

**Integration of Whole Genome
Sequencing into Clinical Medicine:
The MedSeq Project**

Study Protocol and Statistical Analysis Plan

October 5, 2018

Funded by the National Institutes of Health, National Human Genome Research Institute

Clinical Sequencing Exploratory Research (U01) RFA-HG-10-017

Project Period: 12/01/2011 – 11/30/2017

NCT: 01736566

Overall Principal Investigator: Robert C. Green, MD, MPH

Project Principal Investigators:

Project 1: Christine E. Seidman, MD; Michael F. Murray, MD

Project 2: Heidi L. Rehm, PhD, FACMG; Isaac S. Kohane, MD, PhD

Project 3: Amy L. McGuire, JD, PhD; Robert C. Green, MD, MPH

Detailed Protocol for the Partners Human Research Committee

The MedSeq Project

Version 11–Clean

January 25, 2017

I. Background and Significance

Whole genome sequencing (WGS) and whole exome sequencing (WES) services are currently available to and being utilized by physicians and their patients in both research¹ and clinical^{2,3} settings, and recently to anyone in the general public via direct-to-consumer companies⁴. But the widespread availability and use of WGS and WES in the practice of clinical medicine is imminent. In the very near future, sequencing of individual genomes will be inexpensive and ubiquitous, and patients will be looking to the medical establishment for interpretations, insight and advice to improve their health. Developing standards and procedures for the use of WGS information in clinical medicine is an urgent need,⁵ but there are numerous obstacles related to integrity and storage of WGS data, interpretation and responsible clinical integration. The application of WGS to large numbers of individuals has the potential to create unanticipated findings implicating some degree of risk that is, at present, impossible to quantify. The resulting confusion, coupled with the instinct of medical clinicians to order medical tests “just to be safe,” has the potential to needlessly inflate costs and increase iatrogenic harm.^{6,7} And, there is consequently insufficient evidence and enormous uncertainty in how to direct the clinical use of genome sequencing in clinical medicine.^{8,9}

We believe that the appropriate setting for the integration of genome sequence information in health care is within the physician-patient relationship. Patients agree with this as well, for example in a study led by Dr. Amy McGuire, 78% of those responding to surveys through social networks reported that they would ask their physician for help interpreting genetic test results, and 61% felt that physicians had a professional obligation to help them interpret results. And in an unpublished survey of patients enrolled in the Coriell Personalized Medicine Collaborative, 94% of respondents reported that they were very likely or likely to share their genetic profile with their doctor and 67-81% wanted their doctor to help with genetic interpretation.

In order for this to happen, physicians must cope with the dilemma of interpreting and acting upon WGS before there is sufficient evidence to fully guide its use. Genomic information in medicine has been singled out as especially “difficult to interpret,”¹⁰ and as proving that “we understand ... even less well than we currently suppose.”¹¹ Dr. Muin Khoury has described the “evidence dilemma”⁹ and Dr. Jim Evans, has urged us to “deflate the genomic bubble.”¹² Yet managing patients without a complete evidence base is a familiar situation in the culture of clinical medicine. The slow accretion of reliable data and the absence of sufficient evidence in clinical medicine is the subject of a considerable literature,¹³⁻¹⁵ and the actual practice of medicine often necessitates use of tests, tools and procedures with insufficient evidence.¹⁶⁻¹⁸ As the US Preventative Services Task Force has written on this subject “even though evidence is insufficient, the clinician must still provide advice, patients must make choices, and policymakers must establish policies”.¹⁴

Many predict that inexpensive and accurate WGS will be available within a few years.¹⁹ We agree and among the many medical uses for genomic information, we believe that there will likely be two archetypal scenarios. In situations where the patient is basically healthy (or where genomic testing for a particular purpose reveals the entire genome), the genome can be screened for incidental disease variants that meet an agreed-upon threshold for clinical relevance, a scenario we are calling *General Genomic Medicine*. Conversely, in situations where a patient presents with a particular family history, complaint or clinical syndrome, the genome can be specifically interrogated for known or suspected disease variants related to that particular presentation, a scenario we are calling *Disease-Specific Genomic Medicine*.

Disease-Specific Genomic Medicine using WGS is conceptually similar to what we do today in medical genetics. When patients present with histories, symptoms or signs suggestive of a particular genetic disorder, specific genes are interrogated for pathogenic mutations. When WGS is readily available and inexpensive, the practice of Disease-Specific Genomic Medicine will differ from the current practice of medical genetics in three important ways: (1) the cost barrier that currently incentivizes parsimonious or tiered strategies for ordering genetic tests will be gone, and all genes relevant to a particular syndrome can be simultaneously interrogated; (2) clinicians will be free to explore related genes that could be relevant to diagnosis, prognosis or treatment responsiveness of the syndrome at hand; and (3) there will likely be an ethical obligation to recognize and return clinically relevant information from the rest of the genome.

General Genomic Medicine will be conceptually different from anything practiced today in medical genetics. This model envisions a readily understandable report, interpreted elements of the WGS and delivery to any clinician as part of the patient’s regular care. This approach will more closely resemble population-based preventative screening measures in clinical practice for uncommon diseases, such as the current use of newborn screening for metabolic disorders, pap

smears in young women screening for cervical cancer, and mammography or colonoscopy after age 50. General Genomic Medicine will also likely incorporate well-established pharmacogenomic traits so that clinicians (or at least electronic medical health records and the decision support systems within them) can incorporate this information when new medications are prescribed. Since, on average, every individual carries at least 2-3 recessive mutations, General Genomic Medicine will make it easy for patients of all ages to be informed about which recessive Mendelian traits they have,²⁰ and will provide, for those of reproductive age, the option to consider pre-conception screening that could reduce the likelihood of severe childhood disorders in their offspring, as has already been accomplished with cystic fibrosis and Tay-Sachs. Moreover, it is becoming increasingly clear that some historically recessive variants are really semi-dominant and individuals who carry them will be “manifesting heterozygotes” so that carrier status is not, in and of itself, always benign. Some carrier states will have increased risk of actionable medical consequences for the carrier, such as sudden cardiac death in a female Fabry carrier,²¹ early ovarian failure in women carrying one copy of a Fragile X premutation,²² and chronic rhinosinusitis in carriers for CF.^{23,24}

Examining the correlation between genetic variation and the resulting physical traits helps medical care providers and researchers understand the connection between genetic variation and human disease. Treatment for genetic conditions is often best identified if the root cause of the disorder is known, and thus the availability of reliable genotype/phenotype information.

As genomic sequencing technologies are increasingly performed in both clinical and clinical research settings, patients and research participants will receive secondary (or unexpected) findings that are of uncertain clinical significance. Some individuals may not yet have expressed symptoms (late onset) some may never developed them (non-penetrance), and others may be expressing such mild symptoms, either static or progressive that they are not noticeable in their day to day lives (variable-expressivity). In order to best address questions about the clinical significance of the variant returned, the medical community must develop reasonable and effective processes for targeted phenotyping and understand the attitudes and experiences of individuals undergoing such a process.^{25, 26}

It is also crucial to develop genomic medicine in a way that reduces, rather than exacerbates, the disparities that plague our current healthcare system. African Americans/Africans are particularly disadvantaged in the early adoption of genomic medicine for 2 reasons: (1) they are being recruited into clinical genomics research databases at a much slower rate than white populations, and (2) the combination of increased genomic variation due to African American/African race and lower representation in genomic variant databases increases the uncertainty of interpreting variants in genomes of African American/African descent. We will begin to address the vast uncertainties in variant interpretation and reporting to individuals of African American/African race by enrolling individuals with African American/African race.

The MedSeq Project is an exploratory trial of WGS in clinical medicine. Since, in the future, genome sequence information will not be used in just one way, we have elected to explore two relatively “pure” examples of the categories described above using the protocol framework and leadership structure of a clinical trial. At the conclusion of this study, we will have helped create innovative protocols and novel outcome measures that can be applied safely in future large-scale multi-site randomized clinical trials with larger numbers of physicians from broad specialties and with more economically and ethnically diverse patients. Together with our colleagues from across the nation through the U01 consortium formed as a result of this funding, we will have invented a process of implementation and evaluation whereby the fruits of the Human Genome Project can be applied for the first time to the daily practice of medicine for the betterment of human health.

II. Specific Aims

The Specific Aims of this project are to:

1. Recruit, consent and enroll 2 study groups:
 - a. 10 primary care physicians and 100 of their healthy middle-aged patients
 - b. 10 cardiologists and 100 of their patients with cardiomyopathy.
2. Randomize each study group to receive standard of care versus standard of care plus WGS.
3. Monitor the entire protocol for subject safety.
4. Obtain WGS at 30x coverage in Illumina’s CLIA certified laboratory on 100 individuals enrolled and randomized to the WGS arms and determine coverage standards and base-calling accuracy for WGS data.
5. Generate and optimize an algorithm for interpreting WGS data covering the spectrum of human genetic variation, in terms of both previously reported and novel variants likely to influence the health of patients.
6. Create patient reports and provide an interface for communicating clinically relevant genomic information to practicing physicians.

7. Describe physicians' and patients' attitudes toward, and preferences for, the disclosure of WGS results at the start of the study.
8. Evaluate physicians' experiences with receiving and interpreting patients' genetic test results and how they communicate these results to their patients.
9. Explore how patients respond to and use WGS results by administering validated scales of psychological impact, personal utility, and behavioral responses, as well as economic and health outcomes.

The Specific Aims of the extension of this project include:

1. Recruit and enroll an additional 10-15 self-identified, ostensibly healthy African American/African patients into the MedSeq Project.
 - a. Develop methods to tailor the current MedSeq Project sequencing, analysis, interpretation and reporting pipeline for individuals with diverse genetic backgrounds and report results in the MedSeq Project Genome Report.
 - b. Approach participating MedSeq Project primary care physicians to refer self-identified /African American patients from their practice to enroll in the MedSeq Project.
 - c. If needed for recruitment of African American/African participants approach additional primary care physicians within the Partners Health Care system and enroll them in MedSeq protocol.
2. Conduct a targeted phenotype assessment on MedSeq Project patient-participants who received a monogenic secondary finding on the MedSeq Project Genome Report with respect to the particular variant reported.
 - a. Collect data regarding the attitudes and experiences of individuals who undergo the process of a targeted phenotype assessment.

Genome Connect Validation Study

1. Offer an opportunity for the 50 enrolled primary care patients to enroll in a GenomeConnect/MedSeq validation study.
 - a. Partner with the Clinical Genome (ClinGen) Resource's patient portal GenomeConnect to validate the GenomeConnect Body Systems Survey.
 - b. Recruit MedSeq participants to join GenomeConnect and compare patient-reported phenotype data to the medical record.

The Specific Aim of the MedSeq Project Long-Term Follow-Up:

1. To evaluate the health impact and healthcare costs of integrating WGS into the care of patients who participated in a randomized controlled trial of WGS against family history analysis five years after results disclosure.

III. Subject Selection

Physicians

Primary Care Physicians

BWH Primary Care Practice Based Research Network (PBRN) approval was obtained **[see attached PBRN approval letter]**. Primary Care Physicians will be approached through noontime Primary Care conferences and the consent form **[see attached physician consent form – primary care]** will be distributed to interested physicians. Dr. Vassy and the study staff will keep track of the Primary Care Physicians who decline study participation and document the reasons why **[see attached study decline log – physicians]**.

For the targeted African American/African Subject recruitment in the extension phase Primary Care physicians who initially participated in MedSeq will be approached and offered the option of continued participation **[see attached-MedSeq Extension AA Recruitment letter]**. If needed, we will recruit up to 10 additional physicians to recruit 10-15 additional African American/African study participants. BWH Primary Care Physicians known to have a higher percentage of African American patients will be targeted. Dr. Vassy or one of the other MedSeq physicians will call these physicians or approach them in person at meetings to assess their interest in participating in the MedSeq study and per our previous protocol the consent form will be distributed to interested physicians.

Inclusion criteria: Any BWH Primary Care Physician who currently practices at BWH.

Exclusion criteria: Any physician who does not meet the above inclusion criteria.

Cardiologists

Drs. Ho and Seidman will recruit Partners cardiologists and cardiologists at Boston Children's Hospital (BCH) through presentations and one-on-one conversations with information about the study. Drs. Ho and Seidman will distribute the consent form **[see attached physician consent form - cardiology]** to interested physicians. Drs. Ho and Seidman and the study staff will keep track of the cardiologists who decline study participation and document the reasons why **[see attached study decline log – physicians]**.

Inclusion criteria: Any Partners cardiologist or cardiologist at BCH who currently practices in the Partners Healthcare System or at BCH and who has patients under his or her care with cardiomyopathy who are candidates for or who have already had targeted genetic testing for cardiomyopathy.

Exclusion criteria: Any cardiologist who does not meet the above inclusion criteria.

Medical Geneticists

Dr. Vassy, Dr. Green and Ms. Blout will recruit Board Certified medical geneticists who are generally recognized by their peers as clinical experts. Recruitment will occur through one-on-one conversations at national genetics conferences and by direct outreach by email or phone. After recruitment, medical geneticists who are interested in participating will be emailed a secure link to the REDCap-hosted survey. The first page of the web-based survey will include the informed consent document, which the potential participant may read, print, and provide consent by clicking "Agree," at the bottom of the page **[see attached medical geneticist consent form]**.

Inclusion criteria: Any Board Certified medical geneticist.

Exclusion criteria: Any geneticist who does not meet the above inclusion criteria.

Patients

Primary Care Patients

Each primary care physician enrolled in the study will be responsible for recruiting patients from their practice to the study. Each physician will briefly describe the study to eligible patients during routine office visits. If a patient is interested in learning more about the study, the physician will discuss the study with the patient. The physician will provide the patient with a study brochure **[see attached study brochure]** and request verbal permission from the patient to provide the study staff with the name and phone number of the patient.

Physicians may also send a recruitment letter and/or call patients from their own practice directly who are eligible and may be interested in learning more about this study **[see attached template recruitment letter]**. The physicians will schedule an in-person appointment or a phone call to review the study with patients who express interest before requesting verbal permission from the patient to provide the study staff with the name and phone number of the patient.

Additionally, physicians will keep track of the number of patients who decline to learn more about the study and the reasons why **[see attached study decline log – patients]**.

The study staff will call the patient **[see attached recruitment phone script]** and set up an appointment with the patients who express interest in participating in the study for an in-person informed consent meeting. This phone call will last approximately 5-10 minutes.

Study staff will also ask verbal permission of the potential participants to record their informed consent conversation in order to examine the process for consistency across subjects and to explore the types of questions and concerns our participants had during the informed consent process. Audio-recordings will be de-identified and shared with investigators at Baylor and Duke.

GenomeConnect patients will be recruited by phone, email or mail to assess their interest in participating in the GenomeConnect study **[see attached recruitment letter and talking points]**. Interested participants will be sent the URL to read through the electronic study consents. They will also be provided a phone number to contact our study team with any questions.

Inclusion criteria:

- Generally healthy (as defined by the primary care provider and exclusion criteria) adult patients at BWH

- Ages 18 years or older
- All patients must be fluent in English.

Exclusion criteria:

- Patients who do not meet the above criteria
- Patients with a progressive debilitating illness
- Patients with untreated clinical anxiety or depression (as measured by a Hospital Anxiety and Depression Scale (HADS) score ≥ 14 on the anxiety subscale or ≥ 16 on the depression subscale).
- Patients with cardiovascular disease (including Long QT syndrome, arrhythmia, atrial fibrillation, abdominal aortic aneurysm, etc.)
- Patients with clotting disorders
- Patients who are pregnant or patients whose spouses/significant others are pregnant

Extension Phase- Additional Inclusion Criteria

Aim 1

- Above Inclusion and exclusion criteria PLUS:
 - Inclusion: Self identified as African American/ African race

Extension Phase- Additional Inclusion Criteria

Aim 2

Inclusion Criteria

- MedSeq participants determined to have a monogenic finding

Exclusion Criteria:

- Participants not previously enrolled in the MedSeq Project
- Participants not identified to have a monogenic finding

GenomeConnect Validation Study

Inclusion Criteria:

- MedSeq primary care participants randomized to sequencing arm

Exclusion Criteria

- MedSeq patients randomized to the control arm
- MedSeq cardiology participants randomized to either arm

MedSeq Project Long-Term Follow-Up

Inclusion Criteria:

- MedSeq Project primary care participants who received a family history review with or without whole genome analysis

Cardiology Patients

Each cardiologist enrolled in the study will be responsible for recruiting patients from their practice to the study. Each physician will briefly describe the study to eligible patients during routine office visits. If a patient is interested in learning more about the study, the physician will discuss the study with the patient. The physician will provide the patient with a study brochure **[see attached study brochure]** and request verbal permission from the patient to provide the study staff with the name and phone number of the patient.

Physicians may also send a recruitment letter and/or call patients from their own practice directly who are eligible and may be interested in learning more about this study **[see attached template recruitment letter]**. The physicians will schedule a phone call or in-person appointment to review the study with patients who express interest before requesting verbal permission from the patient to provide the study staff with the name and phone number of the patient.

Additionally, physicians will keep track of the number of patients who decline to learn more about the study and the reasons why **[see attached study decline log – patients]**.

The study staff will call the patient **[see attached recruitment phone script]** and set up an appointment with the patients who express interest in participating in the study for an in-person informed consent meeting. This phone call will last approximately 5-10 minutes.

Study staff will also ask verbal permission of the potential participants to record their informed consent conversation in order to examine the process for consistency across subjects and to explore the types of questions and concerns our participants had during the informed consent process. Audio-recordings will be de-identified and shared with investigators at Baylor and Duke.

Inclusion criteria: Patients in the Partners Healthcare System or at BCH who are 18 years or older with a diagnosis of cardiomyopathy who previously had or who are candidates for targeted cardiomyopathy genetic testing through routine clinical practice within Partners or at BCH. All patients must be fluent in English.

Exclusion criteria: Patients who do not meet the above criteria. Patients with a progressive debilitating illness. Patients who are pregnant or patients whose spouses/significant others are pregnant. Patients with untreated clinical anxiety or depression (as measured by a Hospital Anxiety and Depression Scale (HADS) score ≥ 14 on the anxiety subscale or ≥ 16 on the depression subscale).

MedSeq Project Long-Term Follow-Up

Inclusion Criteria:

- MedSeq Project cardiology participants who received a family history review with or without whole genome analysis

IV. Subject Enrollment

Physicians

Primary Care

Dr. Vassy will speak to the physicians identified through noontime Primary Care conferences by phone or in person, answer any questions about the protocol and review the physician consent form. The physicians will also have the opportunity to speak with, Dr. Green or other project leaders about participation in this study. The physician will sign the consent form and send to the MedSeq Project Manager via BWH inter-departmental mail. The MedSeq Project Manager will store the signed consent form in a locked file cabinet in her office. Dr. Vassy and study staff will document reasons for declining study participation [**see attached study decline log – physicians**].

Cardiology

Drs. Ho and Seidman will speak to the physicians interested in participating in the study in person or by phone, answer any questions about the protocol and review the physician consent form. The physicians will also have the opportunity to speak with the MedSeq Project Manager Dr. Green or other project leaders about participation in this study. The physician will sign the consent form and send to the MedSeq Project Manager via BWH inter-departmental mail or in person. The MedSeq Project Manager will store the signed consent form in a locked file cabinet in her office. Dr. Ho and study staff will document reasons for declining study participation [**see attached study decline log – physicians**].

Medical Geneticists

Dr. Vassy, Dr. Green, and Ms. Blout will speak to the medical geneticists identified at genetics conferences and those identified using direct outreach by phone or in person. Geneticists who are interested in participating will be e-mailed a secure link to the REDCap-hosted survey. The first page of the survey will contain the informed consent form for potential participants to review. They will also have the opportunity to contact Dr. Vassy, Dr. Green, Ms. Blout, and other project leaders about participation in this study. After reviewing the informed consent language on the survey, the geneticists will electronically provide consent for participation via the REDCap-hosted web survey. Consent records will be stored securely on the REDCap server.

Patients

Both Primary Care and Cardiology

Prospective patient participants will meet with a member of the study staff in the BWH Center for Clinical Investigation to discuss the study and review the consent form [**see attached patient consent form—primary care and –cardiology**]. The informed consent meeting will last approximately 30 minutes. Prospective participants who wish to participate will sign the consent form. Should prospective participants need additional time to decide whether or not to participate in the

study, the study staff will provide the consent form for the participant to take home and will follow-up one week later with the prospective participant to schedule a second appointment to review and sign the consent form in person. Patients who decide not to participate will not be contacted again, but reasons for decline will be documented **[see attached study decline log – patients]**. The MedSeq Project Manager will store the signed consent forms in a locked file cabinet in her office.

The study staff will randomize the patient to either receive WGS or not (Standard of Care) **[see attached randomization schema]** after the first in-person visit. All patients will be blinded to randomization status until the results disclosure session.

Recruitment in Primary Care and Cardiology will cease once each physician enrolls approximately 10 patients.

In the event of loss to follow-up or patient withdrawal, we will reinstitute recruitment procedures to meet our goals of having 100 patients randomized to receive WGS and 100 patients randomized to not receive WGS who all complete the 6-month follow-up. We plan to recruit and enroll 300 patients in order to ensure that 200 complete the full follow-up.

Should some enrolled physicians be unable to recruit and enroll 10 patients in their practice, we will ask some of the other physicians to volunteer to recruit and enroll over 10 patients from their practice. However, our total number of patients enrolled will not exceed 300.

Should the cost of WGS be reduced considerably during the period of the MedSeq Project grant, we will submit an IRB amendment to allow us to recruit and enroll additional subjects.

In order to increase collaboration between the bio-banking initiative, the Partners HealthCare Biobank (Partners Biobank), and the MedSeq team, we will approach all patients with the opportunity to co-enroll in the MedSeq Project and the Partners Biobank (IRB protocol # 2009P002190). If patients dually consent to the Partners Biobank and MedSeq, three additional tubes of blood will be drawn at the baseline study visit for MedSeq per the Partners Biobank protocol. Patients will be reminded that both projects are completely voluntary, and that they can take their time to decide if they would like to participate in either or both projects.

All MedSeq patient subjects who are scheduled for this first in-person visit with the study staff will be asked if they are also interested in enrolling in the Partners Biobank. Potential subjects may choose to refuse enrollment of one or both projects.

We may contact enrolled MedSeq Project patients by phone or mail regarding opportunities to participate in future MedSeq Project-related research studies after the MedSeq Project is complete.

Extension

African/African American participants will follow the same study procedures outlined above.

For Patients who we have identified to have a monogenic finding, that is a finding that could potentially impact their health risk, we plan to offer additional analysis. We will review their medical records of these participants, specifically with their variant in mind, to see if features associated with the variant were known prior to the study or were identified by further testing or by their physician during the course of the study. For individuals we feel may need further work-up we will contact them by phone, email or mail to offer them the option of coming in for additional phenotyping.

Optional GenomeConnect Validation Study:

GenomeConnect, ClinGen's patient portal, is hosted by PatientCrossroads (<https://www.patientcrossroads.com/>), a platform specializing in patient registries. GenomeConnect is managed by ClinGen study staff at Geisinger Health System **[see the attached GenomeConnect protocol, approved by Geisinger Health System IRB]**.

MedSeq primary care participants in the sequencing arm who have completed the study will be sent a recruitment letter **[see attached recruitment letter]** describing the opportunity to join GenomeConnect and an optional validation study for MedSeq participants. Those interested will go to the provided GenomeConnect URL provided through the PatientCrossroads portal, **[see GenomeConnect protocol appendix 8.5]** to learn more about this Geisinger IRB approved study and consent online. Consented participants will complete the Geisinger approved GenomeConnect consent followed by the Body Systems survey **[see GenomeConnect protocol appendix 8.1 in the GenomeConnect protocol, and Genome Connect Survey]** and will then be prompted to fill out an additional online consent housed within patient crossroads permitting MedSeq staff to access the results of the Body System Survey for validation purposes **[see MedSeq Validation GenomeConnect Consent]**. If they consent to provide MedSeq staff access to their Body System

survey responses, they will then complete the MedSeq SES survey [see **GenomeConnect MedSeq SES Survey**]. The participants will complete the GenomeConnect Body Systems Survey [see **GenomeConnect protocol appendix 8.1 in the GenomeConnect protocol, and/or Genome Connect Survey**], which allows the patient to document their medical history. This information will be made available to MedSeq study staff via an excel database. The patient's self-reported medical history, collected via the Body System Survey, will be compared by MedSeq staff with information in their medical record to review the accuracy of self-reported data. [See **GenomeConnect MedSeq Schema**]. Summary data including no identifiers will be provided and compared with Geisinger's data and shared with ClinGen.

Optional MedSeq Project Long-Term Follow-Up Study:

MedSeq primary care participants who received a family history review, with or without whole genome sequencing analysis, will be sent a recruitment letter tailored to their randomization status [see **attached LTF recruitment letters**] and consent form describing the opportunity to join an optional long-term follow-up study. MedSeq Project staff will call potential participants 14 days after materials are mailed to answer any questions, to ask if individuals are interested, and to review the informed consent document if appropriate. Individuals who cannot be reached after three phone attempts will be sent a follow-up email or letter tailored to their randomization status and contacted via phone up to three additional times [see **attached LTF reminder letters and telephone script**]. Participants will return the informed consent document to study staff using a postage-paid return envelope. Project staff will then sign and mail a copy of the consent form back to the participant. Of note, MedSeq Project participants had been informed that they may be invited to participate in follow-up studies.

V. Study Procedures

Physicians

Both Primary Care Physicians and Cardiologists

Once the physician has signed the consent form and the MedSeq Project Manager has received it, the study staff will assign each physician a study ID number. Then, the study staff will coordinate a time for the physicians to complete a 6-hour physician educational module. The physician educational module will be comprised of 2 hours of class time and 4 hours of online modules and will include a general introduction to WGS in the clinical context, review of case examples and major academic papers in the field of genetics and genomics [see **attached physician educational module outline**]. The physicians will also be introduced to the format of the Genome Report [see **attached sample Genome Report**] and the Genetics Resource Center (GRC), which will be staffed by medical geneticists and genetic counselors as part of the MedSeq Project to offer point-of-care information for the physicians enrolled in this study regarding their patient's WGS results. The physicians will complete a brief knowledge and attitudes assessment pre- and post-completion of the educational module in order to capture the effectiveness of the module and a baseline understanding of attitudes of physicians regarding genomic information prior to education [see **attached pre- and post-MD education surveys**]. The physician educational module classes will be audio and video taped and shared with the MedSeq investigators at Baylor College of Medicine and Duke University. During the educational period, the physicians may begin recruiting patients from their practice to participate in the study.

After education and before the first results disclosure visit, the study staff will contact each physician to schedule a 45-minute in-person qualitative interview [see **attached baseline qualitative interview guide – physicians**]. This qualitative interview will be audio-recorded. The audio-recordings will be de-identified, electronically stored on the MedSeq Project Manager's computer and shared with the study investigators at Baylor College of Medicine and Duke University, which are both funded research subcontracts of this grant to analyze the audio-recordings generated from this project.

The MedSeq Project study staff will distribute all Genome Reports and Family History Outputs to the physicians via Partners Secure File Transfer. Since the Genome Reports will take longer to generate than the Family History Outputs, the study staff will randomly match patients in the intervention (WGS+) and comparison (WGS-) arms within each study group. The MedSeq Project study staff will send these reports out at the same time. This will ensure that results disclosures in both the WGS+ and WGS- arms occur evenly over time throughout the duration of the study. Upon receiving the reports, the physician will have the opportunity to prepare for the results disclosure session, which includes consulting the Genetics Resource Center (GRC) as needed. If a physician consults the GRC, the GRC staff will document the encounter in the GRC logbook [see **attached GRC logbook**].

The study staff will keep track of all of the participant visits and when each patient's set of reports has been sent to the physician. The study staff will check in with the physicians periodically one week after receiving their patient's report(s) to coordinate a time to schedule the results disclosure visit. Once the physician deems his or herself adequately prepared for the results disclosure session with a particular patient, he or she will alert study staff. The study staff will coordinate a time for the physician and the patient to meet for the results disclosure session. The results disclosure visit will take place either in the physician's clinic, office or the BWH CCI. The results disclosure visit will be audio-recorded. The physician will give the audio recording to the study staff, and the audio-recordings will be de-identified, electronically stored on the MedSeq Project Manager computer and shared with the study investigators at Baylor College of Medicine and Duke University. After the disclosure, the LMM will send the Genome Report to the patient's medical record. Approximately one to two weeks after the results disclosure, the physician will complete a one-page post-disclosure visit checklist, which will take approximately 10 minutes to complete **[see attached post-disclosure MD checklist]**. The physician will document anything relevant to the patient's care as a result of this study in the patient's medical record.

Study staff will coordinate with each physician so that the study staff may meet with the patient immediately after the results disclosure session to administer the results disclosure survey in person at the BWH CCI.

Once all of a physician's patients have completed their 6-month follow-up, the study staff will contact the physician to schedule an in-person 45-minute qualitative interview **[see attached final qualitative interview guide – physicians]**.

After Physicians have completed their 6-month follow-up they will be offered the opportunity to come in for an end of study education session. This session will review common errors physician may have made during their results disclosure sessions and be used as a Q&A session. Preliminary MedSeq findings will be provided and we will provide an opportunity for physicians to share their personal experiences with the project.

For the targeted African American/African Subject recruitment in the extension phase Primary Care physicians who initially participated in MedSeq will be approached using the Physician African American/African recruitment letter, which will be sent by mail or email **[see attached MedSeq Extension AA Recruitment letter]**. This letter will ask them to attempt to recruit 1-3 additional African/African American participants. Dr. Vassy may also reach out to additional primary care physicians by phone, email, or face-to-face conversations about the study. If needed we will recruit up to 10 additional physicians as needed to recruit 10-15 additional African American/African study participants.

The patients' WGS data and any reports generated from that data will be stored at the LMM (raw data files for at least the duration of the grant but no less than 2 years and .vcf files and the patients' Genome Reports indefinitely). Genome Reports (if randomized to the WGS+ arm) will also be stored at the BWH Adult Genetics Clinic/Personal Genomic Consultation Service. For any updates sent on a MedSeq Project patient's report, either initiated by the LMM or at the request of the BWH Adult Genetics Clinic/Personal Genomic Consultation Service, the physician will be alerted through the existing BWH Adult Genetics Clinic/Personal Genomic Consultation Service Infrastructure.

Medical Geneticists

After primary care physicians have completed all disclosure sessions, study investigators will identify the primary care patient participants who had at least one monogenic disease variant identified (eleven patient participants). One vignette per selected patient participant will be created, based on disclosure session transcripts, the physician checklist, and data abstracted from the patient's medical record. The de-identified vignettes will include patient medical and family history, monogenic whole genome sequencing result(s), and a summary of the primary care physician's clinical management of the result(s), such as patient counseling, further clinical testing, or referral to specialists. Each vignette will be followed by a series of validated questions assessing the appropriateness of the clinical management, based on the RAND/UCLA Appropriateness Method **[see attached appropriateness surveys]**. The vignettes will be created using REDCap software so that they may be distributed electronically. Vignettes may be reformulated for visual appeal.

Eight to twelve medical geneticists independent of the study will read the vignettes and rate the appropriateness of the clinical management of each patient using the validated RAND/UCLA Appropriateness Method.

Once the geneticist has electronically signed the consent form, he or she will be allowed to proceed to the clinical vignettes and survey questions. After geneticist participants have completed the surveys, the study team will analyze the data according to validated methods published for the RAND/UCLA Appropriateness Method. This method allows the calculation of a *disagreement index*. For those vignettes where there is significant disagreement among the geneticists as to the appropriateness of clinical management, the geneticists will be invited to participate in a one-hour teleconference to discuss the discrepancies. After this round of vignette review, the geneticists will have the opportunity to change their

appropriateness scores in the REDCap-hosted survey. After the completion of this second round of surveys, if applicable, the geneticists' participation will be considered complete.

Patients

Primary Care

After the patient signs the consent form, the study staff will assign the patient a study ID number. Next, the study staff will administer the baseline survey **[see attached baseline survey]**. The baseline survey will be administered electronically using the computer in the room at the BWH CCI and will take approximately 30 minutes. The baseline survey will assess sociodemographics, genetic literacy, numeracy, personal health information, health behaviors, health intentions, health care utilization, insurance behaviors and intentions, shared decision making, general anxiety and depression, motivations for and perceived utility of WGS, preferences for receiving results, risk perceptions, biases and attitudes.

Once the baseline survey is completed, the study staff will immediately review the scales assessing depression and anxiety (The Hospital Anxiety and Depression Scale (HADS)). Should a patient score above our pre-specified cut-off scores for this scale (≥ 14 on anxiety subscale; ≥ 16 on depression subscale), the patient will be excluded. The PI and the genetic counselor will speak to the patient by phone after this visit and make any appropriate referrals.

After the baseline survey is complete, the patient will complete a modified version of the online Surgeon General's "My Family Health Portrait" created for the MedSeq project by a company called 5AM Solutions, Inc. on the computer at the BWH CCI. This modified version of the Surgeon General's tool is identical to the Surgeon General's tool except that instead of asking for the patient's name, it will ask for the patient's MedSeq study number. Additionally, it allows the generated pedigree to be emailed in PDF format directly to the MedSeq Project Manager via a "submit" button. Like the online Surgeon General's tool, the modified version created by 5AM Solutions, Inc. temporarily stores the patient's family history information on servers outside of Partners only for the time needed for the program to generate the pedigree in PDF format. Once the pedigree is submitted to The MedSeq Project Manager, the patient's family history data is erased. Of note, the data that is temporarily stored on the 5AM Solutions servers does not contain any of the 18 HIPAA identifiers, and is thus, de-identified. The study staff will assist the patient in submitting his/her family history to the MedSeq Project Manager via the online program. Once The MedSeq Project Manager receives the family history in PDF, she will send it to MedSeq Project study staff for distribution to the patient's physician prior to the patient's disclosure visit. **[see attached sample Family History Output]**.

In the baseline survey, we ask patients to list any non-prescription medications they are currently taking. The study staff will access the patient's medical record at the baseline visit to obtain and review with the patient the list of prescription medications they are currently taking **[see attached prescription medications checklist]**.

After the family history is complete, the phlebotomist at the BWH CCI will draw three tubes of blood on all participants. Participants will fill out a three-question survey for which responses will inform the blood typing and analysis with the sequencing data. **[see attached blood typing survey]**. After the blood is drawn, the first visit will be complete.

After the patient leaves the BWH CCI, the study staff will randomize the patient to either the intervention (WGS+) or the comparison (WGS-) arm **[see attached randomization schema]**. The patient will remain blinded to the randomization until the results disclosure session. All blood samples will initially be sent to the Partners Laboratory for Molecular Medicine (LMM). Then, one tube of blood will be shipped to Illumina, Inc. for WGS and one tube of blood will be sent to the BWH Blood Bank for red blood cell antigen phenotyping. The LMM will retain one tube of blood for any necessary Sanger sequencing confirmation prior to reporting the results. If the patient is randomized to the comparison arm, both tubes of blood will be safely discarded.

Next the study staff will contact the participants to set up a time to complete the baseline qualitative interview **[see attached baseline qualitative interview guide – patients]**. All interviews will be conducted at the BWH CCI, be audio-recorded and will last approximately one hour. The audio-recordings will be de-identified, electronically stored on the MedSeq Project Manager computer and shared with the study investigators at Baylor College of Medicine and Duke University. Upon completion of the qualitative interview, the participant will receive \$40.

Once the physician has received the Genome Report and/or Family History Output, he or she will schedule the results disclosure session with the patient directly. The physician will alert the study staff of the appointment date and time. The physician will disclose the results to the patient. Patients in the Primary Care will either receive a Family History Output alone (comparison arm/WGS-) or a Family History Output and a Genome Report (intervention arm/WGS+) **[see attached randomization schema]**. The results disclosure session will take place in either the physician's clinic, office or the BWH

CCI. The results disclosure session will be audio-recorded. The audio-recordings will be de-identified, electronically stored on the MedSeq Project Manager computer and shared with the study investigators at Baylor College of Medicine and Duke University, which are both funded research subcontracts of this grant to analyze the audio-recordings generated from this project. During the results disclosure session, the physician will review the patient's family history with the patient for accuracies, gather additional information that the patient did not enter previously, and analyze, interpret and discuss the family history with the patient. The physician will make notes about the patient's family history and place the Output and their notes in the medical record. After the results disclosure visit, the physician will place the Genome Report and/or the Family History Report in the patient's medical record.

After the results disclosure session, the study staff will meet with the patient either at the BWH CCI or in the physician's clinic or office (space permitting) and administer the results disclosure survey **[see attached results disclosure survey]**. This survey will take approximately 30 minutes to complete. The study staff will immediately review the scales assessing depression and anxiety (The Hospital Anxiety and Depression Scale (HADS)). Should a patient score above our pre-specified cut-off scores for this scale, the study staff will alert the PI and the genetic counselor. The genetic counselor will call the patient after the visit, review the elevated score with the patient and ask questions to monitor the safety and well-being of the patient. The genetic counselor will document this conversation **[see attached Safety Monitoring Chart Note]**, and review the case with the PI. The PI and the genetic counselor will make appropriate referrals to the patient's primary care physician and/or a mental health professional as needed. All cases of safety monitoring will be reviewed by the IRB and the MedSeq Project Monitoring Committee according to our AE reporting protocol **[see attached AE reporting/MPMC schema]**.

At six-weeks and six months post-results disclosure, the study staff will contact the patient to set up a time to complete the follow-up surveys. The follow-up surveys will be administered either in person at the BWH CCI or by phone by the study staff. Each survey will take approximately 30 minutes to complete **[see attached six-week- and six-month follow-up surveys]**. Upon completion of the six-month follow-up survey, the patient will be given \$125.

After each six week- and six-month follow-up survey is complete, the study staff will immediately review the scales assessing depression and anxiety (The Hospital Anxiety and Depression Scale (HADS)). Should a patient score above our pre-specified cut-off score for this scale, the study staff will alert the PI and the genetic counselor. The genetic counselor will call the patient after the visit, review the elevated score with the patient and ask questions to monitor the safety and well-being of the patient. The genetic counselor will document this conversation **[see attached Safety Monitoring Chart Note]**, and review the case with the PI. The PI and the genetic counselor will make appropriate referrals to the patient's primary care physician and/or a mental health professional as needed. All cases of safety monitoring will be reviewed by the IRB and the MedSeq Project Monitoring Committee according to our AE reporting protocol **[see attached AE reporting/MPMC schema]**.

All subjects will be invited to participate in an additional qualitative survey at the six-month time point **[see attached 6-month qualitative interview guide – patients]**. Study staff will coordinate a time for the in-person or phone qualitative interview. All interviews will be conducted at the BWH CCI, be audio-recorded and will last approximately one hour. Patients who complete the qualitative interview will receive an additional \$40.

For any subject who withdraws from the study at any time, the study staff will complete a form documenting the reason for withdrawing from the study **[see attached patient withdrawal form]**.

Should a patient withdraw from the study prior to having their results disclosed to them by their physician, we will destroy the Genome Results report.

After all 6-month follow-up visits are complete, the study staff will review each patient's medical record to collect data regarding tests, procedures, referrals, etc. that have been initiated post-results disclosure. To conduct this medical record review, we will utilize the Partners Research Patient Data Registry (RPDR) as well as manual chart reviews.

Additional African American/African participants recruited in the extension phase of the study will all be placed in the whole genome sequencing arm of the study. They will undergo the same activities as the traditional MedSeq participants.

For Patients who we have identified to have a monogenic finding, that is a finding that could potentially impact their health risk, we plan to perform additional analysis. We will review their medical records looking, specifically with their variant in mind, to see if features associated with the variant were known prior to the study or were identified by further testing or by their physician during the course of the study. For individuals we feel may need further work-up we will contact them to offer them the option of coming in for additional phenotyping. If interested participants will sign the updated consent, which includes information about this visit and what will be included, **[see attached Physician Consent Form_Primary**

Care_extension 12.14.15]. If participants consent to participate, they will come in for a physical exam conducted by a clinical geneticist, Dr. Robert Green or Dr. Joel Krier in the BWH CCI. They will have a more extensive family history collected by a certified genetic counselor and/or web-based program. We may also ask them to sign a release of medical records so that study staff can review medical records both within and outside the Partners Health Care System to determine if they have any known features associated with their genetic variant. The goal of this visit will be to determine if they have any previously undetected signs and symptoms of their genetic variant. We may also refer these participants for additional tests or imaging procedures relevant to their genetic variant. If associated features are identified follow-up recommendations will be made to the participant and their MedSeq provider in the form of a clinic note entered into the electronic medical record.

Cardiology

After the patient signs the consent form, the study staff will assign the patient a study ID number. Then, the study staff will administer the baseline survey **[see attached baseline survey]**. The baseline survey will be administered electronically using the computer in the room at the BWH CCI and will take approximately 30 minutes. The baseline survey will assess sociodemographics, genetic literacy, numeracy, personal health information, health behaviors, health intentions, health care utilization, insurance behaviors and intentions, shared decision making, general anxiety and depression, motivations for and perceived utility of WGS, preferences for receiving results, risk perceptions, biases and attitudes.

Once the baseline survey is completed, the study staff will immediately review the scales assessing depression and anxiety (The Hospital Anxiety and Depression Scale (HADS)). Should a patient score above our pre-specified cut-off scores for this scale, the patient will be excluded. The PI and the genetic counselor will speak to the patient by phone after this visit and make any appropriate referrals.

After the baseline survey is complete, the patient will complete a modified version of the online Surgeon General's "My Family Health Portrait" created for the MedSeq project by a company called 5AM Solutions, Inc. on the computer at the BWH CCI. This modified version of the Surgeon General's tool is identical to the Surgeon General's tool except that instead of asking for the patient's name, it will ask for the patient's MedSeq study number. Additionally, it allows the generated pedigree to be emailed in PDF format directly to the MedSeq Project Manager via a "submit" button. Like the online Surgeon General's tool, the modified version created by 5AM Solutions, Inc. temporarily stores the patient's family history information on servers outside of Partners and BCH only for the time needed for the, the patient's family history data is erased. Of note, the data that is temporarily stored on the 5AM Solutions servers does not contain any of the 18 HIPAA identifiers, and is thus, de-identified. The study staff will assist the patient in submitting his/her family history to the MedSeq Project Manager via the online program. Once the MedSeq Project Manager receives the family history in PDF, she will send it to the MedSeq study staff for distribution to the patient's physician prior to the patient's disclosure visit. **[see attached sample Family History Output]**.

In the baseline survey, we ask patients to list any non-prescription medications they are currently taking. The study staff will access the patient's medical record at the baseline visit to obtain and review with the patient the list of prescription medications they are currently taking **[see attached prescription medications checklist]**. For patients enrolled at BCH, medical records will be reviewed under the direction of Dr. Isaac Kohane (co-PI of the MedSeq project and site-PI of MedSeq at BCH).

After the family history is complete, the phlebotomist at the BWH CCI will draw three tubes of blood on all participants. Participants will fill out a three-question survey for which responses will inform the blood typing and analysis with the sequencing data. **[see attached blood typing survey]**. After the blood is drawn, the first visit will be complete.

After the patient leaves the BWH CCI, the study staff will randomize the patient to either the intervention (WGS+) or the comparison (WGS-) arm **[see attached randomization schema]**. The patient will remain blinded to the randomization until the results disclosure session. All blood samples will initially be sent to the Partners Laboratory for Molecular Medicine (LMM). Then, one tube of blood will be shipped to Illumina, Inc. for WGS and one tube of blood will be sent to the BWH Blood Bank for red blood cell antigen phenotyping. The LMM will retain one tube of blood for any necessary Sanger sequencing confirmation prior to reporting the results. If the patient is randomized to the comparison arm, both tubes of blood will be safely discarded.

Next the study staff will contact the participants to set up a time to complete the baseline qualitative interview **[see attached baseline qualitative interview guide – patients]**. All interviews will be conducted at the BWH CCI, be audio-recorded and will last approximately one hour. The audio-recordings will be de-identified, electronically stored the MedSeq Project Manager computer and shared with the study investigators at Baylor College of Medicine and Duke University.

Upon completion of the qualitative interview, the participant will receive \$40.

Once the physician has received the Genome Report, the Targeted Cardiomyopathy Genetic Testing Report (if the patient has not yet learned their results) and/or Family History Output, he or she will schedule the results disclosure session with the patient directly. The physician will alert the study staff of the appointment date and time. The physician will disclose the results to the patient. Patients will receive a Family History Review with their physician and either a re-disclosure or new disclosure of their Targeted Cardiomyopathy Genetic Testing Report (comparison arm/WGS-) or they will receive a Family History Review with their physician, either a re-disclosure or new disclosure of their Targeted Cardiomyopathy Genetic Testing Report and a Genome Report (intervention arm/WGS+) **[see attached randomization schema]**. The results disclosure session will take place in either the physician's clinic, office or the BWH CCI. The results disclosure session will be audio-recorded. The audio-recordings will be de-identified, electronically stored on the MedSeq Project Manager's computer and shared with the study investigators at Baylor College of Medicine and Duke University. After the results disclosure visit, the physician will place the Genome Report and/or the Targeted Cardiomyopathy Genetic Testing Report and notes from the Family History Review in the patient's medical record.

After the results disclosure session, the study staff will meet with the patient either at the BWH CCI or in the physician's clinic or office (space permitting) and administer the results disclosure survey **[see attached results disclosure survey]**. This survey will take approximately 30 minutes to complete. The study staff will immediately review the scales assessing depression and anxiety (The Hospital Anxiety and Depression Scale (HADS)). Should a patient score above our pre-specified cut-off scores for this scale, the study staff will alert the PI and the genetic counselor. The genetic counselor will call the patient after the visit, review the elevated score with the patient and ask questions to monitor the safety and well-being of the patient. The genetic counselor will document this conversation **[see attached Safety Monitoring Chart Note]**, and review the case with the PI. The PI and the genetic counselor will make appropriate referrals to the patient's primary care physician and/or a mental health professional as needed. All cases of safety monitoring will be reviewed by the IRB and the MedSeq Project Monitoring Committee according to our AE reporting protocol **[see attached AE reporting/MPMC schema]**.

At six-weeks and six-months post-results disclosure, the study staff will contact the patient to set up a time to complete the follow-up surveys. The follow-up surveys will be administered in person at the BWH CCI by the study staff. Each survey will take approximately 30 minutes to complete **[see attached six-week- and six-month follow-up surveys]**. Upon completion of the six-month follow-up survey, the patient will be given \$125.

After the six week- and six-month follow-up surveys are complete, the study staff will immediately review the scales assessing depression and anxiety (The Hospital Anxiety and Depression Scale (HADS)). Should a patient score above our pre-specified cut-off scores for this scale, the study staff will alert the PI and the genetic counselor. The genetic counselor will call the patient after the visit, review the elevated score with the patient and ask questions to monitor the safety and well-being of the patient. The genetic counselor will document this conversation **[see attached Safety Monitoring Chart Note]**, and review the case with the PI. The PI and the genetic counselor will make appropriate referrals to the patient's primary care physician and/or a mental health professional as needed. All cases of safety monitoring will be reviewed by the IRB and the MedSeq Project Monitoring Committee according to our AE reporting protocol **[see attached AE reporting/MPMC schema]**.

All subjects will be invited to participate in an additional qualitative survey at the six-month time point **[see attached 6-month qualitative interview guide – patients]**. Study staff will coordinate a time for the in-person qualitative interview. All interviews will be conducted at the BWH CCI, be audio-recorded and will last approximately one hour. Patients who complete the qualitative interview will receive an additional \$40.

For any subject who withdraws from the study at any time, the study staff will complete a form documenting the reason for withdrawing from the study **[see attached withdrawal form]**.

Should a patient withdraw from the study prior to having their results disclosed to them by their physician, we will destroy the Genome Results report.

After all 6-month follow-up visits are complete, the study staff will review each patient's medical record to collect data regarding tests, procedures, referrals, etc. that have been initiated post-results disclosure. To conduct this medical record review, we will utilize the Partners Research Patient Data Registry (RPDR) as well as manual chart reviews. For patients enrolled at BCH, medical records will be reviewed under the direction of Dr. Kohane (co-PI of the MedSeq project and site-PI of MedSeq at BCH).

We will keep audio and video recordings for 10 years after the completion of the study.

Optional GenomeConnect Validation Study:

Participants interested in the GenomeConnect validation study will visit a dedicated GenomeConnect URL (to track all participants referred from MedSeq). Potential participants will be instructed to register for an account at PatientCrossroads (the company hosting GenomeConnect). Following registration, the participant will be required to complete the GenomeConnect informed consent to enroll in the Geisinger IRB approved Genome Connect Study. After this they will be prompted to complete the body systems survey asking questions about his/her health as well as a brief survey to assess their socio-economic status [see **Body Systems Survey**]. They will then be prompted to complete the MedSeq validation study consent this will allow the release of their Body System Survey results from PatientCrossroads to MedSeq staff for validation purposes. They will next be prompted to fill out the **SES survey** [see **GenomeConnect MedSeq SES Survey**]. The self-reported Body System Survey data will be made available to MedSeq study staff for comparison with the participants' BWH medical record by MedSeq staff. Participation in GenomeConnect will continue unless the participant later chooses to end their participation, as described in the GenomeConnect consent and protocol.

The validation study will be conducted with collaborators at Geisinger Health System, who are enrolling their own participants. Only summary data from the MedSeq arm of the validation study will be shared with the Geisinger staff. No PHI will be exchanged between the two institutions [see **GenomeConnect MedSeq schema**].

Participants who complete the first consent and the Body Systems survey will be enrolled in the Geisinger approved GenomeConnect protocol. Participants who do not consent for both portions of the study will not be enrolled in the MedSeq validation study.

Optional MedSeq Project Long-Term Follow-Up

Participants who enroll in the MedSeq Project Long-Term Follow-Up will complete a REDCap web-based survey on the five-year anniversary of their MedSeq Project disclosure session [see **attached LTF Surveys**]. We will also conduct a medical record review to review participants' health statuses, and identify health care services that occurred during the five-year period after physicians reviewed participants' family histories and/or reviewed whole genome sequencing reports as part of the original MedSeq Project period. We will conduct this medical records review utilizing the Partners Research Patient Data Registry (RPDR) and manual reviews of EPIC and LMR records. Of note, MedSeq Project participants had consented for medical records review for the initial MedSeq Project period, but not this follow-up study.

Other study procedures

Procedures for genome sequencing/genetic testing, analysis, interpretation and reporting

The phlebotomist at the BWH CCI will draw two tubes of blood on each patient. For patients randomized to the intervention (WGS+) arm, the study staff will send one tube of blood to Illumina, Inc. for the CLIA-certified Individual Genome Sequencing Service and one tube of blood to the CLIA-certified Partners Laboratory for Molecular Medicine to store for any Sanger sequencing confirmation prior to reporting. The blood typing survey that patients fill out during the baseline visit will be sent to the BWH Blood Bank in addition to the blood tube. The tubes of blood will be labeled and analyzed by using three identifiers which are typically preferred when performing whole genome sequencing in a CLIA-certified setting: 1) patient's name, 2) patient's date of birth and 3) patient's gender. The study staff will discard both tubes of blood drawn for patients randomized to the comparison (WGS-) arm.

Illumina's Individual Sequencing Service is a CLIA-certified laboratory test, which includes variant calling and SNP array genotyping for quality control. Once a patient's sequence is complete, Illumina will send the patient's raw genomic data, variant calls and the SNP array data to the CLIA-certified Partners Laboratory for Molecular Medicine (LMM) on an encrypted hard drive. The LMM will store each patient's data on their secure servers currently used to house clinical whole genome/exome sequencing data. The LMM will then share the genomic data set with the MedSeq Project Investigators at the Harvard Medical School Center for Biomedical Information (CBMI) who will evaluate variants in the data set relevant to cardiac disease. The investigators at the CBMI will generate a list of cardiac disease variants and send to the LMM. The LMM will evaluate the genomic dataset sent from Illumina and the list of cardiac disease variants sent from the CBMI. The LMM will then generate the appropriate reports for each patient. There will be two sections of the Genome Report: 1) The General Genome Report, which will include highly penetrant disease mutations, carrier status for recessive disease, disease-associated risk alleles and pharmacogenetic associations and 2) The Cardiac Risk Supplement, which will contain any piece of genetic information found in the genome that is relevant to the care of a patient with cardiac disease or at risk for cardiovascular disease (depending on whether the Genome Report is delivered in Cardiology or Primary Care) [see **attached sample Genome Report**]. Through standard clinical reporting mechanisms currently in place at the LMM, a board-certified geneticist will sign-off on all reports prior to release. The MedSeq Project

study staff will distribute all Genome Reports and Family History Outputs to the physicians via Partners Secure File Transfer. After the disclosure, the LMM will send the Genome Report to the patient's medical record. All results returned to subjects and entered into their medical record will be limited to tests that are CLIA-certified. All reports will be labeled with the patient's name, date of birth and gender per standards analyzing WGS information [**see attached sequencing and reporting schema**].

Procedures in the event of a deceased participant in the Whole Genome Sequencing Arm

In the event that a patient participant has been randomized to the whole-genome sequencing arm, and the patient has passed away prior to results disclosure the study team will consider releasing these results to the participant's family. We believe this is important as genetic results could have implications for other family members.

The research team will speak with the participant's study physician, who can potentially provide background information about the patient participant and their family. Our outcomes team will then review the deceased patient participant's survey and interview data, if applicable, to make sure there isn't anything in our data that would suggest that the patient participant would not have wanted the results to be offered to their family members (e.g. in the baseline survey the patient participant indicates that he or she would not share results with family members). If based on this information the MedSeq Project Executive Committee and Protocol Monitoring Committee and the patient's MedSeq physician sees no indication that the deceased participant would not want their results shared, we will notify the IRB of this information as well as our disclosure plan and seek permission to update the family with these results. If the IRB is in agreement with the individualized plan, we will provide this to the appropriate family member(s) in conjunction with this plan.

Access will be provided to the Genome Resource Center in the event that the physician has any questions prior to communicating with the family.

Additional related research studies

The TradeSeq Study (PI, Kathryn Phillips, PhD at University of California, San Francisco) seeks to explore key factors influencing the benefit-risk tradeoffs of whole genome sequencing testing. The TradeSeq Study will interview a subset (n=20) of patients from MedSeq at the baseline visit. The MedSeq Project study staff will ask the participant if he or she is interested in participating in this additional interview. If the participant agrees, the MedSeq Project study staff will conduct the interview [**see attached TradeSeq interview guide**]. This interview will be audio-recorded, and the de-identified audio-recording will be shared with the investigators at UCSF for analysis. The TradeSeq Study investigators at the University of Calgary and a research company called RTI International (who are developing the survey for the UCSF investigators) will listen-in to the interview by phone in order to monitor data collection. These interviews will be used to develop a later survey of all the MedSeq Project participants. The MedSeq Project study staff will coordinate all aspects of the TradeSeq Study in terms of participant contact. Only a de-identified dataset will be shared with investigators at UCSF.

During the post-disclosure follow-up period, the MedSeq Project staff will coordinate a mailing of the TradeSeq Study survey. The survey will be accompanied by a letter from Dr. Robert Green inviting the MedSeq participants to complete the survey [**see attached TradeSeq Invitation Letter**]. The surveys will be mailed to the MedSeq Project study staff at Brigham and Women's Hospital, and de-identified survey data will be shared with the investigators at UCSF.

De-identified data from the MedSeq Project surveys and interviews will be shared with the investigators at UCSF in order to inform the TradeSeq Study analyses.

The CSER ACMG 56 Secondary Findings Project

The CSER ACMG 56 secondary findings project is a consortium wide project being undertaken by the Clinical Sequencing Exploratory Research Consortium (CSER). CSER is the NIH consortium that the MedSeq Project is part of. This ACMG 56 secondary findings project has IRB approval by the NIH. The goal of this project is to: To delineate health care utilization among recipients of secondary variants. To explore communication of variant information to at-risk relatives. To explore perceptions of participants' assessment of the benefits and harms of receiving a secondary variant. A brief overview of this project is attached [**CSER ACMG 56 Interview Project**]. MedSeq Project participants have consented for contact regarding future research studies. The MedSeq Project Manager will call the MedSeq participants who received Whole Genome Sequencing as part of the MedSeq study and who received a variant in one of the genes on the ACMG 56 list, to assess their interest in participating in this CSER interview project using the provided phone script [**CSER ACMG 56 Phone Script**]. For those who express interest in participating, their name and phone number will be provided to the NIH genetic counselor/investigator, Dr. Barbara Biesecker, and the study will be conducted as approved by the NIH IRB.

Pilot testing of Genome Reports and Study Surveys

Partners Healthcare System genetics clinics offer clinical whole genome and whole exome sequencing to select patients for genetic diagnosis. These clinics have sequenced a number of genomes to date and expect to sequence additional patients in the future. The patients are consented to undergo Whole Genome Sequencing for clinical purposes, but they have not consented to having their genomic data shared with other research investigators. While the process of interpreting a genome is inherently the same as sequencing individual genes and analyzing, interpreting and reporting variants found in these genes, the mere volume of work involved when analyzing, interpreting and reporting variants from a whole genome is much larger than when examining just a single gene. Thus, it would be beneficial for the MedSeq Project investigators at the LMM to pilot test and hone the workflow of this extensive and time-consuming process on several existing genomes.

In order to pilot test the creation of the Genome Report and pilot test the study surveys, Partners physicians will approach their own patients who have already had their whole genome sequenced to utilize their sequencing data to pilot the creation of the MedSeq Project Genome Report. Approximately 25 patients will be approached. The patient will first be approached by their own physician (a physician with genetics expertise in the Partners Healthcare system who cares for the patient whom already had his/her genome sequenced). If the patient is interested in learning more, the physician will ask verbal permission of the patient to forward his/her name and contact information to the MedSeq Project study staff. The MedSeq Project study staff will then review the details of the study with the patient and set up a time to conduct an in-person consent. The patient's physician will be alerted if the patient enrolls in the study. Additionally, through the consent process, the study staff will ask the patients if they would be interested in pilot testing some survey questions that will be featured in the MedSeq surveys, given their experience already having their genome sequenced **[see attached MedSeq Project/Genetics Clinic consent form]**. The MedSeq investigators are interested in piloting the surveys on these patients who have previously underwent whole genome sequencing to see how a representative population answers certain questions. The study staff will inform them that participation is completely voluntary, let them know they can stop at any time, and remind them that this will not be included in the study data or released to any investigators beyond survey development/refinement.

In return, the MedSeq Project would generate a Genome Report to return to patient via their clinician in the clinical setting. The MedSeq Project patient consent form has been modified for this mechanism of returning Genome Reports to patients in genetics clinics **[see attached MedSeq Project/Genetics Clinic consent form]**.

Procedures for individual variant interpretation

Currently, there is no universally implemented systematic method that clinical molecular laboratories use to evaluate variants, and molecular laboratories currently use a combination of the medical literature, existing tools, such as PolyPhen, SIFT and OMIM, and even the laboratory's past experience and judgment when reporting variants to patients. The MedSeq Project investigators and staff at the LMM will utilize similar principles in approaching the interpretation and reporting of variants discovered through whole genome sequencing. Just as the sequencing of one gene or a panel of a number of genes generates a list of variants, falling on a continuum from very well-established to novel, whole genome sequencing will also generate variants on this continuum. Since the MedSeq Project seeks to explore the clinical reporting of large amounts of genomic data with different levels of maturity in terms of evidence and known clinical significance, the Genome Report will contain variants with three levels of evidence for clinical significance: 1) Variants that meet established standards for pathogenicity 2) variants that have been associated with cardiac disease through GWA studies and 3) variants that are predicted to be pathogenic or possibly pathogenic in silico, or are plausibly linked to a clinically relevant molecular cardiac pathway. Through this process, the MedSeq Project will test a new paradigm in genomic medicine where reports include genomic information with differing levels of maturity. The physicians will be educated on the different levels of evidence for variants in the Genome Report, and the Genome Report will include statements regarding levels of evidence for particular variants to guide the physicians. Additionally, the physicians will have the Genetic Resource Center available to answer questions about particular variants listed on the Genome Report. Although some of the information included on the Genome Report will be very new, the MedSeq Project investigators firmly believe that the era of genomic medicine will be a constant cycle of discovery and validation, the clinicians of the near future will constantly be incorporating new genomic information into the care of patients. Thus it is important to begin testing this paradigm in the context of integrating whole genome sequencing information into the current practice of medicine.

Data Sharing

Data Sharing through NCBI dbGaP: Consistent with the NHGRI goals of deriving ongoing value from large scale

sequencing studies, we plan to share both phenotypic and genotypic study data with other investigators, through the NCBI database of Genotypes and Phenotypes (dbGaP). We will use secure file transfer protocol (SFTP) to upload study meta data in the form of a data dictionary, phenotype data, and sequence read archives (SRAs) resulting from this research to dbGaP.

Provision of access: Investigators that wish to use study data on de-identified outcomes will seek access by contacting the MedSeq Project Executive Committee. Once an investigator has submitted a proposal for data access, we will consider the request using successful procedures employed by the PI in prior NHGRI-funded clinical trials. In brief, inquiries related to data sharing will be received and evaluated by the Executive Committee. Investigator proposals will be evaluated and a specific de-identified dataset containing the variables needed for that particular analysis will be shared with the applicant scientist. We will look for guidance from NHGRI, NHLBI the U01 Cooperative Agreement Consortium on whether to provide access to individual-level phenotypic study data or linked phenotype/genome data in the interest of patient privacy. If patients choose to co-enroll in the Partners Biobank, their sequencing data generated through MedSeq will be shared with the Partners Biobank.

VI. Biostatistical analysis

Given the lack of prior research in this area, and the broad number of topics of interest, the aims of the study are predominantly exploratory. This study is designed as a randomized clinical trial of WGS disclosure, but we do not have a large enough sample for statistical power to make valid cross-group comparisons. Nevertheless, we will explore differences in all domains across all study groups.

Qualitative Analyses

Dr. Amy McGuire at Baylor College of Medicine will lead coding and analysis of qualitative data. Data will be coded and analyzed using both conventional and directed content analysis.²⁷ Directed content analysis will focus on classifying the data according to core ethical principles. Conventional content analysis will allow for identification and classifications of recurring themes in participant responses. All data will be reviewed for competing or alternate meanings or interpretations.²⁸ We will also mark illustrative quotations that convey in illuminating detail how participants think and feel about receiving WGS results and how they have been affected by the information provided.

Analysis of Audio-Recorded Disclosure Conversations

For the analyses of the audio-recorded visits, we will digitally record to audio “.wav” files and they will be coded using the state-of-the art communications analysis system ENCOUNTER program. All coding will be conducted directly with the audio files, rather than transcriptions. Such analysis preserves inflection, volume and other attributes of conversation that assist in coding.

We will conduct a series of communication analyses. The first analysis will be to content code the visit to determine all the health topics discussed in the visit. This will provide us with an overview of the conversation and will allow us to see how long providers and patients discuss genetic test results and family history and to see what other topics they discuss in their visit. The results of the content coding will provide us with graphical output in a color-coded manner that will allow us to easily see the pattern in which various health topics are discussed.

Our second analysis will be to analyze the quality of the discussions by measuring how the providers and patients exchange information regarding genetic test results and family history. Our third analysis will be measuring how providers and patients engage in decision-making based on the genetic test results by using a coding tool modeled after Braddock's Informed Decision Making model.²⁹ This measure will analyze whether there were discussions about: 1) patient role in decision making, 2) clinical issue or nature of the decision, 3) alternatives, 4) pros and cons of a decision, 5) uncertainty with decision, 6) exploring patient preferences, and assessing patient understanding.

Dr. Stewart Alexander at Duke University will oversee the coding of audio recordings using the ENCOUNTER software system. Once the coding of the disclosure conversations is completed, the relational database will be exported to Drs. McGuire and Green for analysis.

Drs. Alexander and McGuire will obtain IRB approval at their own institutions separately for their role in this project.

Quantitative Analyses

A statistician will lead quantitative analyses. Descriptive statistics will be used to characterize physicians and patients in terms of demographic variables, motivations for participating in this study, and disclosure preferences. Descriptive statistics will also be used to characterize patients in terms of genetic literacy and comprehension, the psychological impact and personal utility of testing, and response to the information in the following domains: (a) communication with family and/or other health care providers, (b) changes in insurance purchasing behaviors or intentions, and (c) changes in health behaviors, health care utilization or behavioral intentions (e.g., diet, exercise). For measures where we have both baseline and follow-up survey data we will use standard pre-post analyses (e.g., paired t-tests, repeated measures analyses) to assess whether significant changes occurred in these domains following receipt of test results.

An initial step in our quantitative data analytic plan will be to determine potential differences between the two groups of respondents coming from a primary care setting and a cardiology clinic. Given that those from the primary care clinic do not have any particular underlying condition for which a genetic test is being ordered (unlike the patients with cardiomyopathy), it will be important to determine whether patients from these two groups can be pooled across analyses or should be analyzed separately. We will therefore examine whether respondents from the two clinics differ at baseline on key demographic characteristics as well as on our main outcomes of interest (e.g., disclosure preferences).

Economic Analysis of Utilization Data

A critical question in the application of genomics to human health is whether healthcare costs will be needlessly amplified as a result of providing novel genetic information. To truly measure cost-effectiveness, we would need to measure specific clinical outcomes that will not be apparent over the course of the trial. However, in this exploratory study, we will perform a cost-consequences analysis over the timeframe of the trial. We will use standard methods for cost-consequence analysis.³⁰ We will aggregate the relevant costs and consequences described above and present them in table format. A cost-utility analysis will not be performed because it is unlikely that receiving genomic information will influence patient quality of life to a degree measurable using standard instruments.

After the all the 6-month follow-up visits are complete, the study staff will review each patient's medical record to collect data regarding tests, procedures, referrals, etc. that have been initiated post-results disclosure. For patients enrolled at BCH, medical records will be reviewed under the direction of Dr. Kohane (co-PI of the MedSeq project and site-PI of MedSeq at BCH).

VII. Risks and Discomforts

Common Risks – Patients

Phlebotomy may cause a small amount of pain. In addition, subjects may get a temporary bruise at the collection site. Rarely, people faint when their blood is drawn. Very rarely, the vein may become red, swollen or infected.

There are no additional anticipated common risks associated with participation in this study.

Uncommon Risks - Patients

Uncommon risks may include:

- Emotional or psychological distress from learning genetic information about oneself or family members.
- Emotional or psychological distress from learning unanticipated information, such as alternate paternity or race.
- Inability to obtain insurance coverage not protected by the Genetic Information Nondiscrimination Act (GINA).
- Medical costs from tests ordered and/or additional office visits as a result from specific genetic information discovered.
- Loss of privacy.

Study personnel will take the following measures to ameliorate these uncommon risks:

- Patients enrolled in this study will undergo a detailed in-person informed consent process, which includes discussion of each of these uncommon risks and prepares the patient for the vast amount of possible results that could be discovered.
- The Genome Resource Center (GRC) staff will review all cases for situations that may impact patient safety [**see attached GRC Safety Monitoring Summary Sheet**]. The GRC will create a mechanism to provide feedback regarding miscommunication or misunderstanding of information between the physician and patient during the MedSeq Project. The GRC will write a cumulative report for the MPMC twice annually, or ASAP if the safety issue is deemed to be urgent. The IRB will be alerted of all issues identified through the GRC review in a cumulative adverse event report [**see attached AE reporting/MPMC schema**].

- The MedSeq Project Monitoring Committee (MPMC) will review cases of Serious and Non-serious Adverse Events twice per year at minimum; The PI will monitor all cases and seek action in real-time as appropriate. The IRB will be alerted of all Serious and Non-Serious Adverse Events according to our protocol **[see attached AE reporting/MPMC schema]**.
- Study personnel will take every precaution to keep the patient's personal identifiers confidential and protect each patient's privacy in all parts of MedSeq in which patient data is used.
- Optional GenomeConnect Validation Study: PatientCrossroads houses GenomeConnect on a platform called CONNECT. CONNECT is a registry system that securely stores data collected from study participants **[see GenomeConnect protocol appendix 8.1]**. PatientCrossroads will be providing MedSeq study staff with the identifying information of consented individuals, for the purposes of medical record review. No PHI will be shared with Geisinger Health Systems. Patient Crossroads is both HIPAA and FISMA compliant.
- Optional MedSeq Project Long-Term Follow-up: Surveys will be administered using REDCap. Of note, no information will be collected that is deemed, "high-risk, confidential information."

Risks – Physicians

There are no anticipated common or uncommon risks associated with participation in this study. Physicians will operate within the routine practice of medicine and adhere to professional standards. The genomic information about their patients derived as part of this study is an additional informational resource that may or may not be useful in the care of their patients; physicians are professionally expected to integrate a variety of informational sources into their practice and genomic information is no different.

Physicians may feel uncomfortable with genomic information about their patients derived from this study, but the training offered in the Physician Education Module and the availability of the Genetics Resource Center Staff will support them. The physicians may also contact the MedSeq Project Monitoring Committee directly with any concerns during their study participation.

Risks – Medical Geneticists

There are no anticipated common or uncommon risks associated with participation in this study. Medical geneticists will complete the surveys online at their own convenience, and participation is not expected to detract from standard work commitments. If necessary, the one-hour teleconference will be scheduled at a mutually convenient time.

VIII. Potential Benefits

Potential Benefits – Patients

There may be no direct benefits to participating individuals. Participants may learn genetic information about themselves or family members that is beneficial to them in terms of managing current disease, identifying risk of future disease which would allow the opportunity for surveillance and/or prevention, or identifying genetic information that provides personal utility, such as financial planning, family planning or satisfying one's curiosity about their own genetic makeup.

Potential Benefits – Physicians

There may be no direct benefits to participating physicians. Physicians may learn more about genetics and WGS as a result of participating in this study. Physicians may also benefit from a strengthened physician-patient relationship with their patients enrolled in this study.

Potential Benefits – Medical Geneticists

There may be no direct benefits to participating medical geneticists. Geneticists may learn more about how primary care physicians respond to genetic information in patient sessions, which could better inform future geneticist-physician interactions.

Potential Benefits – Society

There are several potential benefits to society. The time when WGS will be inexpensive enough to be done on the entire population is imminent. Results from this study will provide critical insight into how genomic information may be incorporated into the current practice of clinical medicine and identify areas of further study in subsequent larger randomized controlled trials examining the impact of delivering WGS information to physicians and their patients. There are speculative concerns that information derived from WGS could lead to undesirable outcomes, such as an overutilization of medical resources, vast misunderstanding among physicians and patients, or insurance discrimination. Without actually examining these potential risks within the context of a randomized clinical trial with a physician and patient support system in place, we will not be able to begin to understand the potential benefits, limitations and risks associated with the use of this technology in a clinical setting.

For the GenomeConnect portion of this study, society could benefit if it is determined that patient-entered data is accurate. This could inform the development of tools similar to GenomeConnect to add to the healthcare system as another source of reliable data. If patient-entered data is found to be inaccurate, this could also provide vital information to healthcare systems when designing tools to best incorporate genomic data with phenotypic information.

For the MedSeq Long-Term Follow-Up portion of this study, society could benefit from an improved understanding of the potential benefits, limitations and risks associated with the use of whole genome sequencing in a clinical setting, including its cost-effectiveness.

Patient Compensation

Participants will be compensated with \$125 for completion of the all the surveys that are part of this study. Additionally, participants will be compensated for each qualitative interview with \$40. Parking for study visits will be covered by the study.

Participants who are asked to come back for a full exam and work-up as part of the extension will be compensated \$50. Parking will be covered by the study.

Participants who choose to participate in the GenomeConnect validation study will receive a \$25 Amazon.com gift card. The gift card will be sent electronically to the email address used to register the participant for GenomeConnect, after the participant completes the body systems survey and the GenomeConnect MedSeq SES Survey.

Participants who choose to participate in the MedSeq Project Long-Term Follow-Up will receive a \$100 check.

Lottery for WGS

Participants who have been randomized to the comparison (WGS-) arm will have the opportunity to enter a lottery to receive WGS at the end of their study participation. Participants will be told about the lottery at their disclosure visit (visit 3) by the study staff. Following the disclosure visit with their physicians, study staff will ask participants if they would like to opt into the lottery for WGS. Study staff will remind participants that the lottery is completely voluntary. A total of three WGS will be reported through this lottery.

A drawing of those who have opted into the lottery will take place following the disclosure visit (visit 3) for the 33rd, 66th and 100th participants in the comparison (WGS-) arm. Winners of the lottery will be informed at their 6-month follow up visit (visit 5). At this time they can schedule a blood draw with the lab to be sent in for whole genome sequencing. Results will be reported through their own physician who is also a MedSeq Project enrolled physician. The GRC will be made available for any questions or concerns. If for any reason the patient's physician is unwilling or unable to report WGS results the study physician, Dr. Robert Green, will report the WGS results to the participant at the BWH Center for Clinical Investigation or in the BWH Adult Medical Genetics Clinic. We will not survey or interview patients who received WGS as part of the lottery, however, we will apply the same data-sharing protocol as outlined above and include these patients in the medical record review. It is up to the physician's discretion to document any clinically relevant information learned as a result of this WGS report in the patient's medical record.

Physician Compensation

Physicians will be compensated for their time: Primary Care Physicians who surpassed their recruitment goal of 10 will receive a \$7,500 honorarium; recruiting PCPs who enrolled at least one participant but did not exceed their recruitment goal will receive a \$6,000 honorarium. Cardiologists will receive a \$1000 honorarium for their participation in this study.

Primary care physicians who recruit additional African/ African American participants, as part of the extension will receive an additional \$1000.

Geneticist Compensation

Medical geneticists will be compensated for their time. Each participating geneticist will receive a \$100 e-check for completing the first survey. If a one-hour teleconference is required to resolve significant disagreement on certain clinical vignettes, they will receive an additional \$100 e-check for participation.

IX. Monitoring and Quality Assurance

The PI will be responsible for monitoring the quality of the data collected as part of this study. All survey and audio-recorded data will be analyzed using the patient's study number and not their name or other identifiers. All blood samples and genome data will be analyzed using the patient's name, date of birth and gender in a CLIA-certified setting. The link containing the patient's study ID to personal identifiers will be kept in a locked filing cabinet and on a password-protected Excel spreadsheet in the MedSeq Project Manager's office. WGS and the generation of reports using WGS data will be conducted in CLIA-certified settings utilizing clinical genetics reporting standards already in

place. Patients will be monitored for levels of clinically significant depression and/or anxiety after learning the results of their Genome Report and/or Family History Review. The Genome Resource Center (GRC) staff will review all cases for situations that may impact patient safety [see attached GRC Safety Monitoring Summary Sheet]. An example of a situation that may impact patient safety is the miscommunication of personal genetic information. The GRC will create a mechanism to provide feedback regarding miscommunication or misunderstanding of information between the physician and patient during the MedSeq Project. The GRC will write a cumulative report for the MPMC twice annually, or immediately if the safety issue is deemed to be urgent. The IRB will be alerted of all issues identified through the GRC review in a cumulative adverse event report [see attached AE reporting/MPMC schema]. All cases of safety monitoring will be reviewed by the MedSeq Protocol Monitoring Committee (MPMC) twice per year at minimum. Serious Adverse Events (SAEs) will be reported immediately (within 24 hours) to the PI and within one week to the IRB and the MPMC. Non-serious Adverse Events (AEs) will be reviewed twice annually by the MPMC and reported annually to the IRB. [see attached AE reporting/MPMC schema].

Certificate of Confidentiality

An NIH Certificate of Confidentiality has been obtained for this study, which protects each patient's genomic and survey data generated by the MedSeq Project from forced disclosure.

X. References

1. Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. *Genet Med.* 2012;14(4):393-398.
2. Worthey EA, Mayer AN, Syverson GD, et al. Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet Med.* 2011;13(3):255-262.
3. Illumina. Test process. 2012; http://www.everygenome.com/test_process/process.ilmn. Accessed May 17, 2012, 2012.
4. 23andMe. Exome 80x. 2011; <https://www.23andme.com/exome/>. Accessed May 17, 2012, 2012.
5. Green E, Guyer M. Charting a course for genomic medicine from base pairs to bedside. *Nature.* 2011;470(7333):204-213.
6. Kohane I, Masys D, Altman R. The incidentalome: A threat to genomic medicine. *JAMA.* 2006;296(2):212-215.
7. McGuire A, Burke W. Raiding the medical commons: An unwelcome side effect of direct-to-consumer personal genome testing. *JAMA.* 2008;300(22):2669-2671.
8. Khoury MJ, McCabe LL, McCabe RB. Population screening in the age of genomic medicine. *N Engl J Med.* 2003;348(1):50-58.
9. Khoury M, Berg A, Coates R, Evans J, Teutsch S, Bradley L. The evidence dilemma in genomic medicine. *Health Aff.* 2008;27(6):1600-1611.
10. Varmus H. Ten years on - The human genome and medicine. *N Engl J Med.* 2010;362:2028-2029.
11. Feero W, Guttmacher A, Collins F. Genomic medicine - An updated primer. *N Engl J Med.* 2010;362(21):2001-2011.
12. Evans J, Meslin E, Marteau T, Caulfield T. Genomics. Deflating the genomic bubble. *Science.* 2011;331(6019):861-862.
13. Lenfant C. Shattuck lecture--clinical research to clinical practice--lost in translation? *N Engl J Med.* 2003;349(9):868-874.
14. Petitti D, Teutsch S, Barton M, Sawaya G, Ockene J, DeWitt T. Update on the methods of the U.S. Preventive Services Task Force: Insufficient evidence. *Ann Intern Med.* 2009;150(3):199-205.
15. Downing GJ. Key aspects of health system change on the path to personalized medicine. *Translational Research.* 2009;154(6):272-276.
16. Brauer C, Bozic K. Using observational data for decision analysis and economic analysis. *Journal of Bone and Joint Surgery-American Volume.* 2009;91A:73-79.
17. Moussa I. Coronary artery bifurcation interventions: The disconnect between randomized clinical trials and patient centered decision-making. *Catheter Cardiovasc Interv.* 2011;77(4):537-545.
18. Travis S. New thinking: Theory vs practice. A case study illustrating evidence-based therapeutic decision making. *Colorectal Dis.* 2006;8 Suppl 1:25-29.
19. ESHG. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. *Eur J Hum Genet.* 2010;18(12):1271-1273.
20. Bell CJ, Dinwiddie DL, Miller NA, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. *Sci Transl Med.* 2011;3(65):65ra64.
21. Chimenti C, Pieroni M, Morgante E, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circulation.* 2004;110(9):1047-1053.
22. Wittenberger M, Hagerman R, Sherman S, et al. The FMR1 premutation and reproduction. *Fertil Steril.* 2007;87(3):456-465.

23. Wang X, Moylan B, Leopold D, et al. Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. *JAMA*. 2000;284(14):1814-1819.
24. Wang X, Kim J, McWilliams R, Cutting G. Increased prevalence of chronic rhinosinusitis in carriers of a cystic fibrosis mutation. *Arch Otolaryngol Head Neck Surg*. 2005;131(3):237-240.
25. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565-574.
26. Johnston JJ, Lewis KL, Ng D, et al. Individualized iterative phenotyping for genome-wide analysis of loss-of-function mutations. *Am J Hum Genet*. 2015;96(6):913-925.
27. Hsieh H, Shannon S. Three approaches to qualitative content analysis. *Qualitative Health Research*. 2005;15(9):1277-1288.
28. Barbour R. Checklists for improving rigour in qualitative research: A case of the tail wagging the dog? *Bmj*. 2001;322(7294):1115-1117.
29. Braddock C, 3rd, Edwards K, Hasenberg N, Laidley T, Levinson W. Informed decision making in outpatient practice: Time to get back to basics. *JAMA*. 1999;282(24):2313-2320.
30. Gold MR, Siegel JR, Russell LB, Weinstein MC, eds. *Cost-effectiveness in health and medicine*. New York: Oxford University Press; 1996.