SUMMARY STATEMENT

(Privileged Communication)

Release Date: 10/19/2011

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Application Number: 1 R01 HG006145-01A1

Principal Investigator

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Applicant Organization: ARIZONA STATE UNIVERSITY-TEMPE CAMPUS

Review Group: SEIR
Societal and Ethical Issues in Research Study Section

Meeting Date: 10/06/2011
Council: JAN 2012
Requested Start: 04/01/2012

RFA/PA: PA10-067
PCC: X5JM

Project Title: Liability in the delivery of personalized medicine: driver, impediment, or both?

SRG Action: Priority Score | Percentile

Human Subjects: 10-No human subjects involved

Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Project Year	Direct Costs Requested
1	175,000
2	200,000
3	200,000
TOTAL	575,000

DC Recommended

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R01HG006145-01A1 Marchant, Gary

RESUME AND SUMMARY OF DISCUSSION: This project will evaluate how physician liability may affect the development of personalized medicine (PM). The project is significant as little is known about this area and the fears about liability may play a role in patient care. The investigator is outstanding and has gathered a highly qualified team for the project. After discussion, the reviewers agreed that a legal analyses is appropriate for the project. The research methods are appropriate and the choice of personalized medicine technologies are well justified. The investigators have been responsive to the previous critiques and have added patients to the study. However, there is some concern with the focus on physician liability versus other types of liability and this could have been better justified. Of concern to the reviewers is that the research plan is lacking detail, in particular there is no justification for the number of cases and it is not clear why whether the project will be able to identify the needed cases for the project. In addition, the application may be strengthened by providing greater details on the outreach campaign. The strengths outweigh the weaknesses in this significant project from an outstanding investigator.

DESCRIPTION (provided by applicant): 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, and 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.

CRITIQUE 1:

Significance: 2
Investigator(s): 2
Innovation: 3
Approach: 3
Environment: 3

Overall Impact: This study would provide an analysis of how physician liability might affect the development of personalized medicine in the United States. The question is important. The research methods are well conceived but inevitably entail speculation. The research team is strong. Whether the research can be successfully completed as described may depend in part on the number of cases involving judicial decisions that can be identified. Assuming that enough of these cases exist, which the researchers should be asked to demonstrate, the study is likely to be informative and to stimulate some productive debate.

1. Significance:

Strengths

- The question of how liability will affect the development of personalized medicine in the United States is an important question, and the proposed research will shed light on this matter.

Weaknesses

- The research is partly anticipatory in nature, so it will inevitably remain at least partially speculative.

2. Investigator(s):

Strengths

- Marchant is highly qualified to undertake this research.

Weaknesses

- None noted.

3. Innovation:

Strengths

- The topic of this study has not been sufficiently addressed.

Weaknesses

- The methods, such as doctrinal analysis, are tried and true, not novel.

4. Approach:

Strengths

- The research methods are appropriate for this kind of legal analysis.
- The focus on physicians as the actors most subject to liability in PM gives the project a sharp focus.
- The plan to review all existing judicial decisions in this domain will provide some empirical data that should be valuable for sharpening the anticipatory thrust of the work.
- The comparative and historical analysis against other cases of medical technologies that involved litigation against physicians adds considerable interest to this work, since it provides a better basis for extrapolating from extant cases and doctrine than one would get from a simple trend extrapolation.
- The choice of PM technologies (Warfarin, BRCA, gene expression assays, and whole genome sequencing) is nicely justified in the proposal.

Weaknesses

- An anticipatory project of this sort is inevitably speculative.
- The claim that physicians are the actors most vulnerable to liability is not tightly specified or supported with evidence or argument (does vulnerability here mean the likelihood of being sued, the financial exposure, the likelihood of having decision making affected by liability concerns, etc.?). Clearly test manufacturers, providers or hospitals and clinics, for example, may also face liability problems, so how is their risk being ranked? How might the degree of risk to different players depend on policies and guidelines?
- No basis is provided for the claim that the researchers expect to identify between 100-200 cases with judicial decisions concerning physician liability and PM. The advantages of the comparisons proposed will only be realized if actual cases can be identified, so the researchers should have provided information on this point.
- The investigators note that the impact analysis will be conjectural but a bit more on how these conjectures will developed would be helpful.

5. Environment:

Strengths

- ASU is a strong environment for studies of this type.

Weaknesses

- The research team is geographically dispersed and beyond saying that conference calls will be held the mode of coordination is not described.

Protections for Human Subjects:

- Not Applicable (No Human Subjects)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Significance: 1
Investigator(s): 2
Innovation: 2
Approach: 5
Environment: 1

Overall Impact: The issue of liability on the practice of personalized medicine (PM) needs to be addressed if PM is to flourish. The investigators are highly-qualified for the study. The principal investigator is a major expert on issues of liability in medicine. The team is weakened, however, by the lack of a credentialed expert in bioethics. The study is innovative because of some of the issues discussed, but many investigators have studied liability in general. As for its methodology, the study is more or less an enhanced literature search. The approach of the study is clearly laid out and the investigators have been very responsive to past criticisms. The issues to be studied are excellent. The review of 100-200 actual cases and four case studies will yield rich information about past, present, and future directions of liability law. The approached is weakened, however, by its lack of substantive ethics and its poorly-explained "outreach campaign." Arizona State University and the Mayo Clinic are fine environments for the study. The study, which is relatively strong, is somewhat weakened by its approach.

1. Significance:

Strengths

- Fears about liability in the practice of personalized medicine (PM) may play a major role in offering certain tests, treatments, and prescribed medicines to patients.
- The study promises to generate much-needed knowledge about the extent to which PM is being practiced. It also endeavors to develop tools that will help "liability" benefit rather than harm the field of PM. It would be most significant to have a positive rather than a negative view of liability in PM.

Weaknesses

- The methodology of the study is not new in that it is mostly an enhanced literature search.

2. Investigator(s):

Strengths

- The Principal Investigator is Executive Director of the Center for Law, Science and Innovation at Arizona State University (ASU). His publication and research is indeed on liability in personalized medicine. He is a *self-taught* ethicist.

- One of the co-Investigators from UCLA is an expert on decisionmaking in the context of genetic diagnosis.
- Doug Campos-Outcalt serves on the Evaluation of Genomic Applications in Practice and Prevention (EGAPP). His publications are in the area of personalized medicine.
- Scott David Ramsey has a PhD in health economics. He has been added to the team because of previous critiques that faulted the study for not including an economist.
- Paul Jon Wicks is director of research at PatientsLikeMe, a set of online communities of people with Parkinson's disease or ALS.
- Rachel Lindor has published with Gary Marchant.

Weaknesses

- There is no official bioethicist on the team.

3. Innovation:

Strengths

- More theoretical and empirical work needs to be done on the issue of liability in PM. This study will fill a gap in the literature.

Weaknesses

- It's not really a new methodology. Many investigators have done doctrinal analyses.

4. Approach:

Strengths

- The specific aims are clearly stated.
- The doctrinal issues to be discussed are excellent, especially because there is relative unfamiliarity with the learned intermediary doctrine.
- The review of 100-200 relevant judicial decisions will reveal current patterns in PM-liability cases.
- The investigators have been responsive to most of the criticisms expressed by a previous review panel; for example, they are now doing four case studies instead of two case studies and they have changed the membership of their team in a positive direction.
- Addition of patients to the study strengthens its approach.

Weaknesses

- There is much talk about the law and little substantive talk about ethics per se.
- Plans for the "outreach campaign" are not particularly detailed.
- The study is mainly a literature search.

5. Environment:

Strengths

- The Center for Law, Science & Innovation at Arizona State University is an excellent environment for this kind of study.
- Mayo Clinic Scottsdale is also a very good site for this study as is the University of the Sciences in Philadelphia is.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The investigators have been responsive to most of the past criticisms.

Budget and Period of Support:

Recommend as Requested

Recommended budget modifications or possible overlap identified:

- Budget is acceptable as stated.

CRITIQUE 3:

Significance: 2
Investigator(s): 1
Innovation: 3
Approach: 3
Environment: 1

Overall Impact: The focus on PM liability issues will rapidly emerge as potential results of advances in PM. The PI has responded to the previous review. He is an outstanding qualified investigator as are the resources at ASU to support the study. The methods are not innovative and the focus predominantly on physicians is a weakness. But the study is a highly significant one.

1. Significance:

Strengths

- Liability issues will likely arise as a result of the advancement of personalized medicine. This proposed research is of great significance.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- Dr. Marchant is well recognized and outstanding investigator. He is Executive Director of the Center for Law, Science and Innovation at ASU, which is the oldest law-science center in the nation with 25 faculties.
- Dr. Issa is director of the Program in Personalized Medicine & Targeted Therapeutics and a well recognized investigator.
- The entire team is outstanding.

Weaknesses

- None noted.

3. Innovation:

Strengths

- The topic addresses an emerging issue associated with the advancement of personalized medicine.

Weaknesses

- Methods are not innovative.

4. Approach:

Strengths

- The methods are divided over three years of the project: Year One: Identifying Liability Claims and Doctrine; has two lines of investigation: a) 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). They anticipate finding 100-200 relevant judicial decisions. B) 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 b) Learned intermediary doctrine; and c) Role of clinical guidelines;

d) Loss of chance Year Two: Evaluating PM Liability Risks and Year Three: Impacts, Solutions and Outreach

Weaknesses

- The research plan is absent of detail. Organization of the description is cumbersome.
- The focus on physicians predominantly is a weakness.

5. Environment:

Strengths

- Outstanding institutional resources at ASU.

Weaknesses

- None noted.

Protections for Human Subjects:

Not Applicable (No Human Subjects)

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- PI addresses many of the weaknesses expressed in the previous review.

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html.
The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.