonalizedMedicine_5_5_09.pdf.

Peters, P.G. (2000). The Quiet Demise of Deference to Custom: Malpractice Law at the Millennium, *Wash. & Lee L. Rev.* 57:163-205.

Renehan, J.F. (2009). A New Frontier: The Loss of Chance Doctrine in Medical Malpractice Cases, *Boston Bar Journal*, May/June, at 14-17.

Robson M. & Offit, K. (2007). Management of an Inherited Predisposition to Breast Cancer, *N Eng J Med* 357:154-162.

Roth M. (2007). Personalized Medicine: Using Effective Partnering for Managing the Risk of Legal Liability. *J. Personalized Medicine* 4:329-339.

Roth M. (2009). The Warfarin Revised Package Insert: Is the Information in the Label "Too Thin?" *Houston Journal for Health Law & Policy* 9:279-308.

Rothstein M.A. (2005). Liability Issues in Pharmacogenomics. *Louisiana Law Rev.* 66:117-124.

The Royal Society (2005). *Personalized Medicine: Hopes and Realities,* available at http://www.royalsoc.ac.uk/displaypagedoc.asp?id=23244.

Safer v. Pack, 677 A.2d 1188 (1996).

Sage, W.M. (2003). Medical Liability and Patient Safety. *Health Affairs* 22:26-36.

Secretary's Advisory Committee on Genetics, Health & Society (SACGHS) (2008). *Realizing the Potential of Pharmacogenomics: Opportunities and Challenges*, available at http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_PGx_report.pdf.

Snoo F.D., Bender R., Glas A., Rutgers E. (2009). Gene Expression Profiling: Decoding Breast Cancer, Surgical Oncology 18:366e378.

Sorrel, A.L. (2008). Judging Genetic Risks: Physicians Often Caught Between What Patients Want and What Science Offers, *AmMedNews*, Nov.10, 2008.

Sotiriou, C. & Pusztai, L. (2009). Gene-Expression Signatures in Breast Cancer. *N. Engl. J. Med.* 360:790-800

Studdert, D. M., M. M. Mello, W. M. Sage, C. M. DesRoches, J. Peugh, K. Zapert, and T. A. Brennan. (2005). Defensive Medicine Among High-Risk Specialist Physicians in a Volatile Malpractice Environment. *JAMA* 293: 2609-2617.

Wadelius, M. & Pirmohamed, M. (2007). Pharmacogenetics of Warfarin: Current Status and Future Challenges. *The Pharmacogenomics J.* 7:99-111

Young, W. (2003). Wrongful Birth and Life Suits hit Med-mal Nerve. *New Jersey Lawyer,* Apr. 28, 2003.

CONSORTIUM/CONTRACTUAL ARRANGEMENTS

This project involves three primary researchers: the Principal Investigator from Arizona State University's College of Law, one Co-Investigator from the University of the Sciences Health Policy and Public Health Department, and one Co-Investigator from the University of Arizona medical school. Each of the primary researchers brings a different type of expertise and experience to the project. The University of Sciences will receive $223,336 over three years for personnel costs. The University of Arizona will receive $81,434 over three years for personnel costs. ASU will act as the financial and administrative lead organization.

The appropriate programmatic and administrative personnel of each organization involved in this grant application are aware of the agency's consortium agreement policy and are prepared to establish the necessary inter-organizational agreement(s) consistent with that policy.

The following letter of support was included as part of the original application and is provided with the permission of Dr. Carland. An additional 5 letters were included in the original application but have been redacted to protect the privacy of individuals providing letters of support.

MICA

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February 22, 2011

c/o Gary E. Marchant, Ph.D. J.D
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Re: Application for grant support submitted by
Gary E. Marchant, Ph.D., J.D.

Dear Sir or Madam:

Mutual Insurance Company of Arizona (MICA) is a medical professional liability insurer in Arizona. We are a mutual company owned by our policyholders who comprise nearly three fourths of Arizona's physicians and a significant but substantially smaller percentage of Utah physicians. Formed in 1976 we have seen the increased benefits of medical technology *and* the enhanced liabilities.

New medical technologies create higher expectations for the outcome of medical care and treatment. Rapid adoption is often associated with unexpected adverse consequences (leading to claims of negligence) and delayed adoption is often associated with allegations of substandard care.

Personalized medicine holds promise of providing substantial benefit on a very broad scale. It will also raise significant ethical concerns, patient expectations, and training requirements for physicians and other health related professionals. Given the extensive application expected for personalized medicine, anticipating these issues and preparing for them is critical.

We are extremely interested in following the project Professor Marchant is proposing, and participating in the conference he proposes to organize. This project can serve a useful purpose to the extent it helps physicians and other health professionals anticipate and prevent future liability risks and exposure.

I urge funding support for this study.

Yours truly,

James F. Carland, M.D.

PHS 398 Checklist

OMB Number: 0925-0001

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

☐ New ☒ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

Federal Identifier: AG006145

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:
* First Name:
Middle Name:
* Last Name:
Suffix:

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ☐ No ☐

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes ☐ No ☐

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

5. * Disclosure Permission Statement

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes ☐ No