SUMMARY STATEMENT

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(Privileged Communication)

Release Date: **03/08/2012**

Application Number: **1 R01 HG006460-01A1**

Principal Investigators (Listed Alphabetically):
KAUFMAN, DAVID J PHD (Contact)
MCGUIRE, AMY LYNN JD, PHD

Applicant Organization: JOHNS HOPKINS UNIVERSITY

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

Meeting Date: **02/28/2012**
Council: **MAY 2012**
Requested Start: **07/01/2012**

RFA/PA: **PA11-250**
PCC: **X5JM**

Project Title: **Clinical Integration of Whole Genome Sequencing: A Policy Analysis**

SRG Action: Priority Score | Percentile

Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 3A-No children included, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested
1	376,733
2	399,028
3	464,674
TOTAL	1,240,435

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.

1R01HG006460-01A1 Kaufman, David

RESUME AND SUMMARY OF DISCUSSION: This project will evaluate the regulatory structure for whole genome sequencing (WGS) and will provide policy recommendations for how to translate this information into clinical practice. The project is significant because it will provide new insight into the genome industry and will provide policy recommendations for clinical use of WGS. The investigators are outstanding and have gathered a strong team with relevant expertise. However, there are some weaknesses in the application. The project did not provide a rationale for the three domains to be evaluated. The application indicates that the Delphi method has been modified, but it is not clear how it has been modified. The application is not clear on how the project will integrate the input from experts and stakeholders with the investigators' input; it is not clear if there is a normative analysis. In addition, some key constituents do not appear to have agreed to participate and the composition of the 40 Delphi stakeholders is not clear. The weaknesses detract from the strengths in this potentially significant project from an outstanding research team.

DESCRIPTION (provided by applicant): Innovations in next-generation DNA sequencing technologies, accompanied by exponential drops in cost, have made it possible for clinicians to begin to use whole genome sequencing (WGS) to diagnose, treat, and predict disease. The extent to which WGS will improve health outcomes on a population level, however, will depend on effective oversight of its commercialization and use. The regulations that currently guide the administration of single-gene tests were not designed to address the tsunami of genomic information generated by WGS, and the uncertainties related to its interpretation, clinical utility, and potential indications. New policy approaches may be required to establish a system that guarantees appropriate, broad access to high-quality sequence data and valid reports while encouraging innovation. The proposed research study, which responds directly to the program announcement PA-11-250, will begin to systematically prioritize and address the unique policy challenges involved in translating WGS into health benefits in the United States. This study will identify, prioritize and begin to address some of these policy questions using a modified Delphi process that iteratively engages a diverse group of stakeholders. An initial landscape analysis of the current and emerging WGS industry, enhanced by interviews with industry leaders about the future of clinical WGS, will serve as the basis for understanding how WGS fits into-and how it may disrupt-the current regulatory framework. This analysis will inform the drafting of an initial list of policy questions. A panel of 40 key stakeholders, drawn from the genomics industry, clinical laboratories, insurers, health care systems, providers and patient groups, will then be iteratively surveyed to add to and refine this list, and to prioritize the resulting issues by importance and tractability. Policy approaches to address three high-priority issues related to test quality and validity, insurance reimbursement, and intellectual property will then be developed. Through another series of stakeholder surveys, the research team will collect, refine and evaluate ideas which will be discussed by the stakeholder panel at an in-person meeting to identify areas of agreement and reasons for disagreement. Findings will be distributed to stakeholder and policy communities in concise, accessible formats with the goal of informing policy development. Policy briefings and follow-up meetings with select federal officials, Congressional members and staff will be used to begin focused dialogues on clinical WGS. This project will be among the first to use a collaborative, systematic approach to inform stakeholders and U.S. policymakers about policy priorities surrounding the newest generation of health care genomics. Importantly, it will result in concrete, pragmatic policy approaches developed by a diverse group of experts.

PUBLIC HEALTH RELEVANCE: Patients will soon be able to learn the sequence of their entire genome-all of the DNA they inherited-and share it with health care professionals to help prevent, diagnose, and select treatments for diseases. The laws that ensure that the public has access to high-quality genetic tests were crafted before sequencing the genome was possible. This study will begin to

develop a system of rules to make sure that (1) the new DNA tests are reliable and explanations of the results are accurate, (2) that people have access to these tests through the healthcare system, and (3) that new innovation in the area is rewarded without sacrificing quality or access.

CRITIQUE 1:

Significance: 3
Investigator(s): 1
Innovation: 4
Approach: 4
Environment: 1

Overall Impact: The project's strengths are that it will provide a comprehensive picture of the WGS industry and the industry's projections for the future; identify three high-priority policy issues, one each in the areas of test quality and validity, third-party payment, and intellectual property; determine the policy responses of a group of relevant stakeholders; and disseminate the results to policy-makers. The investigators have responded to the previous reviewers' comments by expanding their industry inquiries to elicit future plans and obtaining commitments to participate from 7 WGS companies and 2 professional groups; by replacing a roundtable model with a Delphi survey process; by proposing to examine industry and professional guidelines as well as statutes and regulations; and by limiting the scope of their policy inquiry to three issues. The application is weakened, however, by the lack of information about how and to what extent the investigators will perform their own policy analyses. The application states merely that the results of the expert survey will be "analyzed" (p. 104); that the study team "will use our knowledge of current standards and policy" as well as the expert survey to "develop a preliminary list of novel policy questions" (p. 109); that the investigators in each of the three broad policy areas will prepare "an initial evaluation" of existing laws, regulations, and industry and professional standards (p. 110); that the team will "outline its own policy approaches" (p. 110); and that "the development of policy approaches" will be primarily Dr. McGuire's responsibility (p. 113). The timeline includes approximately 6 months of time for "staff policy analyses" (112). In addition, the application states that the team will prepare "arguments supporting" each policy response (p. 110), but it is not clear if the arguments will be supplied by the investigators, the experts who were surveyed, or both. All of this calls into question the proposed methodology. How will the project integrate the external policy input from experts and stakeholders with the investigators' internal policy analyses and deliberations? Will the external views merely be used to inform the investigators' own policy analyses and recommendations, or vice versa? When and on what basis, for example, would the investigators' "policy approaches" trump those proffered by the respondents? How will the investigators use their "knowledge of current standards and policy"? Will the investigators evaluate and critique the various policy responses, and if so, according to what norms and in pursuit of what objectives? In short, it is impossible to determine if the project will have a normative dimension, or will instead consist basically of collecting and taking external votes on a series of externally-produced policy options. There is nothing wrong with merely doing the latter, but it is a far less ambitious project than the investigators seem to contemplate and would justify far less effort and resources.

1. Significance:

Strengths

- WGS is growing, and there is a need for greater exploration of policy issues that it raises.

- The project will provide a comprehensive picture of the WGS industry and the industry's projections for the future.
- The project will identify three high-priority policy issues, one each in the areas of test quality and validity, third-party payment, and intellectual property.
- The project will determine the policy responses of a group of relevant stakeholders; and disseminate the results to policy-makers.

Weaknesses

- The application does not adequately explain how the project will correlate the investigators' views, knowledge, and analyses with the input from external sources.

2. Investigator(s):

Strengths

- The investigators are highly expert and represent a broad range of relevant expertise.
- The investigators have an impressive record of engaging policy-makers.
- The investigators have assembled a prominent group of outside advisors.

Weaknesses

- None.

3. Innovation:

Strengths

- The project will provide new insights into the WGS industry and its plans for the future.

Weaknesses

- The methodology, although sophisticated, is not novel.

4. Approach:

Strengths

- The investigators will gather data on the WGS industry and on the views of a diverse group of experts.
- The investigators will use direct research methods to obtain industry data and aseries of Delphi rounds to elicit expert opinion.

Weaknesses

- There is inadequate description about how and to what extent the investigators will perform their own policy analyses, and how they will coordinate their views and analyses with those of outside experts.

5. Environment:

Strengths

- The multiple study sites are institutions of research renown.

Weaknesses

- None.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- The application states that the survey responses will not be personally identified, but it is hard to see how this can be accomplished.

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

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C3A - No Children Included, Acceptable

- There is no targeted enrollment plan.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The investigators adequately responded to the comments by the previous reviewers.

Applications from Foreign Organizations:

Not Applicable (No Foreign Organizations)

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Unacceptable

- There is no plan.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

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

Overall Impact:

Whole Genome Sequencing (WGS) will provide people with often overwhelming information about their genetic status and, in many instances, health status and risks. Therefore, it is very important that we develop an adequate regulatory framework to beneficially integrate WGS into clinical practice and to monitor its industrial development and dissemination. The Investigators for the study are an excellent team for WGS research. Dr. David Kaufman and Dr. Amy McGuire combine significant expertise in genetic science, law, policy and bioethics. Dr. Gail Javitt is well-versed on FDA law and CMS/CLIA regulation of the quality and utility of genetic testing. The other members of the team are nationally-recognized legal and public policy experts. Although the overall methodology of the study is not novel, it is refreshing to see scientists and policy makers in continuous dialogue throughout the study. The role of the Advisory Board, which is now enhanced by representatives with business, industry, and economic experience, is clearly delineated. The approach of the study is much improved over the first submission. The troublesome roundtables, which did not secure sufficient confidentiality, have been replaced by a 40 person stakeholder panel which will help to generate policy ideas through "anonymous brainstorming," comment, and critique. The stakeholders will know who is on the panel but not who is saying what. At the end of the study, the panel will meet with the Investigators to fine-tune the products of the study. The three academic centers involved in the study—Duke University, Baylor University, and Johns Hopkins University—all have the capacity and willingness to support the study. The study is likely to have high impact. It is an example of policy working together with, instead of behind, technology (WGS).

1. Significance:

Strengths

- Whole Genome Sequencing (WGS) is making the transition from research to clinical practice and industrial commercialization very rapidly. Provided it is equitably accessible and judiciously used by clinicians, WGS will give people great knowledge about their genetic status and, in many instances, health status and risks. Therefore, it is very important that we develop an adequate regulatory framework to beneficially integrate WGS into clinical practice and to monitor its industrial development and dissemination.

Weaknesses

- None discerned.

2. Investigator(s):

Strengths

- The co-Principal Investigators, Dr. David Kaufman and Dr. Amy McGuire, combine significant expertise in genetic science, law, policy, and bioethics. Dr. Gail Javitt is well-versed on FDA law and CMS/CLIA regulation of the quality and utility of genetic testing. The other members of the team are nationally-recognized legal and public policy experts. The team as a whole is focusing

on three domains of WGS: oversight of test quality and services; patenting and licensing issues; and the coverage and reimbursement of WGS.

- The role of the Advisory Board, which is now enhanced by representatives with business, industry, and economics experience, is clearly delineated.

Weaknesses

- None discerned.

3. Innovation:

Strengths

- The Investigators will be in frequent contact with policymakers and industrial leaders. Science will be put into continuous dialogue with society.

Weaknesses

- The methodology is tried and true, but not novel.

4. Approach:

Strengths

- Most of the team have worked together before and are ready to go on this ambitious study.
- The aims of the study are clearly articulated and build upon each other systematically.
- The troublesome roundtables, which did not secure sufficient confidentiality, have been replaced by a 40 person stakeholder panel which will help to generate policy ideas through "anonymous brainstorming," comment, and critique. The stakeholders will know who is on the panel but not who is saying what. At the end of the study, the panel will meet with the Investigators to fine-tune the products of the study.
- The Investigators are now focusing on only three areas of WGS: namely, test quality and validity; insurance reimbursement; and intellectual propriety. Previously, their approach lacked this level of focus.
- Letters of support are complete and strong.

Weaknesses

- Inclusiveness could be better achieved by over selecting Delphi panelists for whatever gender, race, and ethnicity is underrepresented.
- The specifics of the modified Delphi approach are not provided. More clarity is in order.

5. Environment:

Strengths

- The three academic centers involved in the study—Duke University, Baylor University, and Johns Hopkins University—all have the capacity and willingness to support the study. The project center will be at the well-regarded Genetics and Public Policy Center at Johns Hopkins.

Weaknesses

- None discerned.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- The Investigators have taken appropriate measures to achieve confidentiality.

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

C3A - No Children Included, Acceptable

- Inclusiveness could be better achieved by inviting more Delphi panelists than are needed and then over selecting for whatever gender, race, and ethnicity is underrepresented. Children are appropriately excluded from the study.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The Investigators have been very responsive to the previous review panel.

Applications from Foreign Organizations:

Not Applicable (No Foreign Organizations)

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

Recommended budget modifications or possible overlap identified:

- Budget is fine as is.

CRITIQUE 3:

Significance: 2
Investigator(s): 2
Innovation: 2
Approach: 4
Environment: 2

Overall Impact: This is an interesting proposal on an important emerging topic – regulatory and policy approaches to the clinical use of Whole Genome Sequencing (WGS). The investigators (including PIs at JHU and Baylor) as well as co-investigators at Duke University and the Center for Medical Technology Policy) are multidisciplinary and highly qualified. The investigators and their institutions have outstanding track records on related topics and the environment is excellent. The investigators appear to have responded to previous critiques in a number of ways – including adding appropriate expertise in economics, business, and regulatory affairs to the advisory group, demonstrating agreements to participate by WGS industry stakeholders, inclusion of professional organizations, restricting the breadth of policies to the three domains described, and expanding on the methods. There are limitations to the approach selected. These include that, in the landscape assessment, the method for analysis is not clear. Notably, in the major part of the project (Aim 2), the pros and cons of the Delphi approach are not addressed, alternative methods are not described, the method for ultimately choosing the top questions in each of the 3 domains and the top policy approaches is unclear, the product of the in-person meeting (vis-à-vis the results of the on-line Delphi results) is unclear. In addition, the rationale for focus on the three domains selected in unclear (and it is interesting that clinical use and ethical issues in such use was not selected). Although the dissemination plan is good, it is not clear who/which groups are planning to use the results of the study in future policy or if relevant groups accept the methodology as a basis for their future consideration of policy changes. Although the investigators are outstanding, it is not clear how they are organized (the proposal does state that the MPIs will speak weekly but the organizational structure for the others and the group as a whole is unclear. Although the investigators are extremely experienced in related questions and techniques, there are no preliminary data regarding the landscape, draft surveys or materials directly applicable to this proposal, and key constituencies planned for the Delphi group (e.g. FDA, FTA, CDC) do not appear to have agreed yet to join; such data would strengthen the feasibility of the proposal. Therefore, the project has substantial potential to exert a sustained influence on the field of WGS and its use, yet specific gaps in methodology detract somewhat from the potential influence.

1. Significance:

Strengths

- Significance is outstanding as the proposal addresses an emerging important issue and convincingly presents this relevance and timely nature of the topic

Weaknesses

- The investigators apparently narrowed the scope (at reviewers' suggestion) and now propose focus on three domains: oversight of test services and quality, patenting and licensing issues, and coverage and reimbursement. While each is important, the rationale for selecting this focus (as opposed to, for example, clinical use and ethical issues) is not clear.

2. Investigator(s):

Strengths

- Exceptionally strong multidisciplinary investigative team

Weaknesses

- Organization of team at 4 sites is unclear. A more minor point: exact roles of some team members unclear.

3. Innovation:

Strengths

- The innovation is primarily in identification and comprehensive focus on an important emerging topic, the use of a multidisciplinary team to address these issues
- The plans for direct dissemination to the policy community (including a communications firm well acquainted with DC and Congress) are innovative.

Weaknesses

- The Delphi approach is applicable but not particularly innovative

4. Approach:

Strengths

- This is a descriptive study and, given the dearth of data on the topic, a descriptive approach is reasonable. The investigators have responded to the reviewers' comments by narrowing the scope of issues to be addressed. They have added a semi-quantitative Delphi approach. The dissemination plan has good potential.

Weaknesses

- As noted above, rationale for selection of the three domains under study is not clear.
- The landscape analysis focuses on the industry only; it does not address regulatory or clinical issues that are likely relevant, the selection of people to be interviewed are unclear ("industry leaders" p 107), and the method for analysis is not clear.
- Regarding aim 2 (Delphi approach to identify and prioritize novel policy questions and approaches), (a) the rationale for the Delphi approach and its pros/cons vis-à-vis other methods is not addressed, (b) the specific modifications of the "modified" Delphi approach planned are not clear, (c) it is not clear roughly how many questions in each domain are sought (and therefore how realistic it will be to address them well), and how they will be selected (the top scores on Likert scales in terms of importance vs. feasibility vs. composite scores? Judgment of investigative team combined with scores?), (d) since the Delphi process does not appear to run until consensus is reached (p 108), it is again not clear how final decisions are made, (e) methods for on-line surveys are not stated, (f) the selection of stakeholders to be in the Delphi group will be critical determinant of the results.
- The proposal would be improved by indicating what proportion of the 40 Delphi stakeholders will be from industry, government (7), patients, clinicians, etc. Now, the proposal lists over 25 types of stakeholders (p 104) in a panel of 40, and so it is not clear what the composition would actually be and what it would actually represent in a meaningful way.
- Methods to assess process or outcome measures re effectiveness of aim 3 are not clear.

5. Environment:

Strengths

- Each participating organization (4) is very strong and it appears that the environment is highly conducive to success.

Weaknesses

- The project team's organization and communication strategy across four sites is unclear.

Protections for Human Subjects:

- IRB does not appear to be mentioned

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

C3A - No Children Included, Acceptable

- satisfactory

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- The Introduction indicates that the investigators have made substantial changes in response to the previous review.

Applications from Foreign Organizations:

Not Applicable (No Foreign Organizations)

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

- Clarification of exact roles of all staff and rationale for their effort would be helpful

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:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

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.