PI: **Kaufman, David J**	Title: Clinical Integration of Whole Genome Sequencing: A Policy Analysis	
Received: 11/04/2011	FOA: PA11-250	Council: 05/2012
Competition ID: ADOBE-FORMS-B1	FOA Title: ETHICAL LEGAL AND SOCIAL IMPLICATIONS (ELSI) OF GENOMIC RESEARCH REGULAR RESEARCH PROGRAM (R01)	
1 **R01 HG006460-01A1**	Dual:	Accession Number: 3439232
IPF: 4134401	Organization: JOHNS HOPKINS UNIVERSITY	
Former Number:	Department: BIOETHICS INSTITUTE	
IRG/SRG: SEIR	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 376,733 Year 2: 399,028 Year 3: 464,674	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
David Kaufman	Johns Hopkins University	PD/PI
Juli Bollinger	Johns Hopkins University	Other (Specify)-Project Director
Rachel Dvoskin	Johns Hopkins University	Other (Specify)-Co-Investigator
Gail Javitt	Johns Hopkins University	Other (Specify)-Co-Investigator
Patricia Deverka	Center for Medical Technology Policy	Other (Specify)-Co-Investigator
Sean Tunis	Center for Medical Technology Policy	Other (Specify)-Co-Investigator
Robert Cook-Deegan	DUKE UNIV	Other (Specify)-Co-Investigator
Subhashini Chandrasekharan	DUKE UNIV	Other (Specify)-Co-Investigator
Donna Messner	Center for Medical Technology Policy	Other (Specify)-Co-Investigator
Amy McGuire	BAYLOR COL OF MEDICINE	MPI

Appendices

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Appendix

Number of Attachments in Appendix: 1

Project Summary

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.

Project Narrative

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.

Facilities and Other Resources

Offices: Faculty and staff have fully equipped offices provided by The Johns Hopkins University, Baylor University, Duke University, and the Center for Medical Technology Policy. All offices provide high-speed internet connections that will enable internet-based video teleconferencing. Investigators and staff in all locations have access to key internet-based search engines including Lexis-Nexis and PubMed. The offices at the Genetics and Public Policy Center in Washington, DC house conference facilities available to the Center for project meetings.

Computers: All of the key investigators and staff have, or have been budgeted to receive powerful desktop/laptop computers that are within two years old. All of these machines, in both locations are secured behind firewalls that allow only encrypted communication from the external network (using SSH). All user accounts are password-restricted with strong password policies. Computers at all facilities are backed up daily via private networks to protect against loss of data.

Scientific Environment

This project will take place at three academic centers (Duke University, in Durham NC, Baylor University in Houston, TX, and Johns Hopkins University in Washington, DC) and the Center for Medical Technology Policy, a private non-profit located in Baltimore. The project center will be the Genetics and Public Policy Center (GPPC), at the Johns Hopkins campus in downtown Washington, DC. GPPC is part of the Berman Institute of Bioethics, a Johns Hopkins entity comprised of a large, interdisciplinary faculty from the Schools of Medicine, Nursing, Public Health, and Arts & Sciences. As a policy grant that will directly engage federal policymakers and disseminate work back to them, the central location in Washington will be especially useful. It will allow the project to plan, hold, and attend relevant policy meetings and discussions and will facilitate plans for dissemination of the study findings.

Duke University

BUDGET JUSTIFICATION

Personnel

Robert Cook-Deegan, MD (Project PI, EFFORT months) - Dr. Cook-Deegan is Director of Genome Ethics, Law and Policy at Duke University's Institute for Genome Sciences and Policy, with appointments as a Research Professor in Duke's Sanford School of Public Policy and Departments of Biology (Arts and Sciences) and General Internal Medicine (Duke School of Medicine). He is overall PI for a P50 CEER grant for the Duke Center for Public Genomics, and PI within that CEER grant for a project on "DNA Sequencing: Technology history, sharing practices, and applications to medicine and personal genomics." He will work closely with Dr. Chandrasekharan, in conjunction with the other investigators, to address the research components that address intellectual property, and will assist the principal investigators in conceiving the plans for policy engagement. As PI for this project, he will ensure that the research objectives of the project are met.

Subhashini Chandrasekharan, PhD (Co-Investigator, EFFORT months) - Dr. Chandrasekharan is a Senior Research Associate in the Institute for Genome Sciences and Policy. With a PhD in Genetics and Molecular Biology and research background in mouse transgenics, she shifted her focus to the study of intellectual property and innovation in applications of genomics when she joined the CEER-funded Duke Center for Public Genomics as a postdoc in 2006. She is PI of an R03 grant to study the impact of intellectual property on DNA diagnostics for multi-allele genotyping and gene expression analysis. She will work with Dr. Cook-Deegan and the other investigators to address the research questions about implications of existing patent claims for integration of full-genome sequence analysis into clinical care.

The salary rate budgeted for Dr. Chandrasekharan assumes a potential 3% annual increase, effective July 1, 2012, and years following. Dr. Cook-Deegan's salary is budgetd at the Institutional Base Salary current at the time of this submission.

Fringe benefit rates are budgeted at the Duke University rate for monthly faculty/staff projected at the time of this budget submission: FY13- 25.2%; FY14- 24.6%; FY15- 24.6%.

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Grant years are the same as Duke's July 1-June 30 fiscal year.

Indirect (F&A) costs are budgeted at the currently negotiated rate of 57%.

Center for Medical Technology Policy

Budget Justification

PERSONNEL

Sean Tunis, MD, MSc, Investigator EFFORT **Year 1,** EFFORT **year 2 and** EFFORT **year 3).** Building on his past experiences as the Chief Medical Officer at CMS and 20 years of professional experience with various aspects of health technology assessment, he will review the landscape analysis and frame the reimbursement policy issues in Year 1. In Years 1 and 2, Dr. Tunis will participate as a consultant in the various stakeholder engagement activities, facilitate the summit meeting and will help to co-author the white paper on policy approaches to address reimbursement challenges. In Year 3, he will participate in policy briefings with key stakeholders and policymakers. Dr. Tunis' input will be critical to ensuring that the reimbursement options are specific and actionable.

Patricia Deverka, MD, MS, MBE, Co-Investigator EFFORT **year 1,** EFFORT **year 2** EFFORT **in year 3).** In Year 1 she will review the output of the landscape analysis to help identify novel policy approaches for addressing reimbursement barriers for WGS test. Working as a Senior Research Director at the Center for Medical Technology Policy, she brings extensive experience regarding effective methods for engaging a broad range of stakeholders in health care research and applied policy projects. In Years 1 and 2 she will identify key stakeholders, consult on the modified Delphi process to develop potential policy approaches and work with other members of the research team to facilitate the summit meeting. She will lead the development of a white paper on policy approaches to address reimbursement challenges for WGS tests in Year 2 that will be submitted in a format suitable for peer-reviewed publication in Year 3. In Year 3 she will help to develop a webinar to disseminate the project results and participate in policy briefings as required.

Donna Messner, PhD, Co-Investigator EFFORT **year** EFFORT **years 2 and 3).** She is currently Senior Project Manager at the Center for Medical Technology Policy (CMTP) and has extensive experience in qualitative social research design and implementation, as well as research experience in federal regulation and policy related to genetic testing. She will assist in review of the landscape analysis and developing novel policy approaches in Year 1. In Year 2, she will collaborate on the design of the Delphi process and analysis of the resulting data. She will also assist in the development of the policy white paper on policy approaches to reimbursement challenges. In Year 3, she will assist in planning, developing content, and hosting a webinar as part of the dissemination activities. She will also participate in developing a peer-reviewed journal publication based on the previously completed white paper.

TBD, Research Associate EFFORT **year 1** EFFORT **year 2,** EFFORT **year 3).** The Research Associate will perform background literature reviews, assist with developing an interview strategy and plan, provide support services in the field, including recording interviews, detailed note-taking, creating a condensed set of summary notes with key points from each interview, archival and management of digital interview files, and will assist with data analysis and report preparation. CMTP's research associates are highly qualified, typically holding master's degrees in public health, epidemiology, health sciences, or other relevant fields.

SUPPLIES

Funds are requested in the amount of $900 in years 1& 2 and $883 in year 3 for project specific office and computer supplies and other expenses including but not limited to: ADP/computer

services, long distance calls/conference calls/fax, project specific photocopying, express mail/postage, and other miscellaneous supplies related to achieving the goals of the project.

TRAVEL

$1,000 is requested for travel in years 1 through 3 to cover the costs of project travel.

OTHER EXPENSES

$800 is requested for meeting related expenses in Years 1 & 2.

INDIRECT COSTS

Funds are requested in years 1 through 3 for indirect costs calculated on total direct costs at a rate of 44%. This rate has been negotiated between CMTP and the Department of Health and Human Services (DHHS) Division of Cost Allocation. The Agency contact name is Darryl Mayes (representative is Andrew Lee), phone 301-492-4855.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

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

2. Human Subjects

Clinical Trial? ☒ No ☐ Yes

* Agency-Defined Phase III Clinical Trial? ☐ No ☐ Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix:
* First Name: Alison
Middle Name: Boublitz
* Last Name: Wampler
Suffix:

* Phone Number: 4105165281 Fax Number: 4105167775
Email: awampler@johnshopkins.edu

* Title: Contracts Associate

* Street1: 3400 N Charles St
Street2: Wyman Park W400
* City: Baltimore
County/Parish:
* State: MD: Maryland
Province:
* Country: USA: UNITED STATES * Zip / Postal Code: 21218

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Tracking Number:GRANT10999946 Funding Opportunity Number:PA-11-250 Received Date:2011-11-04T16:23:48-04:00

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)	M 20_PHS_ResearchPlan_Intro		Delete Attachment	View Attachment
2. Specific Aims	M-21_PHS_ResearchPlan_Speci	Add Attachment		
3. *Research Strategy	M-24_PHS_ResearchPlan_Resea	Add Attachment		
4. Inclusion Enrollment Report		Add Attachment		
5. Progress Report Publication List		Add Attachment		

Human Subjects Sections

6. Protection of Human Subjects	M-17_PHS_ResearchPlan_Prote	Add Attachment		
7. Inclusion of Women and Minorities	M-7_PHS_ResearchPlan_Inclus	Add Attachment		
8. Targeted/Planned Enrollment Table	M-8_PHS_ResearchPlan_Target	Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Children	M-9_PHS_ResearchPlan_Inclus	Add Attachment		

Other Research Plan Sections

10. Vertebrate Animals		Add Attachment		
11. Select Agent Research		Add Attachment		
12. Multiple PD/PI Leadership Plan	M-6_PHS_ResearchPlan_Multipl	Add Attachment		
13. Consortium/Contractual Arrangements	M-12_PHS_ResearchPlan_Consor	Add Attachment		
14. Letters of Support	M-26_PHS_ResearchPlan_Letter	Add Attachment		
15. Resource Sharing Plan(s)	M-14_PHS_ResearchPlan_Resou	Add Attachment		

16. Appendix Add Attachments | Remove Attachments | View Attachments

reviewers' comments

Specific Aims

Next-generation DNA sequencing technologies have placed us on the threshold of affordable WGS for clinical purposes. The extent to which genomics will improve health outcomes on a population level, however, depends in part on effective oversight. The volume of information generated by WGS and the uncertainty about the utility of the data, the indications for which it should be used, who will pay for it, and the extent to which patents and licensing affect access are all issues that command the attention of the policy community. The current regulatory framework that guides single-gene diagnostic testing and newborn screening was not designed to integrate WGS into clinical practice. Thus, 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 study will respond directly to the program announcement PA-11-250 to begin to prioritize and address the unique policy challenges raised by WGS using a systematic consultation that could be applied to future regulatory work in this area.

We have organized a group with expertise in three of the domains where WGS poses unique challenges: oversight of test quality and services; patenting and licensing issues; and the coverage and reimbursement of WGS. In consultation with an expert stakeholder panel, we will systematically delineate and prioritize an authoritative list of specific, tractable questions that policymakers should consider as WGS comes to the clinic. We will select three high-priority questions within our three domains, and work with the panel to develop policy approaches to address them. This work will be informed by an initial landscape analysis of the current and near-future status of the WGS industry, as described by several of its leaders. Building on our team's expertise and extensive experience in both genetic testing policy and stakeholder engagement methods, we propose the following aims to answer the call for regulatory science needed to inform decision making in the face of rapid developments in genomic healthcare.

Aim 1. Describe the current whole genome sequencing industry to establish a basis for identifying and addressing related policy issues. To provide a clear understanding of WGS, we will conduct the first U.S-centered landscape analysis of the current WGS industry, focusing on the generation, delivery, and interpretation of genomic data. A review of literature, websites and company materials will be enhanced by interviewing industry leaders about the future of commercial clinical WGS.

Aim 2. Identify and prioritize novel policy questions posed by whole genome sequencing, and develop policy approaches for the most pressing, tractable issues using a modified Delphi process to iteratively engage key stakeholders. Using our landscape analysis, our interview data, and our knowledge of current standards and policy, we will develop a preliminary list of policy questions unique to the clinical use of WGS. A panel of 40 key stakeholders will then be iteratively surveyed to add to and refine this list and to rank the resulting questions in terms of importance and tractability. An authoritative list of clear policy priorities related to the clinical use WGS will result.

We will then develop policy approaches to address three high-priority issues, one from each area of our team's expertise: test quality and validity, healthcare reimbursement, and intellectual property. We will systematically analyze the extent to which current laws, professional guidelines, and industry standards contribute to or address the selected questions. Using this analysis as a starting point, we will again iteratively survey stakeholders to solicit and refine a variety of policy approaches to the questions. The resulting set of approaches will be discussed by the stakeholder panel at a summit meeting to identify areas of agreement and reasons for disagreement. A report summarizing how our methods and findings might be applied to the broader range of WGS policy issues will be developed and disseminated.

Aim 3. Disseminate findings to policymakers and key stakeholders. Beginning with the landscape analysis, we will distribute our findings in concise, accessible formats (e.g., white papers, briefs, webcasts) to a broad range of stakeholders to inform policy development. Two public briefings for Washington-based policymakers will be held to disseminate findings from the Delphi process. Follow-up meetings with select federal officials, Congressional members and staff will be used to begin focused dialogues on clinical WGS.

RESEARCH STRATEGY

A. SIGNIFICANCE

This application responds directly to one of the primary goals of the NHGRI program announcement "Ethical, Legal and Social Implications (ELSI) of Genomic Research Regular Research Program" (PA-11-250),[1] which reads "New legal and regulatory approaches need to be crafted in anticipation of or in response to rapid developments in genomic research and genomic health care....Research will be needed to explore the effects of existing policies and regulations and to provide data to inform the development of new policies and regulatory approaches."

Rapid innovation in next-generation DNA sequencing technologies has brought us whole genome sequencing (WGS) that can be generated quickly and cheaply enough to be used for clinical purposes. In 1996, President Clinton tantalized the public when he said: "I think it won't be too many years before parents will be able to go home from the hospital with their newborn babies with a genetic map in their hands that will tell them, here's what your child's future will likely be like." Jay Flatley, CEO of Illumina, predicted that WGS would be "technically feasible and affordable" by 2014 and "routine" by 2019.[2] Exactly five years ago, in October 2006, the cost of sequencing an entire human genome was $10.4 million; today it is 1,000 times less expensive.[3] The NHGRI has recently committed an additional $18 million to spur development of faster technologies.[4] Some researchers predict that five years from now it will be possible to sequence an entire human genome in a matter of hours for $100 or less.[5,6]

Demonstrating the clinical potential of these new technologies, whole exome sequencing (WES) and WGS have already been used successfully to diagnose and treat disease,[7-10] and insurance companies have agreed to cover the cost of WGS in at least two cases.[11] A growing number of diagnostic laboratories are adding next-generation sequencing to their menu of services.[12] Some experts think genomic sequencing is ready for routine clinical use.[13,14]

Although the technology had advanced to the point where it can be used address specific clinical questions an emerging consensus that the U.S. health care system does not have an established system of procedures, knowledge and resources to effectively interpret and deliver WGS information to patients and providers. The extent to which genomic medicine improves health outcomes on a population level will depend on the effective oversight of clinical WGS. The current regulatory framework that guides single-gene diagnostic testing and newborn screening were not designed with the complexity of whole genome sequencing in mind, and will not suffice without new approaches or creative applications of existing policy.

Eric Green and Mark Guyer recently wrote that "the amount and heterogeneous nature of the data, which will include both expected and unexpected results, will antiquate current mechanisms for delivering medical information to patients".[15] The mechanisms currently in place are themselves the result of extensive research to craft a system of regulatory policies that guide the practice of genetic testing.[16-18] The nature and character of the data referred to by Drs. Green and Guyer would seem to necessitate a call for forward-thinking policy research and guidance. New policy approaches will be needed to establish a system that promotes appropriate, broad access to high-quality sequence data and valid reports while encouraging innovation.

WGS's rapid transition to clinical use has prompted a wide range of initiatives, including NIH's National Center for Advancing Translational Sciences,[13] and NHGRI's most recent ELSI program announcement,[19] and heightened the importance of efforts like the FDA and NIH's collaborative regulatory science initiative[20] and the Genetic Testing Registry. In June 2011, the FDA held a public meeting to discuss approaches to establish the safety and effectiveness of clinical genomic sequencing. Likewise, insurers and pharmacy benefits managers are creating positions for the management of genomics services.

There are numerous policy needs that require the attention of stakeholder groups with diverse, strong interests in the governance of WGS. Among the many challenges we face are: ensuring the quality and utility of WGS data and interpretation; defining the indications for which WGS should be used; determining who will pay for it; developing systems of patents and licensing that maximize access while rewarding innovation; the

storage and integration of data into medical records; issues of ownership and privacy; personnel and training needs; and whether the technology is best used for diagnostic purposes or health screening.

We have organized a research team with expertise in three of these domains: the oversight of test quality and services; patenting and licensing issues; and the coverage and reimbursement of molecular diagnostics. WGS is likely to raise several important questions in each of these areas. How should a WGS test, which could simultaneously produce a result with clear utility, a result with unintended consequences, and a result whose interpretation will change with future research, be categorized under the FDA's proposed risk-based approach to regulation?[20] How will insurers address the complexity of the information created by WGS technology? Will the lack of clinical utility data limit or prevent coverage? Will clinical laboratories be able to offer a complete genome sequence when some of the genomic landscape is restricted by intellectual property patents?[21] Are licensing restrictions likely to reduce the utility of the available sequence?

With little empiric data available to answer such questions, there is a large degree of uncertainty about the nature and relative importance of these policy domains. However there is an immediate need for critical thought about what the policy priorities are and how we may begin to address them.

In the absence of data about the validity, accuracy or utility of WGS, or how strong the enforcement of patent claims against WGS laboratories will we will develop a set of policy priorities for clinical WGS by consulting a diverse group of stakeholders, including WGS technology and informatics companies, clinical laboratories, health care professionals, insurers, regulatory and public health agencies, health economists, and patient groups. The findings of this study will be driven primarily by the experiences and opinions of experts who are currently developing, monitoring and regulating the tools and technology for the clinical use of WGS

A modified Delphi process will be to elicit expert stakeholders' input on all relevant policy issues and their relative importance and tractability. This highly structured approach to stakeholder engagement allows a geographically and professionally diverse group of experts to anonymously provide one another with quantitative and qualitative feedback about the ideas of others on the panel. Analysis of this feedback can lead to a prioritized list of WGS issues as defined by the entire community of stakeholders, or a detailed critique of policy options to address a given policy problem. Points of agreement between stakeholders and reasons for disagreement can be identified. To ensure that this work is based on an understanding of the actual capabilities and business models of WGS companies, we will begin by conducting the first U.S-centered landscape analysis of the current WGS industry, focusing on the generation, delivery, and interpretation of genomic data. Throughout the course of the study we will distribute our findings in concise formats that are accessible to policymakers.

Conducting policy planning now, as this rapidly-advancing technology begins to mature, presents an opportunity to evaluate and influence both the industry and policy options. This work will help to ensure that policymakers have sound access to existing evidence and policy options based on wide-ranging expert opinions and rigorous research. A significant portion of the impact of this project will come from active efforts to disseminate our findings to policymakers in order to stimulate discussion and inform efforts to enact appropriate regulatory reform.

B. Innovation

[[This proposal is innovative in four ways. First, it will be one of the first comprehensive projects to systematically assess U.S. policy needs since whole genome sequencing (WGS) has become available for clinical use.[13,15] Conducting policy work now, just as WGS is becoming clinically available and before this rapidly-advancing technology matures, will allow us to consider policy questions as they arise in real time, and offers the prospect of influencing the early practices and expectations of those involved with clinical WGS. To date, policy work related to the clinical use of WGS has been largely theoretical. Our proposed policy analysis is innovative in that it is based on direct engagement with WGS companies and other key stakeholders. This will ensure a forward-looking description of the WGS industry, and the production of policy priorities and approaches that are grounded in a broad range of highly relevant experiences.]]

Second, most policy work to date has focused on issues primarily related to single gene testing and is typically limited to a single policy domain. This proposal explores and prioritizes the most pressing policy questions across three major areas: quality assurance, reimbursement, and patents and licensing. The breadth and depth of the project staff's expertise facilitates the simultaneous development of policy approaches in these domains. By disseminating the policy priorities, we hope to stimulate the development of policy approaches among experts in other areas such as equitable access to services, privacy, and data access and storage.

[[Third, we propose using an innovative modified Delphi approach to ensure the systematic incorporation of a wide range of highly relevant perspectives in our priority setting and policy development. Members of the stakeholder panel anonymously review and propose revisions to other panel members' ideas as the study progresses. The results are conclusions that have been vetted from many different perspectives at a high level. The strengths and weaknesses of each policy approach, as viewed by the range of stakeholders will be of tremendous value as policymakers and stakeholders begin earnest discussions to guide the implementation of WGS. If the Delphi process is successful and productive, it could result in the establishment of a framework, or methodological pipeline, to evaluate additional WGS policy issues moving forward.]]

Finally, the direct dissemination of findings to the policy community will increase the uptake and use of this work. Washington-based policy briefings, issue briefs, and online media tools will be used to distribute our landscape analysis, policy priorities, policy approaches, and an account of the Delphi process. The expertise of Burness Communications will help to ensure the success of our outreach efforts.

C. Approach

We plan to combine straightforward methods of landscape and policy analysis with a modified Delphi process, in which a diverse panel of key stakeholders are iteratively surveyed for their opinions and feedback, to **systematically identify and prioritize novel policy questions posed by whole genome sequencing**, and to **develop policy approaches to address the most pressing, tractable issues, as judged by our stakeholder panel**. As with all policy analysis, the first step is to identify and clearly define the process being governed and the nature of the issues that need to be addressed. We will begin in Aim 1 by conducting the first systematic, landscape analysis of the current WGS industry to clearly define the business methods and services involved in that are being employed to commercialize clinical WGS. To inform the development of forward-thinking policy, and gain first-hand knowledge of emerging business models, we will interview industry leaders about the future of commercial clinical WGS. This innovative, comprehensive landscape analysis will provide a framework for identifying and prioritizing novel policy questions, outlining policy-relevant aspects of the WGS industry including self-imposed quality standards, capabilities and services being offered, targeted indications and markets, patents held and health claims being made. This assessment of the industry's approaches to clinical sequencing will directly inform the development and prioritization of major policy issues related to WGS in Aim 2.

[[In Aim 2 we will engage a diverse panel of experts to define and prioritize major policy issues related to WGS. A preliminary list of policy questions will be generated from the landscape analysis and our knowledge of current standards and policy. We will use a modified Delphi process to systematically collect and integrate the opinions of ~40 key stakeholders. A modified Delphi process adds an in-person meeting of stakeholders and project staff to the traditional process of iterative stakeholder surveys.[22] The stakeholder panel will be drawn from the WGS industry, including WGS technology companies, informatics companies, trade associations, and clinical laboratories; the health care system, including public and private insurers, pharmacy benefits managers, healthcare systems, provider groups, professional associations, clinical geneticists, and genetic counselors; and policymakers, academics and the public, including regulatory and public health agencies (FDA, FTC, CMS, HHS, PTO, CDC, Congress), health economists, patient groups, and intellectual property expert.[22,23] Stakeholders will be iteratively surveyed (see Figure 1). The results of each survey will be summarized and analyzed by project staff, and returned to the panel members for criticism and comment in the following round. A final in-person meeting will be used to gather more detailed opinions about policy approaches to three high priority questions This process will result in three products: (1) a prioritized list of policy questions for consideration by the policy community, (2) policy approaches developed to address three of the most pressing issues as defined by the panel, and (3) a summary of the Delphi process as a technique for developing these approaches. The policy priorities and

the resulting set of draft approaches will be disseminated in a timely and accessible fashion to federal and state regulators, genome technology developers, investors, health care providers, and other stakeholder groups in Aim 3.]] A preliminary list of stakeholders is found in the Appendix.

This project will leverage the expertise, insight, and working relationships established by an accomplished study team and a diverse panel of stakeholders to efficiently and comprehensively collect and analyze information relevant to WGS policy decisions. In this section we describe: (1) the research team and expert advisory board; (2) the research plan and timeline; (3) potential limitations of the study; and (4) a brief summary of relevant preliminary work.

C.1 Research team and advisory board

The research team will be led by David Kaufman and Amy McGuire, who combine significant expertise in genetic science, law, policy, and bioethics with extensive experience engaging stakeholders and developing and disseminating policy options.[24-32] Analysis of the oversight of WGS quality will be led by Gail Javitt, one of the nation's foremost experts on FDA law and CMS/CLIA regulation of genetic testing quality and utility. Ms. Javitt led the Genetic Testing Quality Initiative at the Genetics and Public Policy Center, which identified gaps in federal oversight of single-gene genetic test quality and delivered recommendations to policymakers using a wide variety of formats. More recently she published recommendations for a blueprint of a genetic test registry[33] and led the GPPC effort to evaluate the policy implications of DTC genetic testing.[34] This proposal builds on Ms. Javitt's prior work by applying her detailed knowledge of the regulatory bodies that have jurisdiction over genetic testing to quality assurance issues raised by next-generation sequencing methods with different standards, data output, reports and error rates.

Issues of intellectual property, technology transfer, and relevant aspects of policy engagement will be addressed by Robert Cook-Deegan, who is the director of the Duke University Center for Genome Ethics, Law & Policy, and a leading expert on the effects of patents and licensing practices on genetic testing. Since 2009, Dr. Cook-Deegan has published an extensive number of peer-reviewed articles related to human gene patenting. Among his many contributions to the field are patent case studies that served as the basis for the 2010 SACGHS Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests.[35] The study will extend his work to consider policy approaches to patent and licensing issues presented by clinical applications of WGS.

Sean Tunis, Pat Deverka, and Donna Messner of the Center for Medical Technology Policy (CMTP) in Baltimore, MD, will address issues of insurance coverage and reimbursement policies for WGS. As founder and Director of CMTP, Dr. Tunis is a recognized leader in the assessment of medical technologies, including molecular diagnostics, and the development of guidance for insurance coverage of these tools. As the Chief Medical Officer at CMS, he supervised the development of national coverage policies and quality standards for the adoption of new technologies by Medicare and Medicaid providers. He is joined by Dr. Deverka, an expert in the identification of policy approaches to improve the clinical translation of personalized medicine. At CMTP, Dr. Deverka is currently engaging stakeholders on several projects related to personalized medicine which use Delphi panels and other methods to set priorities for care. [[Dr. Messner is a specialist in qualitative social research methods, including stakeholder engagement methodologies and use of the Delphi process to gather opinions on topics including FDA regulation, genetic testing, and gene patenting. Dr. Messner will lead the selection of the stakeholder panel and development of the Delphi process.]]

In addition, an eight-member expert advisory board will provide guidance throughout the project. [This advisory board is distinct from the key stakeholder panel (Delphi panel) that we will engage in the Delphi process; its function is to serve as a sounding board for project staff, and to advise the project on dissemination of findings]. Letters of agreement for the advisory board members are attached. Advisory board members include: Jim Evans, a physician and molecular biologist at the University of North Carolina School of Medicine, and Director of UNC's Clinical Cancer Genetics Services; George Church, an innovator in genome sequencing technology and the Director of the Center for Computational Genetics and the Personal Genome Project, and founder of Knome Inc; Dietrich Stephan, the co-founder of Navigenics and a pioneer in the development of new business models for genetic testing; Arti Rai, a renowned legal scholar at Duke University who served as director of external relations for the US Patent and Trademark Office; [[David Veenstra, an associate professor

of pharmaceutical outcomes research at the University of Washington and an established scholar on the economic implications of pharmacogenomics; Sarah Botha, an attorney in the Bureau of Consumer Protection at the Federal Trade Commission where she has focused on consumers' legal rights and protections when purchasing genetic tests; Jonathan Rothberg, the founder and CEO of 454 Life Sciences and Ion Torrent, two of the largest companies responsible for current advances in sequencing technology; and Heidi Williams, an Assistant Professor of Economics at MIT where she is an expert on the economics of innovation in genome-related markets.]]

The advisory board will meet five times during the course of the study via Internet-based video teleconferencing to minimize travel expense and burden. The first meeting at the outset of the study will clarify study goals. At the second meeting the research team will present WGS landscape analysis and discuss relevant policy questions. In year two the board will help to select three issues to develop policy approaches for, based on results from the Delphi process, and define criteria that should be considered when developing the policies. Towards the end of year two, the panel will review the approaches developed through the Delphi surveys. Finally, the research team will update the board on major findings, solicit ideas for dissemination, and discuss plans for future research. Throughout the study, we will ask individual board members for input on specific aspects as appropriate.

C.2 Aim 1: Conduct a systematic landscape analysis describing the current whole genome sequencing industry.

Despite intense interest in the use of WGS for diagnostic and prognostic purposes, there are many gaps in our understanding of how the technology will be harnessed to provide relevant and reliable health information to providers and patients. New companies are emerging with a variety of tools to interpret sequence data. A single company may sell a variety of platforms with different research and clinical capabilities. The range of business models used to promote and distribute WGS has not been systematically assessed. The extent to which new oversight will be effective in regulating these business models depends in part on policy development based on a clear understanding of the clinical WGS industry. We will conduct a systematic landscape analysis of the current industry, and interview leaders in the field to learn how clinical WGS is likely to develop in the near future. This description of the emerging WGS industry could not have been performed until quite recently. The assessment of the industry's approaches to clinical sequencing will directly inform the development and prioritization of major policy issues related to WGS in Aim 2. We also intend for this resource to be regularly updated and used by the wider research and policy communities.

ACGT, INC.	Genome Sciences Centre*
Ambry Genetics	Helicos BioSciences Corp.
Amplicon Express	IBM*
Applied Biosystems	Illumina
Beckman Coulter Genomics	Inst. for Molec. Med. Finland
BGI Americas	Ion Torrent
BioNano Genomics	Knome
CD Genomics	Life Technologies
Centrillion Biosciences, Inc.	Macrogen*
Cofactor Genomics	Pacific Biosciences
Complete Genomics	Perkin Elmer*
Elim Biopharma	Polonator
Eurofins MWG Operon*	Prognosys Biosciences
Expression Analysis	Roche Diagnostics
Fasteris*	SeqWright
Febit	Xcelris Labs*
GE Global Research*	ZS Genetics

Table 1. Existing Whole Genome Sequencing Companies
*Service not offered yet

Web-based landscape analysis: Drawing on our experience monitoring companies offering direct-to-consumer (DTC) genetic testing,[34] we will systematically identify and track WGS companies (Table 1). We will include companies, universities and other entities developing whole genome sequencing technologies and equipment, providing sequencing services (whole or exomic), or offering clinical annotation or interpretation of sequence data. Companies involved in WGS will be identified by searching the Internet and PubMed using relevant search terms such as "whole genome sequencing," "exomic sequencing," "next-generation sequencing," , "next-next-generation sequencing", "genomic(s)", "personalized medicine", "individualized medicine" and "personal genome" and monitoring media reports through searches of NEXIS. We will search each company's website, examine publicly available descriptions and documents, such as the USPTO database and Lexis-Nexis, and, when necessary, contact companies to collect policy-relevant information including but not limited to: (1) technologies used (platforms) and their capabilities, (2) services provided (e.g., instruments, sequencing services, or interpretation), (3) customer bases, (4) patents held and current patent claims, (5) health-related claims being made, (6) CLIA certification status and (7) whether uses are being covered by third party payers. Additional relevant features may also be identified. We will classify the range of business models used to promote and deliver WGS based on the policy-relevant information we collect. We will refine and narrow

our definition of WGS companies, eliminating any that are not offering relevant products or services. The landscape report will include sections identifying the companies, the service models for clinical WGS, the markets being addressed, and who is paying for the services.

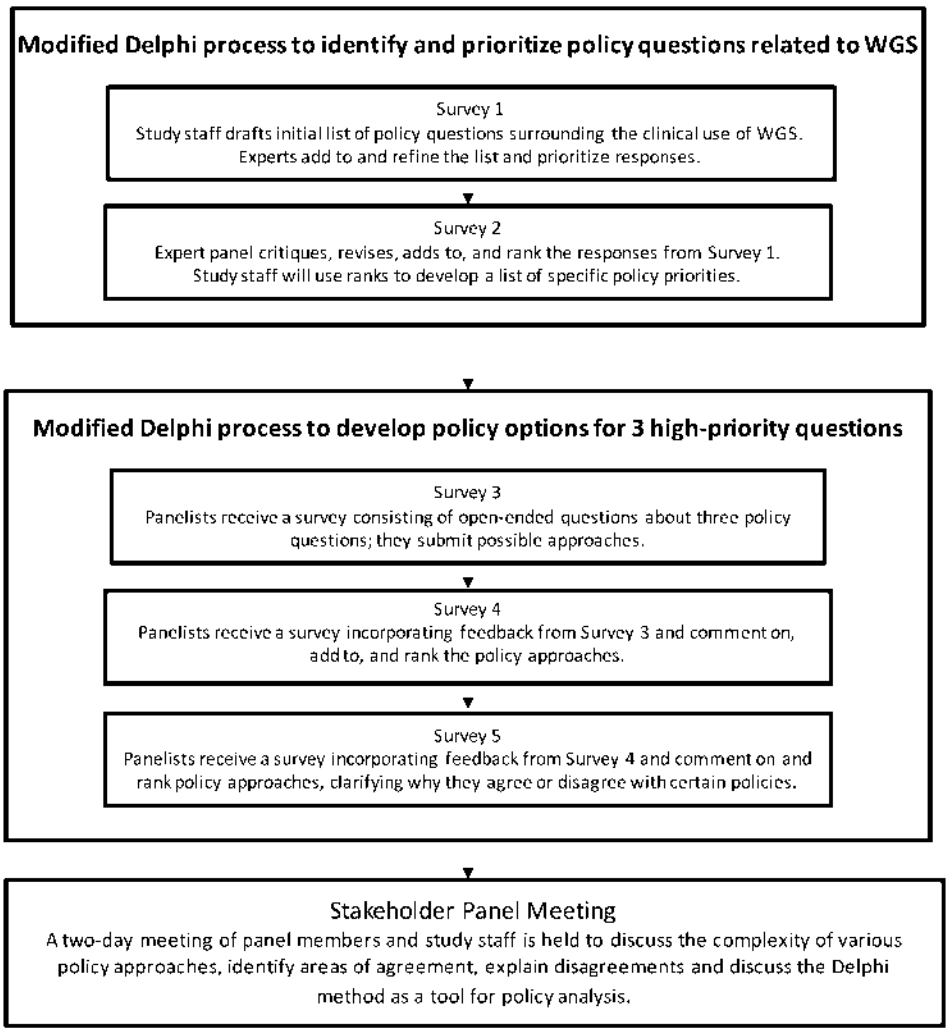
[[Interviews with industry leaders: WGS business models and technologies are changing rapidly. To anticipate these developments as we draft policy approaches, project staff at GPPC will conduct semi-structured interviews with a purposive sample of up to 20 industry leaders to seek their perspectives on the future of clinical WGS. Interviews will not ask leaders about specific business plans, as this information is unlikely to be divulged. We will recruit chief executives and senior scientific and business officers from companies identified in the landscape analysis. Recruitment will cease when saturation of interview findings occurs or 20 interviews are completed. Based on GPPC and CMTP's experience recruiting scientists and professional stakeholders for other interview studies, we believe we will be able to enroll 20 individuals from what we expect will be at least 40 companies with at least three eligible staff each.

An interview guide will be drafted, piloted among advisory board members, and revised. The guide will contain a small number of general questions designed to evoke a conversational tone and elicit opinions about the future directions of clinical WGS. Questions might include how participants think WGS is most likely to be integrated into care, or what companies need to do to prepare for the many possible clinical uses of WGS. We will also use this opportunity to collect information about industry standards and self-regulation. Telephone interviews lasting 30-40 minutes will be audio taped using two recording devices to prevent data loss. All interview materials will be de-identified and kept confidential; no data will be reported on the individual level. Tapes will be transcribed. After all personal identifiers are deleted, transcripts will be entered into the qualitative data analysis software NVivo version 9.0. We will apply an abbreviated content/thematic analysis to assimilate the interview data: a fairly simple coding scheme will be applied to code transcripts for major themes related to the future of clinical WGS (e.g., "emerging business models" or "pathways to clinical integration"). The entire research team will meet to review the coded transcripts, discuss the themes that emerged, and integrate the findings into the landscape analysis.

Effective evaluation of the policy and oversight implications of WGS will require careful, ongoing monitoring of the industry throughout the study to identify new entrants into the marketplace. Throughout the course of the study we will search for emerging companies and business models, and we will document changes in existing WGS companies by regularly collecting screen shots of Web sites showing test offerings and changes in services.]]

[[C.3 **Aim 2: Identify and prioritize novel policy questions posed by whole genome sequencing, and develop policy approaches for the most pressing, tractable issues using a modified Delphi process that iteratively engages key stakeholders. [[Note to reviewers: this Aim is new and replaces a more traditional policy analysis.*]]**

There is a great deal of uncertainty about how whole genome sequencing will be incorporated into clinical medicine, both generally and in the United States' healthcare complex. There is a general consensus that whole genome sequencing will disrupt the patchwork of systems that currently guide clinical single-gene testing and newborn screening, including existing codes and policies for reimbursement and insurance coverage, appropriate indications for testing, standards to ensure genetic test quality, and intellectual property rights. However, the relative magnitude and importance of these disruptions and the roles that different governing bodies might play to effectively address these issues are not well-understood. Scant empirical data exists to measure the performance of clinical WGS. Nevertheless, the issues appear to be approaching rapidly and may overwhelm policy makers in a manner that is similar to, but perhaps more profound than, the emergence of direct-to-consumer genetic testing.



In order to efficiently prioritize and address policy needs in an area with little empirical data and a high level of uncertainty, we have chosen to use a modified Delphi process, which systematically draws on and distills the informed judgments of a broad range of experts and stakeholders. The Delphi method is a structured, facilitated process of group communication. It is designed to allow for expert stakeholders from diverse locations and areas of expertise to focus on complex issues where little empirical data exists.[22,23,36] Briefly, an expert panel is surveyed about a question (i.e. "given the landscape of the whole genome sequencing industry, what are the most important questions policymakers should address to implement clinical WGS?"). Anonymous brainstorming by the panel generates a list of ideas. Study staff, who serve as informed facilitators, organize the responses and present them back to participants in the form of quantitative group results and qualitative summaries. The panel is then asked to anonymously critique, revise, add to, and/or rank the results. In some cases, several rounds of this Delphi process are used to reach consensus among stakeholders. Achieving consensus, however, is not the goal of the work proposed here, as complete agreement is an unrealistic expectation for the diverse group we will query. Rather, our goal is to conduct a structured discussion around expert stakeholders' diverse preferences with respect to the future regulation of clinical WGS.

The first set of two Delphi surveys will be used to develop and prioritize an authoritative list of specific policy questions for consideration. The second set of three surveys will be used to develop a variety of policy approaches to address three of the highest-priority policy issues that fall within our project team's areas of expertise. The "modified" Delphi process we propose concludes with an in-person meeting of the stakeholder panel and project staff. This meeting provides the opportunity for an in-depth conversation to explore the complexity of the various policy approaches, identify areas of broad agreement, and clarify reasons for disagreement.[22,23] By providing a forum for the experts to review our summaries of the surveys, the meeting can also lead to improved construct validity of the Delphi process[37].

Recruitment of the Delphi Panel: Forty candidates will be selected to represent the following categories of stakeholders: the WGS industry, including WGS technology companies, informatics companies, trade associations, and clinical laboratories; the health care system, including public and private insurers, pharmacy benefits managers, healthcare systems, provider groups, professional associations, clinical geneticists, and genetic counselors; and policymakers, academics and the public including regulatory and public health agencies (FDA, FTC, CMS, HHS, PTO, CDC, Congress), health economists, patient groups, and intellectual property experts. Candidates will be identified through searches of academic and trade literature, and discussions with industry leaders and the advisory board. The project team will preference-rank candidates in each subgroup according to demonstrated interest in policy development and overall expertise and contact candidates from each group in order of preference. The validity of the Delphi process

does not depend on recruiting large or representative samples. A sample size of 40 panel members will accommodate all relevant stakeholder groups while maintaining an administratively manageable group.[38,39] Once personal assurances of participation are obtained, non-response and attrition rates in Delphi processes tend to be very low.[37]

It is imperative that participants understand the nature of the Delphi process. To this end, recruitment will include a detailed overview of the purpose, tasks, and timeline of the process, which will involve five online surveys and a two-day meeting in Washington, D.C. spanning the course of 20 months. The confidentiality and anonymity of participants' responses to the surveys will be emphasized. [[Based on the experience of GPPC, BCM, and CMTP with recruiting and maintaining expert technical working groups, stakeholders, advisory groups, and Delphi panels for multiple projects, we are confident in our ability to recruit high-quality participants for this panel. We have obtained letters of support from WGS technology and informatics companies, and two provider groups. The buy-in of these organizations, our interviews with industry leaders in Aim 1, our dissemination of the landscape analysis to policymakers (Aim 3),and the presence of industry and thought leaders on the advisory panel will all serve as catalysts for additional recruitment.]]

Preparation of the Delphi Panel and Delphi Materials: Maintaining panel members' anonymity in their survey responses encourages unconventional or unexpected ideas and questions.[40] Hence, each panel member will be assigned a two letter code that panel members and study staff will use to refer to each other during the surveys.[22] However, complete anonymity can undermine the process; participants need confidence that their fellow participants are respected peers. A brief group building exercise will be conducted at the outset to develop this confidence. Panel members will be asked to submit their names, affiliations, and areas of expertise, as well as their concerns and hopes for the Delphi process. A summary of this information will be disseminated to all participants. Panel members will also be sent the landscape analysis from Aim 1, which will provide important context for the identification and consideration of policy questions. The initial surveys for both problem identification and the development of policy approaches will be carefully developed ahead of time by staff and piloted with advisory board members. Instruments for the later rounds will be determined by the panel responses.

Identification and prioritization of novel policy questions posed by WGS: The stakeholder panel and project staff will engage in two rounds of input to clearly identify and prioritize unique policy questions related to the clinical use of WGS. Prior to the first round of the Delphi process, the entire study team, in consultation with the advisory board, will use our landscape analysis and our knowledge of current standards and policy to develop a preliminary list of novel policy questions we believe are raised by clinical WGS. This "straw model" of policy questions will be submitted to panel members for consideration as the first survey. Participants will be asked to review the issues, add issues, comment on any issues they wish, and rate the importance, validity, and technical and political feasibility of addressing each issue using 5-point Likert scales.[22,41,42] The use of these scales does not exclude other forms of classification of the policy questions; we will consider the findings of our landscape analysis and recommendations of the advisory panel to identify other measures by which these questions might be categorized.

The team will assess and summarize the responses. The resulting annotated list of policy questions will be presented back to the panel, who will use a second online survey to review the issues, make additional comments, and again rate the importance, validity, and technical and political feasibility of addressing each issue. The feedback will be summarized to produce an annotated list of policy questions. The questions will be prioritized using the ranked scale data. Numerical values for importance and validity will be summed to form a "Priority" scale ranging from 0 to 8, while values for technical feasibility will be summed to form a "Tractability" scale ranging from 0 to 8. An Overall scale summing all four items (range 0-16) will also be tallied. Median values for the individual and combined scales will be calculated for each policy question. Numerical priority rankings will be computed after sorting the list of questions by median Overall rating, then Priority. A second list of ratings will be computed, sorting by Overall rating followed by Tractability. An annotated, ranked, sortable list of priorities with median values of each composite and individual scale will be published and disseminated in a variety of formats to the broader stakeholder communities to inform the development of WGS-related policy.

Development of multiple policy approaches to address the most pressing, tractable issues in our areas of expertise: The goal of generating policy approaches is to provide policymakers and others with several alternatives to address policy needs for the effective integration of WGS. Ideally, alternative approaches vary in terms of timing, mechanism, distribution of burden, extent of federal and state government involvement, and stakeholder support. The second round of the Delphi process will be used to develop approaches that might not have emerged from a less structured stakeholder conversation that could be led or dominated by members with particular viewpoints. The process will also provide a detailed understanding of where various factions converge and diverge, and the nature of disagreements. These data help to identify aspects of policy that will require negotiation and compromise.

Selection of the policy questions to address: We have organized a team with expertise in three policy areas identified by the program announcement as important to the success of clinical WGS - analytic validity and testing quality (GPPC), patenting and licensing (Duke), and reimbursement and payment (CMTP). We will address the most important, tractable issue identified by the panel in each of these three categories. We recognize that the panel will identify several important issues that lie outside of these domains, and we will encourage others with appropriate expertise to take up the development of policies to address them. We will consult the advisory board on our choice of issues.

Analysis of the current legal and regulatory framework surrounding the three selected issues: Each policy group (GPPC, Duke, and CMPT) will prepare an initial evaluation of the current federal and state laws and regulations, [[professional and association guidelines, and standards being adopted by the WGS]] industry that apply to the issues being addressed. We will consider the intended purpose of these rules, whether they are both broad and precise enough to address the policy issues being considered. We also will examine whether and by whom compliance with existing laws is enforced. Finally, we will determine whether there are conflicts or redundancies between different laws and guidelines that may need to be resolved. These analyses will be written up into white papers and disseminated to panel members to provide them with context for the development of policy approaches. Drs. McGuire and Kaufman will coordinate the efforts of the three teams to ensure that they produce comparable evaluations that can be combined and examined together. Throughout the study, regular project meetings involving all key staff will be conducted to ensure timely progress, as well as comparable goals and products among the different teams.

Development a range of potential policy approaches: To begin developing policy alternatives, Delphi panel members will be asked to "brainstorm" in response to the third survey consisting of open-ended questions about how best to address the three policy issues. Panelists will be asked to consider the landscape of the industry and the current policy environment as well as more specific outcomes such as the impact on public health, cost implications for the government and stakeholders, and the impact on access to WGS and other services. Additional criteria for consideration may also be identified. The project team will simultaneously outline its own policy approaches using the policy analysis framework developed by Patton & Sawicki.[43]

Combining stakeholder input with the project team's approaches, we will prepare a straw model of policy alternatives to address each issue. Following the policy Delphi approach of,[44] the straw model will take the form of a series of resolutions and arguments supporting each resolution. In survey four, participants will rank the desirability and feasibility of each resolution, and the importance and validity of each supporting argument. Panel members may add resolutions and propose supporting or opposing arguments for resolutions. The staff will "moderate" the discussion by feeding mean and median rankings, comments and suggestions back to panel members for a final survey to collect rankings and feedback. The staff will combine and summarize comments in the case of identical arguments.

Before disseminating the policy approaches more broadly, we will review our findings at an in-person meeting of the Delphi panel members and project staff. This final round of the modified Delphi process will take place over two days in Washington, D.C. Findings, as described above, will be made available to participants before the meeting. Sean Tunis of CMTP will facilitate the discussion. Consent will be obtained to audio tape and transcribe the meeting. Transcripts will be de-identified, and the tape will be destroyed.

The first goal of this meeting will be to ascertain whether we accurately reflected the results of the Delphi process. We will present what we identified as the preferred policy approaches, our perceived areas of

agreement, and reasons that stakeholders disagreed. Using real-time, anonymous personal voting technology at the meeting, we will survey and immediately summarize and display panel members' agreement with specific conclusions. These quantitative data will serve as the starting points for discussions to explore the major policy approaches and clarify reasons for disagreement.[22],[23] We will conclude the discussion of each issue by discussing the possible implications of the most favored policy approaches for clinical WGS generally, and particular stakeholder panel. The second goal of the meeting will be to discuss the perceived utility of the Delphi process as tool for bringing stakeholders together, integrating diverse perspectives, identifying and prioritizing the policy questions, and developing potential policy alternatives. The transcript of the meeting, and the responses to the real-time surveys will be analyzed using the same thematic analysis employed in the interviews. We will explore themes related to the Delphi method itself, stakeholder agreement and disagreement, specific policy preferences, and critiques of and recommendations for the use of our data. These themes will be coded, analyzed and summarized in a summary report. Any refinements to the policy approaches and supporting arguments will be included.

The policy priorities and the policy approaches will be presented in separate policy briefings for Washington-based policymakers (see Aim 3). We will solicit feedback and encourage follow-up. Any such feedback will be considered in the development of our summary report.

C.4 Aim 3: Disseminate findings to policymakers and other key stakeholders

The Delphi process will begin the process of disseminating study findings to key stakeholders. We will encourage panel members to disseminate findings to their respective communities. The advisory board will also be consulted about audiences and venues for dissemination.

In order to facilitate dialogue about WGS-related policy, a clear plan to disseminate the study findings and bring discussants together is needed. Our combined experience communicating with policymakers suggests that communication must be established early on with policymakers and decision makers. The intellectual products of the project, including the landscape analysis, policy priorities, policy approaches, and summary of our Delphi process, must be made accessible in a timely fashion, using a variety of concise formats. These products include white papers summarizing current policies, issue briefs on policy questions, webcasts summarizing our findings, and electronic copies of our landscape analysis and prioritized list of policy questions.

To achieve these goals, we will engage stakeholders and policymakers early in the project and encourage their input throughout. We believe early engagement with stakeholders will (1) help to establish policymakers' awareness of the issues raised by WGS, (2) inform our analysis on emerging issues that have not yet been identified by traditional sources, and (3) help to create a sense of investment in the study and encourage participation. Sharing the goals of the study, incorporating feedback where appropriate, and increasing awareness of the issues can lead to well-informed discussions in which participants already share some of the study's interests and vocabulary.

The members of this research team have extensively engaged a wide variety of stakeholders and policymakers, and have built reputations as honest brokers of stakeholder opinions. To maximize the reach of the project, the team will leverage the outreach expertise of Burness Communications, an experienced Washington-based policy-engagement firm that has worked with Dr. Cook-Deegan over the past two years to increase visibility and access to study findings and enhance the potential to influence policymaking. Burness Communications will assist staff in identifying key stakeholders and developing and implementing a communications strategy. Burness will also provide guidance to ensure successful policy briefings and help to document and archive the events to expand their reach.

To reach out to and involve policymakers and stakeholders in WGS we plan the following:

(1) Identification and contact of key policymakers and stakeholders (see Appendix for categories of stakeholders and specific examples). We will inform contacts about the study and invite their comments and participation in all public events.

(2) Early engagement. We will broadly disseminate the results of our landscape analysis and industry interviews to policymakers and key stakeholder group and invite comments and feedback. We intend for the landscape analysis to be updated and used by the wider research and policy communities, and we will actively solicit feedback throughout the study using email and social media.

(3) In years two and three, policy briefings will be held on Capitol Hill for those making policy decisions in the executive branch, Congress, non-government and trade organizations and other target audiences. Media and bloggers will be invited to attend. The briefing in year two will present the policy priorities developed in the first half of the Delphi process and solicit feedback to inform the study. In year three we will brief policymakers on the approaches developed using the Delphi process, including the views and priorities of different stakeholder groups. After both briefings we will immediately follow up and schedule meetings with appropriate federal officials, congressional Members and staff to begin focused, open dialogues on specific issues. A summary of each briefing will be posted on the GPPC Web site.

C.5 Research Timeline

	Year 1				Year 2				Year 3			
Project Task	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Advisory board meetings												
Traditional landscape analysis												
Develop interview guide												
Recruit and conduct interviews												
Analyze interviews												
Integrate interviews and traditional landscape												
Disseminate landscape analysis												
Develop initial list of policy questions												
Stakeholder panel recruitment and prep												
Survey 1 develop and pilot												
Survey 1 in the field												
Analyze survey 1/ prepare survey 2												
Survey 2 in the field												
Analyze survey 2; produce ranked list of questions												
Policy briefing on priorities, follow up meetings												
Choose three policy questions for analysis												
Staff policy analyses												
Devise third survey (soliciting policy ideas)												
Survey 3 in the field												
Analyze Survey 3, prepare survey 4												
Survey 4 in the field												
Analyze survey 4, prepare survey 5												
Survey 5 in the field												
Analyze survey 5; teams summarize Delphi Policy approaches												
Delphi meeting preparation												
Delphi meeting; integrate feedback												
Summarize use of the Delphi process												
Policy briefing on policy options, follow up meetings												
Disseminate findings and use of Delphi												

C.6 Potential Limitations

The whole genome sequencing industry is moving quickly. We may identify business models, technologies and policy questions that will be out of date by the time our research is complete. Because these changes are not completely foreseeable, we intend to address this issue by continually assessing the research strategy. To help ensure that the issues identified in the study reflect the most current developments in WGS, we will closely monitor and incorporate related technological innovations, regulations, and litigation throughout the study. We will leverage existing relationships with key stakeholders and develop new relationships to keep abreast of developments. In addition, we will give priority to broad policy issues that are likely to cut across technologies and business models, even as they evolve.

There is also no guarantee that stakeholders will see or consider the work completed here. To increase the effectiveness, we will adopt a multifaceted dissemination strategy outlined above and draw on the expertise of Burness Communications, with its extensive background in nonprofit communications and the dissemination of research findings to policy audiences. We will explicitly devote resources to reconfigure research materials for use by policymakers and stakeholders in formats that are most accessible to them.

C.7 Relevant Preliminary Work

Policy analysis: Combining this team's collective experience at a time when clinical WGS is becoming a growing reality provides a unique opportunity.
The Genetics and Public Policy Center has been at the forefront of policy analysis to ensure the health care system provides access to high-quality genetic tests with transparent properties. In 2005, GPPC launched a seminal initiative to improve the safety and quality of genetic tests. GPPC undertook a strategy similar to the one proposed here to identify gaps in oversight of genetic testing laboratories and evaluate regulatory enhancements that would improve quality, and to educate stakeholders to enable their effective involvement in policy deliberations. As a result of this work[45,46,47], GPPC was asked to provide expert advice and assistance to Senate committees drafting two bills in 2007 to address gaps in genetic testing oversight[48,49]. More recently, Center efforts led by Gail Javitt have generated recommendations for the creation of a genetic testing registry[33, 33, 50] and have begun to evaluate the policy implications of direct-to-consumer (DTC) genetic testing using a landscape analysis of DTC business models similar to the one proposed here[34]. The proposed project is a logical extension of the Center's work in the oversight of genetic testing, and will leverage its experience developing and disseminating high-quality policy analyses.
The experience of GPPC will be augmented by the expertise of the other project staff. Dr. Amy McGuire has recently completed work on the regulation of DTC genetic testing and on policy issues related to research uses of WGS[24,31]. She serves on the ethics advisory board of the X Prize in Genomics, to be awarded to the research team that can develop fast, accurate, affordable genome sequences. The work proposed here on the policy implications of intellectual property practices' impact on WGS is a natural progression of research currently being performed by Dr. Cook-Deegan's team in two existing NHGRI-funded projects. An R03 grant awarded to Dr. Chandrasekharan describing intellectual property concerns in multi-allele genetic testing and the Duke's Center for Public Genomics, led by Dr. Cook-Deegan which is examining the history and applications of DNA sequencing technologies, including key patents and business models. The study proposed here would extend this work to clearly examine the policy implications of different patent practices being described. The proposed study also flows logically from work that Drs. Tunis and Deverka have recently completed focusing on some of the policy challenges related to reimbursement and coverage decisions for molecular diagnostics and pharmacogenomics[51,52].

Stakeholder engagement: The research team also has extensive experience in stakeholder engagement work. GPPC has completed several stakeholder engagement projects, using both qualitative and quantitative methods to conduct policy-relevant social science research, craft robust policy recommendations, convene and consult key stakeholders to identify common ground, and influence national genetics policy. A National Genetic Policy Summit held in Washington, D.C., in 2006 drew more than 60 leaders from regulatory agencies, professional organizations, the diagnostics, therapeutics and biologics industries, and genetic testing laboratories to identify policy changes supported by all attendees and develop strategies for their implementation, and articulate the basis for any disagreements. In 2010, GPPC secured agreements from the DTC genetic testing companies 23andMe, Navigenics and deCODEme to survey their customer bases. Currently GPPC is recruiting human geneticists and biobank leaders for interviews and surveys about human subjects policies in genetic research. GPPC has surveyed directors of U.S. genetic testing laboratories about their current practices and opinions regarding genetic testing quality and oversight. Three studies of public attitudes about participation in large-scale biobanks have made use of focus groups, town halls, interviews, surveys and discrete choice analysis. At CMTP, Dr. Deverka is currently engaging stakeholders on several personalized medicine–related projects where Delphi panels are being used. Dr. Messner is a specialist in qualitative social research methods, who has extensively used qualitative methods to gather attitudes, opinions, and recollections of stakeholders on topics including FDA regulation, genetic testing, and gene patenting. At CMTP, Dr. Messner is currently leading three projects requiring qualitative assessment of opinions and attitudes of stakeholders, assembly of stakeholder meetings and panels, and the execution of a Delphi panel.

HUMAN SUBJECTS AND RESEARCH

1. Protection of Human Subjects

The components of this project involving human subjects include the interviews of stakeholders to inform the landscape analysis and the Delphi process to identify and prioritize policy questions and to develop policy approaches. The Delphi process is iterative and consists of five surveys and one summit meeting with the Delphi participants. The protection of human subjects will be discussed for each component separately.

1.1 Risks to Subjects

1.1a Human Subjects Involvement and Characteristics

Stakeholder interviews: Up to 20 chief executives or senior scientific and business officers will be recruited from the companies identified in the landscape analysis. Leaders of sequencing and informatics companies will be recruited. Because the demographic makeup of these various stakeholder groups are not well defined, it is not possible to project the number of women or minorities that will be included. However, there will be no exclusions based on gender, race or ethnic background. Interviews will be conducted over the phone.

Delphi process: Approximately 40 stakeholders with various interests in the development and regulation of clinical whole genome sequencing will be contacted and invited to participate in the Delphi process because of their unique expertise and interest in whole genome sequencing. Stakeholders are likely to come from among legislators at the federal and state level, policy staff at agencies including FDA, NIH, the Centers for Medicare and Medicaid Services, the Federal Trade Commission, the US Patent and Trademark Office, manufacturers of DNA sequencing technologies, informatics companies, direct-to-consumer genetic testing companies, professional organizations, pharmacy benefits managers, clinical laboratories, patient advocacy organizations, intellectual property lawyers, human geneticists and genetic counselors, clinicians, and academic and research administrators. Because the demographic makeup of these various stakeholder groups are not well defined, it is not possible to project the number of women or minorities that will be included. However, there will be no exclusions based on gender, race or ethnic background. Delphi participants will be expected to participate in all five surveys and the summit meeting.

1.1.b Sources of materials

Stakeholder interviewees and Delphi participants: The method for identifying stakeholders for the interview and Delphi component of the project is the same. Key stakeholders will be identified though internet searches, professional directories, scientific literature, and congressional, federal and state staff directories. In addition, we will also seek recommendations from our advisory board members and suggestions from stakeholder interviewees. Recruitment emails explaining the study and requesting participation will be sent by study staff to selected stakeholders.

1.1c Potential risks

The potential risks to participants in both components of this project are minimal. Participants may feel uncomfortable about some of the questions. Participants will be informed that they do not have to answer a question if they are uncomfortable and that they can end the interview or withdraw from the Delphi process at any time. There is the remote possibility however, that a participant could offer an opinion or information (for example, information about patent infringements) that could potentially be subpoenaed. To ameliorate this risk, a certificate of confidentiality will be requested from the NIH, and a copy of the certificate will be given to all participants. Participants will be informed of this risk.

2. Adequacy of protection against risks

Stakeholder interviewees: Identifying information from the interviewees will be kept in a locked, secured location, and will not be associated with audio tapes or transcripts, and will only be accessible to the co-PIs and co-investigators. It is not the intention of the project staff to associate any of the materials collected in the interviews with the participants when results are discussed or published.

Delphi participants: Four online-administered surveys will be conducted with Delphi participants. For each survey, Delphi participants will be sent an email including the link to participate in the internet-based survey, and a unique password to access the survey. Survey responses will be recorded electronically in encrypted, password-protected files. No personal identifiers will be collected or retained. All Delphi participants will be asked to participate in an in-person summit meeting. In order to protect the privacy of the Delphi participants, the meeting will be closed to any outside participants and all comments made will be kept strictly confidential. Audio recordings of the conference will be kept in a locked, secure location accessible to only the co-PIs and co-investigators. No personal information will be associated with the transcript. All comments will be analyzed only in aggregate. No press will be allowed to attend the meeting.

2.a Recruitment and informed consent:

Stakeholder interviews: Recruitment emails explaining the study and requesting participation will be sent by study staff to selected key stakeholders identified by project staff as being potentially informative to our analyses. Invitees will be asked to call project staff to schedule an interview. An email confirming the date and time of the interview with a description of the study, the certificate of confidentiality, and a copy of the informed consent document will be sent. The consent form will be reviewed on the phone before the interview begins and verbal consent is obtained.

Delphi participants: Recruitment emails explaining the study and requesting participation will be sent by study staff to selected key stakeholders identified by project staff as being potentially informative to our analyses. Invitees will be asked to call project staff to discuss participation. Staff will review the requirements of the study over the phone. A description of the study, the certificate of confidentiality, and a copy of the informed consent document will be sent to those who are interested, and a second call will be placed to review the consent form and obtain verbal consent. For each Delphi survey, a link to the survey, and a unique password to access the survey will be emailed to each panel member. When participants go to the link, they will see

a display page that provides information about the survey including the explanation that potential participants give implied consent when they agree to participate in the survey. Members can choose whether they want to participate or not.

All Delphi participants will be sent an email confirming the date and time of the summit meeting along with a copy of a description of the study, details about the Delphi summit meeting, the certificate of confidentiality, and an informed consent form for the summit meeting. Study staff will contact the Delphi participants by telephone to confirm their attendance. The consent form will be reviewed on the telephone and verbal consent will be obtained prior to the Delphi summit.

2.b Protections against risk

Identifying information from the interviewees and panel members will be kept in a locked, secured location and only made accessible to the co-PIs and co-investigators unless permission to use this information is granted by the interviewee. The audio tapes of interviews and the summit meeting will be identified only by number and date, and will be transcribed and stripped of identifiers before being sent to researchers for analysis. The audio tapes will be kept in a locked, secure location accessible only to the co-PIs and co-investigators. No personal individual identifying information will be associated with interview transcripts.

3. Potential benefits of the proposed research to the subjects and others:

The only benefit of participating in this study is ensuring that the stakeholder's perspective is included as we develop policy options for the oversight of whole genome sequencing. There will be no other direct benefit to the participants in this research study. Results from this study, however, have a broader benefit in that they will help inform the design and implementation of policies to enhance the regulation and broad use of whole genome sequencing to improve health outcomes. The risks, however, of not conducting such a study in an ethical and thoughtful way and with the cooperation and input of citizens from all segments of society are great.

4. Importance of the knowledge to be gained

This project will provide valuable additional information about gaps that exist in public oversight of genetic testing that must be considered as the use of whole genome sequencing for medical purposes becomes a reality.

Inclusion of Women and Minorities

Interviewees and Delphi participants will be drawn from a wide range of professional categories where data is not readily available on the distribution of women and minorities. No exclusions will be made on the basis of gender, race or ethnic background, and study staff will make every effort to include a broad range of participants. Because demographic data are not available on many of the industries we will be drawing participants from, and because we are likely to interview only two or three stakeholders from any given sector, we have not provided a targeted enrollment table.

Rationale for exclusion: Those under 18 will be excluded because the primary goal of the proposed cohort study is to enroll adults with extensive experience related to the conduct and regulation of whole genome sequencing.

Inclusion of Women and Minorities

Stakeholders who participate in interviews, the Delphi method and summit meeting will be invited from a wide range of professional categories where data is not readily available on the distribution of women and minorities.

No exclusions will be made on the basis of gender, race or ethnic background, and study staff will make every effort to include a broad range of stakeholders.

Because demographic data are not available on many of the industries we will be drawing participants from, we have not provided a targeted enrollment table.

Targeted/Planned Enrollment Table

N/A

Inclusion of Children

Justification for Exclusion of Children

Children will be excluded from this study because their participation is not relevant to the research topic to be studied, development of policy related to whole genome sequencing.

Project Leadership Plan

Dr. McGuire and Dr. Kaufman will provide oversight of the entire program as well as development and implementation of all policies, procedures and processes. In these roles, Dr. McGuire and Dr. Kaufman will be responsible for implementing the Leadership Plan and Research Plan and accomplishing the specific aims. They will work together to ensure that systems are in place to guarantee institutional compliance with US laws and DHHS and NIH policies.

The PIs will share responsibility for Aim 1 (the landscape analysis). In Aim 2, Dr. Kaufman will be responsible for execution of the components of the Delphi method while Dr. McGuire will be primarily responsible for the development of policy approaches. Dr. Kaufman will be responsible for Aim 3, stakeholder engagement and dissemination of findings. Dr. Kaufman will serve as contact PI. He will be responsible for communication with NIH and submission of annual reports, and will assume fiscal and administrative management, maintaining communication among PIs and key personnel through monthly meetings. The two Co-PIs will share decision making over budgetary and personnel issues.

The PIs will communicate weekly—by phone, e-mail, video teleconference or in person to discuss progress of the landscape and policy analyses, coordination of the multiple project teams, roles for upcoming meetings and stakeholder contacts, support and resources needed, and all administrative responsibilities. PIs will share their respective research results with one another, key personnel, and consultants.

The PIs will work together to discuss any changes in the direction of the research projects and the reprogramming of funds, if necessary. A publication policy will be established based on the relative scientific contributions of the PIs and key personnel.

Conflict Resolution

If a potential conflict develops, the PIs shall meet and attempt to resolve the dispute. Both PIs pledge to raise issues as they emerge so that problems are addressed early on, before they are established as patterns. If the PIs cannot resolve the dispute, they will refer the dispute to Dr. Cook-Deegan and Ms. Javitt, both senior staff on the study. If the dispute cannot be resolved with the help of study staff, or involves the study staff such that it would be inappropriate to seek resolution from these staff members, the disagreement shall be referred to an arbitration committee consisting of one impartial senior executive from each PI's institution and a third impartial senior executive mutually agreed upon by both PIs. No members of the arbitration committee will be directly involved in the research grant or disagreement.

Change in PI Location

If a PI moves to a new institution, attempts will be made to transfer the relevant portion of the grant to the new institution. In the event that a PI cannot carry out his/her duties, a new PI will be recruited as a replacement at one of the participating institutions.

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The following letter of support was included as part of the original application and is provided with the permission of Dr. Evans. An additional 17 letters were included in the original application but have been redacted to protect the privacy of individuals providing letters of support.

UNC
SCHOOL OF MEDICINE
DEPARTMENT OF GENETICS

David Kaufman, Ph.D.
Director of Research and Statistics
Genetics and Public Policy Center
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Washington, DC 20036

October 27, 2011

Re: PA 11-250 Ethical Legal and Social Research Regular Research Program

Dear Dr. Kaufman:

Thank you for inviting me to participate in your timely research project on the regulation of genome sequencing. I am pleased to provide this letter of agreement to the Johns Hopkins University Genetics and Public Policy Center in support of your proposal, "Clinical Integration of Whole Genome Sequencing: A Policy Analysis." I would be delighted to serve on your expert advisory group to provide ongoing input throughout the three year grant period.

I am eager to lend my skills to this project. I have experience in the realm of genetics and public policy which I hope to employ in my interactions with your team. I served on the Secretary's Advisory Committee for Genetics, Health and Society from 2004 to 2010, headed SACGHS's task force on the impact of gene patenting and spearheaded a set of recommendations to the Secretary of HHS regarding this topic. I have written a number of commentaries on policy issues which have appeared in JAMA, The New England Journal and Genetics in Medicine, the official journal of The American College of Medical Genetics, of which I am Editor-in-Chief. In the summer of 2010 I was asked to testify to the US Congress regarding regulatory issues surrounding Direct-to-Consumer Genetic Testing. Thus, I hope that I can bring some degree of expertise to your efforts.

Your project team's tremendous capabilities in research, policy analysis, legal scholarship, and outreach will bring new, critical thinking to the challenging problems associated with translating genomic sequencing into products and services that improve health. I am confident that your team's experience conducting research and analysis on many of the major policy issues that must be considered in the context of whole genome sequencing will produce a series of pragmatic policy options. The team's past successes reaching key stakeholders should pave the way for dissemination of your findings to the relevant policymakers and decision leaders in the field.

I understand that as a member of your expert advisory group I will participate in five 2-hour videoconference calls over the course of meeting, and may be asked to provide advice about specific issues during the project as needed. I also understand as a member of the advisory group I will be paid $2500 over the three-year grant period as a consultant.

I look forward to working with you and your team on this important project.

Sincerely,

James P. Evans MD, Ph.D
Bryson Distinguished Professor of Genetics and Medicine

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RESOURCE SHARING

We are aware of, and intend to fully comply with the NIH data sharing requirements. We intend for the findings (the landscape analysis of the whole genome sequencing industry in year one, a prioritized list of policy questions in year two, and policy approaches to three questions, and a summary of the Delphi process in year three) to be shared as widely as possible. We intend to release these findings in multiple formats in order to encourage uptake by broad audiences. Data and analyses from this project will be submitted for publication in the peer-reviewed literature and presented at scientific meetings. In addition, our findings and recommendations will be made available on our web site and in briefings for the public and policymakers.

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: HG006460

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