Overview

The National Human Genome Research Institute (NHGRI) Ethical, Legal and Social Implications (ELSI) Research Program frequently receives requests for examples of funded grant applications. Several investigators and their organizations agreed to let excerpts of their ELSI grant applications be posted online.

Acknowledgement

We are grateful to the investigators and their institutions for allowing us to provide this important resource to the community. To maintain confidentiality, we have redacted some information from these documents (e.g., budgets, social security numbers, home addresses, introduction to revised application), where applicable. We do not include other SF 424 (R&R) forms or requisite information found in the full grant application (e.g., budgets, biographical sketches, letters of recommendation or letters of support). NIH grant formats or rules may have changed since these applications were prepared; therefore, applicants should always follow the application format instructions included in the funding announcement.

PI: **Yu, Joon-Ho**	Title: Returning Exome and Whole Genome Results To Underserved Minority Populations	
Received: 03/12/2014	FOA: PA14-042	Council: 10/2014
Competition ID: FORMS-C	FOA Title: NIH PATHWAY TO INDEPENDENCE AWARD (PARENT K99/R00)	
1 K99 HG007076-01A1	Dual:	Accession Number: 3679730
IPF: 9087701	Organization: UNIVERSITY OF WASHINGTON	
Former Number:	Department: Pediatrics	
IRG/SRG: SEIR	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 92,437 Year 2: 93,736 Year 3: 161,165 Year 4: 161,165 Year 5: 161,165	Animals: N Humans: Y Clinical Trial: N Current HS Code: HESC: N Evaluative Info	New Investigator: Early Stage Investigator:

Senior/Key Personnel:	*Organization:*	*Role Category:*
Joon Ho Yu	University of Washington	PD/PI
Wylie Burke M.D.	University of Washington	Other Professional-Mentor
Michael Bamshad M.D.	University of Washington	Other Professional-primary Mentor
Deborah Bowen Ph.D	University of Washington	Other Professional-Advisor
Charmaine Royal Ph.D	Duke Institute for Genome Sciences & Policy	Other Professional-Advisor
Holly Tabor Ph.D	Seattle Children's Research Institute	Other Professional-Advisor

Reference Letters

Reference name

Reference name

Reference name

Reference name

Reference name

Additions for Review

Accepted Publication recent publications

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier
HG007076

b. Agency Routing Number

2. DATE SUBMITTED

Application Identifier
A89695

c. Previous Grants.gov Tracking Number
Grant11059425

5. APPLICANT INFORMATION

Organizational DUNS*: 605799469

Legal Name*: University of Washington
Department: Office of Research
Division: Office of Sponsored Programs
Street1*: 4333 Brooklyn Ave NE, 17th Floor
Street2: Box 359742
City*: Seattle
County: King
State*: WA: Washington
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 98195-9472

Person to be contacted on matters involving this application

Prefix: Ms. First Name*: Lynette Middle Name: F Last Name*: Arias Suffix:

Position/Title: Director
Street1*: 4333 Brooklyn Ave NE, 17th Floor
Street2: Box 359742
City*: Seattle
County: King
State*: WA: Washington
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 98195-9472
Phone Number*: 206-543-4043 Fax Number: 206-685-1732 Email: osp@uw.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 61-6001537

7. TYPE OF APPLICANT* H: Public/State Controlled Institution of Higher Education

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

❍ New ● Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).

❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Returning Exome and Whole Genome Results To Underserved Minority Populations

12. PROPOSED PROJECT

Start Date* 09/01/2014
Ending Date* 08/31/2019

13. CONGRESSIONAL DISTRICTS OF APPLICANT
WA-007

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: Joon Ho Middle Name: Last Name*: Yu Suffix:

Position/Title: Senior Fellow
Organization Name*: University of Washington
Department: Pediatrics
Division: Genetic Medicine
Street1*: 1959 NE Pacific Street, HSB RR349
Street2: Box 356320
City*: Seattle
County: King
State*: WA: Washington
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 98195-6320
Phone Number*: 206-685-3491 Fax Number: 206-221-3795 Email*: joonhoyu@uw.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$947,887.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$947,887.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: Ms. First Name*: Lynette Middle Name: F Last Name*: Arias Suffix:

Position/Title*: Director
Organization Name*: University of Washington
Department: Office of Research
Division: Office of Sponsored Programs
Street1*: 4333 Brooklyn Ave NE, 17th Floor
Street2: Box 359742
City*: Seattle
County: King
State*: WA: Washington
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 98195-9472
Phone Number*: 206-685-3491 Fax Number: 206-221-3795 Email*: osp@uw.edu

Signature of Authorized Representative*
Kathryn Hovick

Date Signed*
03/12/2014

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:1248-Coverletter_FINAL.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Washington
Duns Number:	6057994690000
Street1*:	4333 Brooklyn Ave NE
Street2:	Box 359472
City*:	Seattle
County:	King
State*:	WA: Washington
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	98195-9472
Project/Performance Site Congressional District*:	WA-007

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	University of Washington
DUNS Number:	6057994690000
Street1*:	1959 NE Pacific Street, HSB RR349
Street2:	Box 356320
City*:	Seattle
County:	King
State*:	WA: Washington
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	98195-6320
Project/Performance Site Congressional District*:	WA-007

File Name

Additional Location(s)

Funding Opportunity Number: PA-14-042. Received Date: 2014-03-12T12:47:13.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ● **Yes** ○ **No**

IRB Approval Date:

Human Subject Assurance Number 00006878

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ○ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	1243-ProjectDescription_FINAL.pdf
8. Project Narrative*	1244-PUBLIC_HEALTH_RELEVANCE.pdf
9. Bibliography & References Cited	1245-References_FINAL.pdf
10.Facilities & Other Resources	1246-Joon_Bamshad_Facilities_FINAL.pdf
11.Equipment	
12. Other Attachments	1247-Referees.pdf

Funding Opportunity Number: PA-14-042. Received Date: 2014-03-12T12:47:13.000-04:00

ABSTRACT

Exome sequencing (ES) and whole genome sequencing (WGS) are transformative new tools for discovery of genetic risk factors for both rare and common diseases and offer the potential of personalized genetic risk profiling in a single, cost-effective test. Because of the large number of variant results simultaneously identified, the number of results with potential clinical utility—including those that are unanticipated, and the evolving utility of results over time—use of these technologies challenges existing models of returning results to research subjects and patients. This has generated widespread interest in developing and testing innovative strategies for returning results from ES/WGS studies. Almost all strategies currently being studied, however, focus on returning results to European Americans—despite evidence of differences among racial and ethnic groups for preferences for results, the interpretation of clinical utility, and the impact of receiving genetic results. This situation reflects the broader challenge of involving racial and ethnic minority communities in genetic research in order to ensure parity in the benefits of advances in genomic medicine. Accordingly, it is imperative that we understand the attitudes and preferences of racial and ethnic minorities toward genomic research and specifically return of ES/WGS results, and assess the outcome of receiving ES/WGS and its impact on minority participation. I am choosing to devote my career to further the ethical and scientific translation of genomics to benefit all people, especially underserved racial and ethnic minorities. Through formal training at leading research institutions, mentored research and publications with experts in their respective fields, I will capitalize on my prior training in public health genetics and complete my transition to an independent investigator by (1) acquiring skills in quantitative survey development, conduct, and analysis; (2) acquire skills to work with culturally diverse racial and ethnic minority communities to conduct collaborative research; and (3) broaden my understanding of theoretical and empirical work on group harms and benefits from bioethics, anthropology and the social sciences. To compliment my formal training, I will utilize these skills to conduct two mentored research projects including (1) a survey of healthcare providers and community leaders who serve racial and ethnic minority communities and (2) focus groups with racially and ethnically diverse adults, about participation in genetic research and return of ES/WGS results. In the independent phase of this proposal, I will (1) characterize and describe attitudes of underserved populations toward return of ES/WGS results by using a survey and (2) characterize individual preferences for receiving ES/WGS incidental finding through interviews with participants who are using a newly developed web-based tool called My46. Also using this tool, I will (3) study the outcomes of returning ES/WGS incidental findings to a cohort of African Amerian individuals.

PUBLIC HEALTH RELEVANCE

Exome sequencing (ES) and whole genome sequencing (WGS) are transformative new tools that are revolutionizing gene discovery for Mendelian disorders and complex traits. The prospect of participating in ES/WGS research and returning results from ES/WGS presents numerous challenges including the need to ensure equal benefit to underserved racial and ethnic minority populations, and the potential for group benefits and harms. I propose to learn about the perspectives of racial and ethnic minority populations on participation in ES/WGS research and receiving ES/WGS results.

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BUDGET JUSTIFICATION (YR01-02)

PERSONNEL
Current fringe rate is 28.7%

Joon-Ho Yu, MPH, PhD, Principal Investigator (EFFORT **in YR01-02)** Dr. Yu is a Senior Postdoctoral Fellow in the Division of Genetic Medicine, Department of Pediatrics at the University of Washington School of Medicine. He trained in the interdisciplinary program of Public Health Genetics where he focused on genetic epidemiology, bioethics, and medical anthropology. Dr. Yu's work has focused on the use of race and genetic ancestry in human genetics research, developing interventions to address barriers that contribute to health disparities, minority participation in research, and ethical issues related to informed consent and return of results for whole genome sequencing. Dr. Yu will lead the project, assume primary responsibility for the direction and oversight of all activities of the project, and will supervise all aspects of the day-to-day execution of the study. A 3% increase in Dr. Yu's salary is included in Year 2. Salaries in Years 3-5 are expected to be commensurate to that of an assistant professor and includes 4% annual increases.

TUITION (YR01: $1,128; YR02: $1,128)
Faculty Staff Tuition Exemption Program & Fees
Funds are requested for selected courses at the University of Washington to acquire skills in conducting quantitative survey research (Training Goal 1) and conducting research with underrepresented minority populations (Training Goal 2). The UW's Faculty Staff Tuition Exemption Program will allow Dr. Yu to take up to 6 credits per quarter without tuition. Exceeding 6 credits in a quarter incurs a cost of $900 per quarter. Additional per quarter costs include $35 registration fee and $41 technology use fee. Assuming the planned course of study in Year 1 includes 10 credits in Autumn, 10 credits in Winter, and 5 credits in Spring, Year 1 tuition is $1,128. Assuming the planned course of study in Year 2 includes 5 credits in Autumn, 10 credits in Winter, and 5 credits in Spring, Year 2 tuition is $1,128.

SERVICES (YR01: $10,000; YR02: $19,300)
Transcription Costs
Funds are requested for transcription of audio-recordings from key informant interviews (n=40) with community leaders and healthcare providers about participation in genetic research and the return of ES/WGS results, and issues raised by professional recommendations for reporting incidental findings in clinical and research contexts (K-Research Aim 1 in YR01) and 20 focus groups to characterize adult perspectives on the risks and benefits of participating in genetics research and receiving ES/WGS results (K-Research Aim 2 in YR02). Assuming that each interview will be 1 hour in length and 5 hours of transcription will be required for 1 hour of audio-recording at $30 per hour, transcription cost per interview is estimated at $150. Assuming that each focus group will be 1.5 hours in length and 5 hours of transcription will be required for 1 hour of audio-recording at $40 per hour, transcription cost per focus group is estimated at $300. Transcription for 40 interviews is $6000 in Year 1 and for 20 focus groups is $6000 in Year 2.

Participant Incentives (YR01: $4,000; YR02: $10,000)
Funds are requested to provide interview and focus group participants with an incentive gift card for their participation. A total of 40 interview participants (K-Research Aim 1 in YR01) will receive a $50 gift card. Survey respondants (K-Research Aim 1 in YR01) will be given the opportunity (an approximately 1 in ~20 chance) to win a $200 gift certificate. Assuming approximately 200 respondents, $200 x 10 groups of 20 = $2,000. A total of 200 participants in focus groups on return of ES/WGS results (K-Research Aim 2 in YR02) will receive a gift card at

$50 per participant at the end of each focus group. The participant incentives are $2,000 for interviews, $2,000 for surveys and total $4,000 in YR01 and $10,000 in YR02.

Focus Group Costs (YR02: $3,300)
Funds are requested to enable convening focus groups (K-Research Aim 2). On average we estimate room rentals at $50, childcare at $50, and meeting supplies at $65 per 2 hr focus group. We estimate $3,300 for 20 – 2 hour focus groups in Year 2.

TRAVEL (YR01: $12,000; YR02: $4,000)
Funds are requested for travel for Dr. Yu to the following:
1. Two scientific meeting per year at $2,000 per trip per year (5 days per trip). Dr. Yu plans on attending the American Society for Human Genetics and the American Society for Bioethics and Humanities (Training Goals and 1 and 2 in YR01-02).
2. University of North Carolina Summer Research Institute $4000 including registration fees in year 1 (5 days). Dr. Yu plans to take course work on Family Research: Conceptual & Methodological Issues; Instrumentation: development, Testing & Revision; and Mixed Methods Research (Training Goal 1 in YR01).
3. University of Michigan Summer Institute in Survey Research Techniques $4,000 including registration fees in year 1 (5 days). Dr. Yu plans to take course work on Applied Questionnaire Design and Question Testing Methods (Training Goal 1 in YR01).

MATERIALS AND SUPPLIES (YR01: $1,850; YR02: $500)
Computers
Funds are requested for the purchase of one laptop computer for Dr. Yu at $1,200 in year 1 to be used for research and training activities throughout the award period.

Software
Funds are requested for purchase of Atlas.ti qualitative research software at $650 in year 1 for analysis of focus group and interview transcripts, and STATA statistical analysis software at $500 in year 2 for analysis of survey data. This software will be used extensively during the award period to support Dr. Yu's qualitative analysis of focus group, interview and survey data (K-Research Aims 1 & 2) and to acquire skills in conducting quantitative survey skills (Training Goal 2).

Non-Paid Mentors and Advisors

Wylie Burke, MD, PhD, Co-Mentor is Professor and former Chair of the Department of Bioethics and Humanities at the University of Washington. She is also PI of the University of Washington Center for Genomics and Healthcare Equality (CGHE), an NIH-funded Center of Excellence in Ethical, Legal, and Social Implications (ELSI) Research. Her research addresses the social, ethical and policy implications of genetic information. Dr. Burke will help guide Dr. Yu's overall training activities including formal coursework to develop skills in working with culturally diverse populations on collaborative research and in the conduct and analysis of survey/mixed methods research (Training Goals 1 and 2) and related research activities (K-Research Aim 1 and 2), mentor his scholarly development through a directed reading on group harms and benefits, and facilitate his formation and guide his leadership of a workgroup on group harms and benefits through the CGHE (Training Goal 3). She will also ensure his direct

involvement in core research activities, seminars, etc. of the CGHE and the Department of Bioethics and Humanities at the University of Washington. Dr. Burke's role as mentor will be critical to developing relationships with CGHE's network of community and academically-based investigators, including those working with Native American and Alaska Native communities. In the R00 phase, Dr. Burke will provide feedback in developing survey (Specific Aim 1) and interview questions (Specific Aim 2) and in planning the variant review process (Specific Aim 3). Dr. Burke will work closely with Dr. Bamshad to provide mentorship to Dr. Yu during his K99-phase activities and meet with Dr. Yu at a minimum of every other week and also will be available to meet *ad hoc*. She will not receive salary support for this role.

Michael Bamshad, MD, Co-Mentor, is Professor and Chief of the Division of Genetic Medicine in the Department of Pediatrics at the University of Washington and Seattle Children's Hospital, Adjunct Professor of Genome Sciences, Director of the Center for Clinical Genomics (CCG), and PI of the UW Center for Mendelian Genomics (CMG). The CCG provides infrastructure, expertise, and staff to support translational genetic studies and the CMG provides ES/WGS for gene discovery efforts to investigators worldwide. Dr. Bamshad is well established in the fields of human, population, and clinical genetics, and the molecular basis of both monogenic and complex traits. He has extensive experience in large-scale, population-based genomic studies in diverse ethnic / racial groups, research at the intersection of race, genetics, and ancestry and return of genetic / genomic results. Additionally, he has, along with Dr. Holly Tabor, developed a web-based tool, My46, for self-guided management of results from genetic / genomic testing. Dr. Bamshad will guide Dr. Yu's overall training activities and related research activities (K-Research Aim 1 and 2), mentor his scholarly development, develop collaborations with genome scientists and medical geneticists that enable joint translational genomics research, and provide the perspective of an interdisciplinary senior scientist to help Dr. Yu frame his research products so as to reach an audience of medical geneticists and genome scientists. Dr. Bamshad, as a collaborator in the R00-phase, will provide access to My46 for use in conducting the proposed interview study about preferences for exome and whole genome sequencing results (Specific Aim 2) and in conducting a return of results outcome study (Specific Aim 3). Additionally, Dr. Bamshad will provide guidance on variant review and assist in CLIA validation of results as needed (Specific Aim 3). Dr. Bamshad will work closely with Dr. Burke to provide mentorship to Dr. Yu during his K99-phase activities and meet with Dr. Yu at a minimum of every other week and also will be available to meet *ad hoc*. He will not receive salary support for this role.

Deborah Bowen, PhD, Advisor, is Professor in the Department of Bioethics and Humanities at the University of Washington School of Medicine. She is a former professor and Chair of the Department of Community Health Sciences in the School of Public Health. Her expertise is in behavioral research including use of qualitative, quantitative, and mixed methods. She has extensive experience conducting health disparities research in diverse populations, and collaborative research with underserved communities, including racial and ethnic minority communities. Dr. Bowen will advise Dr. Yu as he develops skills in survey development, conduct, and analysis (Training Goal 1) and specifically provide methodological advice as he plans and implements a survey of healthcare providers and community leaders (K-Research Aim 1) and conducts focus groups with diverse racial and ethnic communities (K-Research Aim 2) about participation in genetic research and return of exome and whole genome sequencing results. Dr. Bowen will be available to provide advice in the R00-phase, as Dr. Yu develops plans to conduct a national survey (Specific Aim 1), a interview study about preferences (Specific Aim 2), and plans for studying health utilization, behavioral, and psychometric outcomes associated with returning results (Specific Aim 3). She will meet with Dr. Yu quarterly and on an *ad hoc* basis. She will not receive salary support for this role.

Holly Tabor, PhD, Advisor, is Associate Professor in the Divisions of Bioethics and Genetic Medicine, Department of Pediatrics at the University of Washington School of Medicine, a member of the Treuman Katz Center for Pediatric Bioethics at Seattle Children's Research Institute, and the integrated bioethicist in the Center for Clinical Genomics. She is trained in epidemiology and bioethics, specializing in pediatric bioethics and translational genomics. She was the NHGRI's first recipient of a K99R00 award and developed, along with Dr. Bamshad, the model of an "integrated ethicist." In collaboration with Dr. Michael Bamshad, Dr. Tabor is a PI of a R01 on return of results entitled "Innovative Approaches to Returning Results in Exome and Whole Genome Sequencing Studies." In the mentored phase of the award, Dr. Tabor will advise on the design and conduct of focus groups on risks and benefits of receiving results from whole genome and exome sequencing research (K-Research Aim 2). In collaboration with Dr. Bamshad, Dr. Tabor leads qualitative and quantitative research on participants' use of My46. In the R00-phase, at the request of Dr. Yu, she and Dr. Bamshad will provide access to existing preference and outcomes data collected from ~150 European Americans and share her experience in conducting analysis of survey and My46 navigation data to aid Dr. Yu's study of outcomes of returning ES/WGS results (Specific Aim 3). She will meet with Dr. Yu quarterly and on an *ad hoc* basis. She will not receive salary support for this role.

CONSULTANTS

Charmaine Royal, PhD, Advisor, is Associate Research Professor in the Institute for Genome Sciences & Policy and the Department of African and African American Studies at Duke University. Her research and scholarship focus primarily on issues at the intersection of genetics/genomics and concepts of "race", ancestry, ethnicity, and identity. As a mentor with expertise and experience in working with underserved communities on the ethical, legal, and social implications of genetics and genomics, she will provide guidance on planning interviews with community leaders and healthcare providers on participation in genetic research and return of ES/WGS results (K-Research Aim 1) and is committed to participating in the workgroup lead by Dr. Yu on group harms and benefits (Training Goal 3). She will also assist Dr. Yu with the preparation of his R00 resubmission, and upon Dr. Yu's request, work closely with Dr. Quarells (see Quarells & Royal letter) to facilitate the recruitment of African Americans and plan and conduct research with community members generally (Specific Aim 3). She is available to meet with Dr. Yu at least quarterly to discuss the project. She will not receive salary support for this role.

ADDITIONAL COST CONSIDERATIONS FOR YEAR 3-5

Seema M. Jamal, MS, Genetic Counselor. Ms. Jamal is a board certified and licensed genetic counselor (see biosketch) and serves as genetic counselor for My46. Ms. Jamal is board certified through the American Board of Medical Genetics and the Canadian Association of Genetic Counselors. Ms. Jamal previously worked at Boston University Medical Center for seven years as a clinical genetic counselor and served as a clinical instructor and assistant professor of pediatrics as faculty in Boston University's genetic counseling program. Currently, Ms. Jamal serves as "lead" research genetic counselor in the Center for Clinical Genomics and the University of Washington where she is returning research exome results in an NHGRI-supported project titled "Innovative Approaches to Returning Results in Exome and Genome Sequencing Studies" (PI: Dr. Holly K. Tabor). Ms. Jamal also has expertise in developing phenotype-specific educational content. Ms. Jamal will serve as an expert resource to Dr. Yu and his research throughout the K99 phase of the grant, and as genetic counselor in the independent investigator phase. Specifically, Ms. Jamal will serve as a genetic counseling and

educational resource for interviews about preferences for ES/WGS results (Specific Aim 2, YR02) and as project genetic counselor, results administrator, and variant revew committee member to return sequencing results to 100 African-American participants to study outomes (Specific Aim 3, YR03).

Lake Research Partners (LRP). LRP is an international public opinion and political strategy research firm with over 20 years of experience in public opinion research for public entities and private enterprises—from survey research design through analysis. LRP has conducted qualitative and quantitative research on behalf of non-profit groups, foundations, governmental and corporate clients, elected officials, associations, ballot measures and political campaigns in every region of the country, LRP offers technical experience in conceptualizing, designing, administering, and analyzing a wide range of research methodologies and have nationally recognized expertise on reaching diverse U.S. populations on a wide range of issues including health, healthcare, and reproductive health issues. LRP has experience with hard-to-reach populations and has conducted thousands of research projects among nearly every segment of the U.S. population. LRP is available on a contract services basis to assist in the planning, design, and implementation of a national survey of 800 racial and ethnic minorities on participation in genetic research and return of results from exome and whole genome sequencing (Specific Aim 1, YR01). Through RRP vendors, they have access to over 6 million active participants allowing for targeted recruitment based on gender, race, and other desired qualities. LRP will work with Dr. Yu to establish the validity and reliability of the instrument, pilot test the survey in targeted segments, and conduct the survey in the field and monitor its progress. Dr. Yu will receive clean, raw data files, univariate summaries and bivariate cross-tabulations, and results of our planned analysis; and LRP will be available to assist in conducting multi-variate level analysis.

Exome sequencing. If fewer than 100 African-American participants are recruited from MH-GRID participants who already have whole exome sequence available, additional individuals may be recruited from studies at Morehouse and UW who will require exome sequencing. Although this is not anticipated, this would incure additional sequencing cost of ~$500 per individual.

CLIA Confirmatory Testing. Individual genetic results that are eligible and recommended for return by the Variant Review Committee and filtered by participant preferences, will undergo confirmatory testing at an in-house (UW) or commercial CLIA certified lab (Specific Aim 3). Confirmatory testing is expected to range from $150 to $250 on average for genotyping of a known mutation and upwards of $1000-$2000 for custom sequencing. Depending on the number of results being returned to an individual, the most cost effective method will be used for confirmatory testing (including genotyping, sanger sequencing or clinical exome).

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OMB Number: 0925-0001

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

Prefix: Dr.
First Name*: Joon Ho
Middle Name:
Last Name*: Yu
Suffix:

2. Human Subjects

Clinical Trial? ● No ○ Yes
Agency-Defined Phase III Clinical Trial?* ○ No ○ Yes

3. Permission Statement*

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

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

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

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

Funding Opportunity Number: PA-14-042. Received Date: 2014-03-12T12:47:13.000-04:00

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ○ Yes

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

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

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ○ Yes ● No

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

Previously Reported*: ○ Yes ○ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Career Development Award Supplemental Form

OMB Number: 0925-0001

Introduction (if applicable)	
1. Introduction to Application (for RESUBMISSION applications only)	1249-INTRODUCTION TO RESUBMISSION APPLICATION_FINAL_FINAL.pdf
Candidate Information	
2. Candidate's Background	1250-Candidate background_FINAL.pdf
3. Career Goals and Objectives	1251-Career Goals and Objectives_FINAL.pdf
4. Career Development/Training Activities During Award Period	1252-Career Development Training Activities_FINAL_FINAL.pdf
5. Training in the Responsible Conduct of Research	1253-Training in the Responsible Conduct of Research.pdf
6.Candidate's Plan to Provide Mentoring (as applicable)	
Statements of Support	
7. Plans and Statements of Mentor and Co-Mentor(s)	1254-Combined_mentor_Statement.pdf
8. Letters of Support from Collaborators, Contributors, and Consultants	1255-Yu_Letters_Of_Support_FINAL.pdf
Environment and Institutional Commitment to Candidate	
9. Description of Institutional Environment	1256-Institutional Environment_FINAL.pdf
10. Institutional Commitment to Candidate's Research Career Development	1257-InstitutionalAgreement_FINAL_FINAL.pdf
Research Plan	
11. Specific Aims	1258-Specific Aims_FINAL_FINAL_FINAL.pdf
12. Research Strategy*	1259-Research Plan_FINAL_FINAL_FINAL.pdf
13. Progress Report Publication List (for RENEWAL applications only)	
Human Subject Sections	
14. Protection of Human Subjects	1260-HumanSubjectsResearch_FINAL.pdf
15. Inclusion of Women and Minorities	1261-Inclusion of Women and Minorities_FINAL.pdf
16. Inclusion of Children	1262-Inclusion_of_Children_v2.pdf
Other Research Plan Sections	
17. Vertebrate Animals	
18. Select Agent Research	
19. Consortium/Contractual Arrangements	
20. Resource Sharing Plan(s)	
Appendix (if applicable)	
21. Appendix	
Citizenship*:	
Personal Info	

Tracking Number: GRANT11605736

Funding Opportunity Number: PA-14-042. Received Date: 2014-03-12T12:47:13.000-04:00

Title: Returning Exome and Whole Genome Results to Underserved Minority Populations

Candidate's Background

My goal is to lead efforts to assure that U.S. minority populations benefit from genomic research and medicine. To this end, I seek support for training and empirical studies on minority participation in genomic research, incorporating views on the potential benefits and risks of the return of genetic results. My employment and education have provided me with experience in engaging racial and ethnic minority communities about health issues and an appreciation for the nuances of genomic research in the context of cultural understandings of racial and ethnic identity. I also have firm grounding in qualitative research methods for the study of stakeholder perspectives. However, I need further training to enhance my skills to conduct mixed-methods, population-based studies essential for developing strategies to improve minority participation in research and to translate genomic knowledge into healthcare benefits for underserved communities.

My commitment to the healthcare needs of minority communities stems from my non-profit experiences to improve the health status of Asian American and Pacific Islanders (AAPI). Working with diverse AAPI ethnic groups (e.g., Samoan-Americans in Long Beach, CA and Hmong-Americans in the Twin Cities, MN) taught me the importance of the unique history and varied cultural beliefs of each community to the success of programs to implement health initiatives, conduct community-based research, and develop local strategies to address health disparities. While working in the public health sector, I completed an additional collegiate degree in biology and was struck by the potential of genetic knowledge to improve population health. This prompted me to pursue a graduate degree in Public Health Genetics at the University of Washington (UW).

I pursued a multidisciplinary course of study in genetic epidemiology, under the guidance of Dr. Cornelia Ulrich at the Fred Hutchinson Cancer Research Center and Dr. Karen Edwards at the UW Center for Genomics and Public Health, and in bioethics, under Dr. Kelly Edwards in the Department of Bioethics & Humanities. This training gave a strong foundation in genetic epidemiology, an appreciation for racial/ethnic population variation in genetic contributors to diseases, and a deep appreciation of the relevance of justice in genetics research. It afforded me the opportunity to observe the perspectives of diverse communities on genetics as a project coordinator for UW NHGRI Community Genomics Forum in 2004.

As a doctoral student in Public Health Genetics and a pre-doctoral trainee in the Center for Genomics and Healthcare Equality (CGHE), I worked with Dr. S. Malia Fullerton on a dissertation entitled "What Are Our AIMs? Public Health Genetics and the Practice of Ancestry Informative Markers." I demonstrated how the conflation of race and genetic ancestry is an interdisciplinary problem and can occur at different stages of the research process including the translation of genetic discovery to health care. This work provided me training in qualitative research methods and added to my understanding of genetics and minority inclusion. My graduate training reinforced my commitment to pursue a career in translational genomics research, specifically in bioethical issues of access and engagement with underserved minorities. This led me to become a post-doctoral fellow in the lab of Dr. Michael Bamshad, Chief of Genetic Medicine in the Department of Pediatrics at the UW.

Dr. Bamshad is a leader in translational genomics and the use of exome / whole genome sequencing (ES/WGS) in research and clinical applications. He and Dr. Holly Tabor, Assistant Professor of Pediatrics in the Division of Bioethics, have collaborated to conduct empirical bioethics research that is "integrated" with the applications of these technologies, and develops and tests solutions to emerging bioethical challenges. Under their mentorship, I have begun to explore bioethical issues related to ES/WGS, including conducting focus groups (n=19) with diverse racial groups about the potential benefits and risks of WGS research and return of results. I have played a key role in the development of a web-based tool, My46, for self-guided management of results from ES/WGS, conducting >30 interviews with African American participants about their preferences for return of results. The results of these focus groups and interviews serve as preliminary data in this application. These experiences have helped me realize the power of data in evaluating ethical issues, and have highlighted my need for more training in social science methods and applications.

Career Goals and Objectives

My long term career goals are to: (1) pursue an academic career that combines the disciplines of bioethics and human genetics; (2) establish a research program to develop and test models for enhancing the participation of minority populations in genomic research and the translation of genomic knowledge to health benefits for minority populations; and (3) become a leader in the inclusion of minority populations in translational genomic research, including an understanding of the potential benefits and harms of such research and of research practices that maximize benefit and minimize harm.

To acquire the skills and experience to become an independent investigator focused on translational genomics studies in minority communities, I propose three short-term training goals: (1) improve my skills in quantitative survey development, conduct, and analysis, thereby enhancing my ability to do hypothesis-driven mixed methods research; (2) develop further expertise in working collaboratively with culturally diverse racial and ethnic minority communities; and (3) broaden my understanding of theoretical and empirical work on group harms and benefits from bioethics, anthropology and the social sciences and their implications for research practices that promote inclusion, participation, and effective translation of genomics into minority healthcare.

I propose to implement two mentored research aims during the K training period. **K-Research Aim 1** is to characterize and analyze the perspectives of community leaders and healthcare providers in minority populations about participation in genomic research. I will assess their perceptions of individual and group benefits and harms, with specific attention to the return of ES/WGS results as both a consideration for participation and a responsible research practice. This aim will utilize key informant interviews and a survey. **K-Research Aim 2** is to characterize the perspectives of individuals from underserved minority populations on the risks and benefits of participating in genomic research and receiving ES/WGS results through qualitative focus group research. An overview of my planned training activities is provided in Table 1.

Table 1: Training Goals and Activities

Training goal	Training Activities	Training Research
1. Acquire skills in quantitative survey development, conduct, and analysis	Courses in survey research methods, psychometrics and outcomes, mixed methods, and cultural psychology.	**K-Research Aim 1.** Characterize and analyze the perspectives of community leaders and healthcare providers of minority populations about participation in genomic research.
2. Acquire skills to work with culturally diverse racial and ethnic minority communities to conduct collaborative research.	Courses in cultural competence, health & culture, culture & communication.	**K-Research Aim 2.** Characterize the perspectives of individuals from underserved minority populations on the risks and benefits of participating in genomic research and receiving ES/WGS results.
3. Acquire detailed understanding of theoretical and empirical work in bioethics, anthropology and the social sciences on group harms and benefits	Directed reading with Drs. Wylie Burke and Janelle Taylor. Convene/lead workgroup on group harms and benefits.	Produce conceptual review paper on group benefits and harms focused on implications for return of ES/WGS results.

Career Development/Training Activities During the Award Period

During the mentored phase of this proposal, I will work under the mentorship of Dr. Wylie Burke in the Department of Bioethics and Humanities at UW School of Medicine (UWSOM) and Dr. Bamshad in the Department of Pediatrics at the UWSOM. During this period, I will meet with Drs. Burke and Bamshad every other week at a minimum, to plan and implement training activities and research and solicit feedback on research progress including research benchmarks and manuscripts. I will meet with my advisors Drs. Deborah Bowen, Charmaine Royal, and Holly Tabor individually at least quarterly as well *ad hoc*, and I will meet with them collectively along with my mentors semiannually by teleconference to discuss training and research progress; review next steps; address any problems; and discuss career development activities.

Training Goal 1: *Acquire skills in quantitative survey development, conduct, and analysis.* I will take courses at the UW to provide formal training in survey research, the use of psychometric instruments in outcomes research, and cultural psychology. Dr. Deborah Bowen *(see letter)* will serve as an expert advisor for my training. I will also take selected established intensive research methods courses at the University of North Carolina Summer Research Institute and the University of Michigan Summer Research Institute.

Table 2. Proposed coursework to acquire skills in quantitative survey development, conduct, and analysis

Topics	Course/Description
Survey research	HSERV 527 Survey Research Methods (4 credits) Spring Term Provides students with skills in questionnaire development and survey methods.
Psychometrics & outcomes	HSERV 584 Assessing Outcomes in Health and Medicine (3 credits) Winter Term Qualitative research and psychometric methods applied to health outcomes assessment.
Mixed methods	UNC Summer Institute: courses including Family Research: Conceptual & Methodological Issues; Instrumentation: Development, Testing & Revision; and Mixed Methods Research Michigan Summer Institute: courses entitled Applied Questionnaire Design and Question Testing Methods. Summer Term
Cultural psychology	PSYCH 478 Cultural Psychology (4 credits) I&S Leu Autumn Term Surveys cultural influences on cognitive, emotion, morality, self-concept, and mental health from a multicultural perspective.

Training Goal 2: *Acquire skills for conducting research with racial and ethnic minority communities.* I will take courses at the UW on cultural competence, health and culture, and health communication to enhance my prior experiences working with AAPIs, and to enable me to better work with other minority communities. I will discuss these courses with Dr. Burke on a regular basis and solicit Dr. Royal's perspective as needed.

Table 3. Proposed coursework to acquire skills for working with culturally diverse racial and ethnic minority communities

Topic	Course/Description
Cultural competence	HSERV 571 Cultural Competency for Public Health Practice (4 credits) Spring Term Application of cultural competency to clinical practice, healthcare management, and health services research when working with culturally diverse populations.
Health & culture	NURS 597 Health in the Context of Culture (5 credits) Winter Term Examines socio-cultural, environmental, economic, political, and ecological factors that influence, health, health promotion, illness, disability, and death.
Culture & communication	COM 484 Cultural Codes in Communication (5 credits) Autumn Term Social and cultural codes in interpersonal communication, with special reference to contemporary American subcultural groups and their communication patterns. COM 578 Intercultural Communications (5 credits) Autumn Term Focuses on the nature of communication between different cultures, including the processes as they occur on sojourns, immigration, negotiations, and conversations across national boundaries.
Cultural studies	COM 563 Black Cultural Studies (5 credits) Autumn Term Takes a critical approach to studying media representations of blackness.

I will also work with Dr. Burke to develop relationships with tribal research partners and community leaders, to explore interest in pursuing the research questions in this project among AI/AN communities. As outlined in her letter, Dr. Burke currently works in partnership with tribal organizations on several projects incorporating genetics, including The Northwest-Alaska Pharmacogenomics Research Network (U01GM092676, Thummel/Burke PIs), a project assessing interest in return of genetic results in Alaska Native communities (Ethics of Dissemination, RO1HG005221 Boyer/Burke Dual PIs), and a recently funded NARCH grant (U26 1 IHS0079 Dillard, PI) for which Dr. Burke serves as an academic partner. Dr. Burke will provide mentored opportunities to pursue exploratory conversations among these partners and other contacts they may suggest.

Training Goal 3: *Acquire detailed understanding of theoretical and empirical work in bioethics, anthropology and the social sciences on concepts of group harms and benefits and their implications for research practices that promote inclusion, participation, and effective translation of genomics into minority healthcare.* Studies suggest that consideration of group harms and benefits may influence individual and group views about the acceptability of genetic research and testing[1-3] and may inform preferences for receiving results from

sequencing.[4-6] For instance, a national phone survey has shown that the risk of racial stigma and discrimination from genetic research reduces interest in research participation among both African-Americans (AA) and European-American (EA) respondents.[4] In the context of genomic research, and specifically, practices related to returning ES/WGS results, there is a tension between the current research regulatory framework of individual benefit/risk and the potential for group benefits/harms for racial and ethnic minorities. This tension is one example of the broader challenge of assessing and weighing social implications in research.[7] Key questions include how to define group benefit/harm? When must it be considered and by whom? What are its implications for the use of ES/WGS in research and clinical settings? Under the joint supervision of Dr. Burke and Dr. Janelle Taylor *(see Dr. Burke letter)*, I will conduct a literature review and directed reading on group harms and benefits. I will also convene and lead a workgroup launched by the UW Center for Genomics and Healthcare Equality (CGHE) on group harm/benefit from genomic research. The group will start in April 2014 and meet monthly to discuss specific topics and relevant studies. The initial product of the workgroup, anticipated completion in early 2015, will be a joint manuscript exploring the application of current understandings of group harm and benefit to genomic research.

Locally, I will participate in regularly scheduled seminars and career development opportunities (see Table 4).

Table 4. Local training activities

TKC Pediatric Ethics Seminar (weekly)	Treuman Katz Center for Pediatric Bioethics (TKC)
TKC Pediatric Bioethics Conference (annually)	
B&H Faculty Research Meeting (monthly)	Dept. of Bioethics & Humanities, UW (BH)
UW Genome Sciences Seminar (weekly)	
UW Genetic Medicine Seminar (weekly)	
ITHS Career Development Series (biweekly)	Institute for Translational Health Science (ITHS)
UW Grants Management Workshops (periodic)	University of Washington (UW)

Training Phase Research Plan Significance: Despite dramatic advances in genomic research, participation among minority groups who experience high rates of health disparities has lagged significantly,[8-15] threatening the potential for translational benefits for minority communities. The work proposed will address this concern in three ways: (1) my training and research goals will enhance my ability to work collaboratively with minority communities to define and implement trustworthy research practices; (2) I will develop new knowledge about the views of community leaders and potential participants on barriers and incentives to participation in genomic research, including how they conceptualize potential individual and group level benefits and harms of genomic research; and (3) as a key element of genomic research practice, I will identify preferences of minority participants for return of incidental findings from ES/WGS. This issue has been controversial[16-19] for many reasons including the need for input from multiple stakeholder groups.[20] While research on preferences is underway, few investigate the perspectives of racial and ethnic minorities on the return of ES/WGS results. Because minority views about the potential benefits and risks of genetics have been shown to differ in some ways from those of EA populations,[6; 10; 13; 21; 22] and may affect research participation, **understanding stakeholder perspectives on research participation and return of individual research results is critical to ensuring parity in future genetic services from ES/WGS.**

Innovation: Community leaders and healthcare providers are respected figures of authority and their perspectives likely influence community attitudes toward genomics.[23-26] **This study will (1) engage community leaders and providers about participation in genomic research and the specific issue of return of ES/WGS result, (2) provide key insights about how to ascertain community members' perspectives, and (3) establish community partnerships for future research**. Working with multiple populations can be difficult because communities may differ in their interest and ability to engage in research related to genomics. T**he proposed training-phase research is an opportunity to continue to build relationships that form a basis for community partnerships to answer these and related questions.**

K-Research Aim 1. Characterize and analyze the perspectives of community leaders and healthcare providers of minority populations about participation in genomic research.

Approach. I will conduct a survey of community healthcare providers and leaders of community-based organizations that serve minority populations on participation in ES/WGS research and return of ES/WGS results. Key informant interviews will inform survey development, addressing the following questions:

- What do healthcare providers and community leaders who serve racial and ethnic minority populations perceive as the potential benefits and risks of participation in genomic research?
- What do healthcare providers and community leaders who serve racial and ethnic minority populations perceive as the potential benefits and risks to returning results from ES/WGS?
- What do healthcare providers and community leaders think about the role of autonomy (e.g., preferences) in offering genetic results from ES/WGS to their patients and communities?

- What considerations do healthcare providers and community leaders think must be taken into account to develop effective mechanisms to engage underserved racial and ethnic minority populations about ES/WGS, broadly, and return of results from ES/WGS, specifically?

Methods. Interviews: To inform survey development, I will interview (locally in-person, otherwise via phone) adult community leaders and healthcare providers (n=40) who both identify as members of and serve racial and ethnic minority populations (approximately 8 African American (AA), 8 Hispanic/Latino (HL), 8 Asian American (AS), 8 Native Hawaian Pacific Islander (NHPI) and 8 American Indian/Alaska Native (AIAN)). Given the need for input across multiple racial/ethnic populations, conducting 40 primarily local interviews is realistic. Providers/leaders will be presented an introduction to health-related genomic research involving ES/WGS and the issue of return of ES/WGS results, and asked their perspectives on potential risks and benefits of research participation, obligations for return of results, and role of participant preferences. I will then present and solicit their responses to 3 to 5 vignettes about research participation and return of results that probe these topics in greater detail. Interviews will end with discussion about challenges and effective engagement. **Survey:** Given the lack of validated measures on return of results, I will draw upon recent studies conducted with genetic professionals,[27-33] qualitative studies with community leaders,[25; 26; 34] coupled with provider/leader interview results to develop the proposed survey under the guidance of my mentors and advisors. I will use validated demographic items used in national provider surveys[35] to assess respondent race/ethnicity, age, gender, profession, location, and service population demographics such as race/ethnicity, SES, and other measures of interest. Interview results will be used to develop ~40 survey items for a 15-minute survey that will be administered both online and hard copy. The survey will be programmed and administered online using Redcap and participants will be invited by email to take the survey. If a valid email address is unavailable, participants' will be invited to complete a paper version by mail.

Recruitment. Interviews: I will invite Seattle area medical directors from Federally Funded Federally Qualified Health Centers, commonly referred to as community health centers (CHCs), and executive directors or their designate from community-based organizations (CBOs) identified from public directories from national minority health organizations to participate in in-person or phone interviews. **Survey:** I will invite by email and letter CHCs medical directors and CBO executive directors to take the survey. There are >1100 CHCs in the U.S. and 58 sites in King County, Washington.[36] Racial and ethnic minority populations constitute 73% of clients seen at CHCs, most through Medicaid, thus, CHCs are often located in regions with high density of targeted populations (e.g. Asian Health Services, Oakland, CA).[36] I have identified ~800 organizations and tribal facilities throughout the U.S.[37-41] I estimate the sampling pool to be 2000 FQHC and health-related racial/ethnic-specific community based organizations, from which I need to recruit a minimum of 200 survey respondents (to detect a 10% difference in survey response proportions from chance assuming .80 power). I expect to achieve a 50% response rate by sending a personal email/letter invitation, providing incentives (chance to win a $200 gift certificate), and up to five follow up reminder emails or phone calls.[42-44] I will start recruitment by approaching 400 entities to reach this target but may increase this number as needed.

Analysis. Interview: Transcripts will be analyzed using a directed content analysis approach.[45] This strategy is well-suited to analyses informed by prior data and theory, as is the case with favorable yet critical attitudes toward genetic testing and return of results.[46; 47] These data will qualitatively inform survey question inclusion and development, based on participants' ability to respond to questions and the background required, as well as inform range of responses categories to each question. **Survey:** Online and paper-based responses will be combined and analyzed in Stata. Univariate analysis will be conducted to characterize respondents' and their responses to survey items. Distribution of responses will be assessed between providers and leaders to determine if stratified analysis is needed. Bivariate analysis will be conducted to characterize and explore attitudes toward return of results and demographic variables such as race/ethnicity of service population. Association testing will be done by chi-squared or other comparable test, but as a cross sectional survey, power will be limited to infer associations.

Deliverables. At least three manuscripts are planned from this Aim: (1) an analysis of key informant interviews, (2) survey results of healthcare providers' and community leaders' perceptions about benefits and harms of ES/WGS and about return of ES/WGS results, and (3) implications of the findings for research practices to engage minority constituents in ES/WGS research.

Anticipated challenges. Adequate recruitment is a challenge that I will address with a large sampling frame, incentives for participation, and repeated attempts using multiple modalities for contact. Because respondents may be unfamiliar with ES/WGS to respon, I will use a vignette-based approach to questions and provide introduction to genomic research and return of ES/WGS similar to that I have used in focus groups.[6]

K-Research Aim 2. Characterize the perspectives of racially/ethnically diverse populations on the risks and benefits of participating in genomic research and receiving ES/WGS results.

Approach. I will use focus groups to elicit views on group benefits/harms related to participation in genomic research and about receipt of ES/WGS results among participants from four racial/ethnic groups experiencing health disparities. This research will extend my postdoctoral work on consent and return of ES/WGS to additional underrepresented populations and will further explore factors influencing research participation. My prior work found that AA and EA groups held different views about psychosocial harms of genetic information, trustworthiness of medicine, and relevance of time, family, ethnic identity, and religious faith in offering and receiving ES/WGS results, underscoring the importance of research to further characterize minority views.[6]

Research questions. Although there is broad recognition of the potential for clinical/personal benefit from genetic research and technologies, minority groups may differ in their interest in genetic testing[48; 49] and their views about the value of genomic research. I seek to learn about the range of the attitudes among African Americans (AA), Hispanic/Latino(a) Americans (HL), Asian Americans (AS), and Native Hawaiians Pacific Islanders (NHPI) toward genomic research involving ES/WGS, addressing three specific questions:

- What are AA, HL, AS, and NHPI, participants' attitudes toward participation in genomic research? Why?
- What do they perceive as the benefits and risks of receiving ES/WGS results and do these perceptions differ by population? If so, how do they differ?
- How do their perceptions of benefits and risks relate to their expectations about what results are made available and how they are returned (e.g., mandatory return versus return by preferences)?

Recruitment. I will recruit adult participants via existing regional research collaborations. Collaborators include: (1) the UW Pediatric Care Center (*see letter from Dr. Jeffrey Wright*) whose patients reflect the racial/ethnic diversity of the Seattle-King County region (American Indian Alaska Native 1.0%; Asian American 15.5%; Black of African American 6.5%, Native Hawaiian and other Pacific Islander 0.8%; White, non-Hispanic 63.8%; Hispanic Latino 9.2%); (2) the Asian & Pacific Islander Communities Acting Together (APICAT) comprised of 24 Seattle area ethnic-specific Asian American and Pacific Islander organizations (*see letter from Elaine Ishihara*); (3) Meredith Mathews YMCA of Greater Seattle that serves the Central area of Seattle (*see letter from Chip Byrne*); and (4) Odessa Brown Children's Clinic which predominantly serves African American and Hispanic Latino children (83% non-White or Latino of which 8% Asian; 38% African American; 17% Hispanic) (*see letter from Dr. Ben Danielson*). In addition, the PI of three on-going HL community health studies in the lower Yakima Valley of Washington State (*see letter from Dr. Beti Thompson*) has committed to supporting recruitment. Approach to recruitment varies with each collaborating organization and may include flyers, phone, and face-to-face recruitment.

Methods. I will convene 20 focus groups of ~10 adults each from underserved racial and ethnic minority groups (approximately 5 AA, 5 HL, 5 AS, 5 NHPI) for 90 minutes. This number balances the diversity of sub-populations within racial/ethnic groups with cost. Focus groups with HLs will be conducted in Spanish, as needed, with the aid of a linguistic and/or cultural translator to maintain consistency in moderation across focus groups. After completing a demographic survey, focus groups will receive an introduction to health-related genomic research involving ES/WGS, potential information derived from ES/WGS, and how such information might be used in health care. They will be asked to discuss their views on participation in such research and on receiving ES/WGS results both in general and in response to examples of results that differ in clinical utility, disease severity, age of onset. Following a description of professional recommendations on incidental findings, participants will discuss the relative potential benefits and harms of three models of return: (1) mandatory return of incidental findings per American College of Medical Genetics & Genomics (ACMG) recommendations[50; 51]; (2) preference-based return of ACMG's recommended list of incidental findings; (3) preference-based return of all available incidental findings. Follow up clarifying interviews will be conducted as needed after initial review of focus group results.

Analysis. Focus group transcripts will be analyzed for thematic content using a content analysis approach.[45] I will analyze participants' general discussion and responses to example results to characterize their views of the potential risks and benefits of receiving ES/WGS results and to learn what underlies their perceptions. I will analyze discussions of different models of returning results to characterize the relative importance of preferences and choice to receiving results. Themes from the analysis will be compared between racial and ethnic focus group strata to identify similarities and differences.[45] Exploratory analysis of themes will be conducted across focus groups according to participant demographics such as gender, socioeconomic status, and rural versus urban geographic residence to generate hypotheses about perceptions on return of results.

Deliverables. Two manuscripts are planned from this research: (1) overall and group-specific perceptions of potential benefits and risks of receiving ES/WGS results including what underlies these perceptions, and (2) perspectives on acceptability of professional recommendations for return of incidental findings. **These deliverables will provide the framework for developing survey tools for assessing preferences for genetic results and impact of receiving results in the R00 proposal**.

Anticipated challenges. To address adequate participant recruitment and retention, I have identified multiple well-established community partners for recruitment for each population and will provide incentives for participation. Content may be challenging for participants so, as needed, I will conduct educational sessions, clarifying interviews or more focus groups. For all aims, I recognize that the applicability/generalizability of findings to heterogeneous racial and ethnic groups is a significant limitation and likely unwarranted. I will attend to this in all research phases, particularly in analysis and manuscript preparation.

Table 5. Training and research activities during mentored phase	**Year 1** Q1	Q2	Q3	Q4	**Year 2** Q1	Q2	Q3	Q4
Training Goal 1: Acquire skills in the development, conduct, and analysis of quantitative surveys	Courses							
Training Goal 2: Acquire skills for conducting research with racial and ethnic minority communities	Courses							
Training Goal 3: Acquire detailed understanding of theoretical and empirical on concepts of group harms and benefits	CGHE work group on group harms/benefits							
K-Research Aim 1: Characterize and analyze the perspectives of community leaders and healthcare providers of minority populations about participation in genomic research.	Interviews	Survey	Analysis		Manuscripts			
K-Research Aim 2: Characterize and analyze the perspectives of racially/ethnically diverse populations on the risks and benefits of receiving ES/WGS results.				Recruit	Focus groups	Analysis	Manuscripts.	

Training in the Responsible Conduct of Research

Prior RCR Training

Since 2002, I have participated in the UW training requirement to complete the online Collaborative Institutional Training Initiative (CITI) courses in the Biomedical Human Research Curriculum (last certification completed on June 8, 2011). CITI focuses on history and ethical principles, regulations and process, informed consent, research with protected populations, group harms, HIPAA and human subjects research, and conflicts of interest in research involving human subjects.

Planned RCR Training During the Award Period

In Year 1, I will take the UW course entitled the Biomedical Research Integrity series. This training in the responsible conduct of research covers the following topics through five, 1-hour long lectures and corresponding discussions sections: conflict of interest, data acquisition and ownership, peer review, responsible authorship, research misconduct, researcher/trainee responsibilities and collaborative science. Also, specific to the concerns of research involving parents and their children, I have participated in and will continue to participate in the Seattle Children's Pediatric Bioethics Seminar series.

In Year 1, I will take the UW course entitled the Ethics in Biomedical Research (Genome Science 580, Spring Quarter). This course in the responsible conduct of research covers the following topics through five, 2-hour long sessions: teaching/mentoring; integrity of data acquisition, management, analysis; collaboration, sharing and resources; responsibilities in genomic research; and publication practices.

ENVIRONMENT AND INSTITUTIONAL COMMITMENT TO THE CANDIDATE

Description of Institutional Environment

University of Washington (UW)

The UW is a public research university located in Seattle, Washington that provides a stimulating and well-funded environment for multidisciplinary and interdisciplinary research. In fiscal year 2012, the UW received over $1.4 billion total in sponsored grants and contracts, UW currently serves nearly 50,000 students. The UW School of Medicine ranks first among public medical schools in federal research funding and second among all medical schools. There are over 290 specialized research centers at the UW, including over 20 NIH Research Cores and Centers of Excellence. The **University of Washington School of Medicine** is a regional resourse for Washington, Wyoming, Alaska, Montana and Idaho, the WWAMI states. It is consistently recognized as one of the nation's top providers of instruction. Researchers within the school explore every aspect of health and disease. In fiscal year 2011-2012, UW Medicine faculty received $608 million in National Institutes of Health research awards. Five UW faculty members have won Nobel Prizes in medicine since 1990, more than any other institution during that time period. Additionally, the UW boasts 52 Institute of Medicine members and 64 National Academy of Science members. The commitment to training is evident in the mission statement of the UW School of Medicine "to improve the health of the public by advancing medical knowledge, providing outstanding primary and specialty medical care to people of the region, and preparing tomorrow's physicians, scientists, and other health professionals."

Department of Pediatrics, Division of Genetic Medicine

Dr. Yu is a Senior Fellow, Dr. Bamshad is a Professor, and Dr. Tabor is an Assistant Professor in the UW Department of Pediatrics. The Department of Pediatrics has over 170 faculty members with many engaged in research. Dr. Bamshad is Chief of the Division of Genetics and Developmental Medicine in the UW Department of Pediatrics, a division committed to providing excellence in clinical care, education and research related to a broad spectrum of genetic disorders, birth defects and developmental disabilities. The division, with 27 faculty, is one of the largest in the U.S. and offers ample opportunities for intellectual interactions and empirical investigations.

Department of Bioethics and Humanities (B&H), and Center for Genomics and Healthcare Equality (CGHE)

The Department of Bioethics and Humanities is home to the Center for Genomics and Healthcare Equality of which Dr. Yu is a former trainee. Dr. Wylie Burke is Professor in B&H and CGHE PI. Dr. Bowen is Professor in B&H and Co-Investigator with CGHE. The Department faculty is multidisciplinary and pursue a broad range of scholarship including ethical theory, clinical ethics, public health genetics, and empirical bioethics. Thirteen core faculty collaborate with an additional 39 Adjunct and Affiliate faculty including Dr. Tabor. The faculty has an especially strong reputation for and commitment to mentoring and offers opportunities for professional and intellectual interactions through Bioethics Grand Rounds, Biomedical Research Integrity Series, Summer Seminar in Healthcare Ethics, annual Charles Bodemer Lecture and other sponsored activities. The CGHE currently supports eight trainees, and convenes a semiannual all-investigators meeting, biweekly trainee seminar, and quarterly works in progress sessions. Dr. Burke convenes a faculty writing group that supports manuscript writing and publication. B&H and CGHE offer Dr. Yu a supportive environment for career enhancement.

Center for Clinical Genomics (CCG)

The CCG assists investigators conducting translational genetics/genomics research and is a part of the Translational Technologies and Resources Core (TTRC) of the Institute of Translational Health Sciences, a partnership between the University of Washington, Fred Hutchinson Cancer Research Center, Seattle Children's Hospital and other regional institutions along with community and tribal groups. The CCG is directed by Dr. Bamshad and Dr. Tabor serves as its lead integrated ethicist. The CCG provides expertise on study design, guidance on regulatory issues for translational genetics projects, and infrastructure to collect, organize and maintain phenotypic information and DNA from individuals and families. The CCG will provide Dr. Yu opportunities to work with clinical genetics/genomics investigators to develop and conduct collaborative research on the ethics of translational genomic research.

1. SPECIFIC AIMS

The unprecedented informational power of exome sequencing (ES) and whole genome sequencing (WGS)[52-55] has motivated rapid growth in health research utilizing ES/WGS and commercialization of ES/WGS for clinical service. Furthermore, research participants, patients, and the public have affirmed the importance of receiving individual genetic results[56-58] as a motivation for participating in research.[59; 60] Given the wealth of information generated by ES/WGS, procedures and policies are needed to address the scope of individual results that should be considered for return and methods for offering individual results. These questions are active topics of research and deliberation among genome researchers and bioethicists.[61-65] However, little is known about the views of individuals from minority populations. Moreover, despite some evidence that preferences and potential harms and benefits of receiving genetic results vary among people from different racial and ethnic groups, there is inadequate power to study this issue when respondents are recruited to reflect the general U.S. population. For this reason, most studies of return of ES/WGS results have been based almost solely on results from European-American (EA) participants,[66-68] resulting in a major gap in knowledge about appropriate practices for offering ES/WGS results in communities other than EA. Rather than risk disenfranchising a large, growing segment of the U.S. population, it is imperative to understand minorities' conceptions of the potential harms and benefits of participating in ES/WGS research and associated return of results. Important and unresolved questions about ES/WGS research involving underserved minorities include: (1) what are the attitudes of racial and ethnic minorities toward participation in ES/WGS research and to what extent are attitudes influenced by policies and procedures for return of ES/WGS results? (2) what preferences do racial and ethnic minorities have about the offer and return of ES/WGS results? (3) what outcomes do racial and ethnic minorities who receive ES/WGS results experience? (4) how do these answers compare to similar data from EA early adopters?

To begin systematically addressing these questions, I propose to complete the following specific aims, as a foundation for developing and testing strategies for return of ES/WGS results to underserved minorities:

Aim 1: Characterize and describe attitudes of underserved populations toward return of ES/WGS results in clinical and research settings. I will develop, pilot test, and conduct a survey on return of results from ES/WGS in African American (AA), Hispanic Latino/a American (HL), Asian American (AS), and Native Hawaiian & Pacific Islander American (NHPI) individuals (n=800). The survey will assess attitudes toward receiving results in the context of research participation and healthcare, specifically, attitudes toward types of results, role of choice, benefits and harms, method of return, and sharing results. The instrument will include items to assess dis/trust of research/healthcare/medicine, racial/ethnic identity (solidarity/centricism), genetic knowledge, experiences with genetics, and spirituality/religiosity. Correlations between these constructs and attitudes toward return of results will be assessed. The survey will be developed and evaluated for its cross-cultural validity and reliability.

Aim 2: Characterize individual preferences for receiving ES/WGS incidental findings. I will assess individual preferences for categories of results in a sample of minority adults (n=90 total, 30 AS, 30 NHPI, 30 HL) using the web-based tool, My46 (www.my46.org). Adults will undergo in-depth interviews and complete surveys before and after setting preferences to describe their decision-making process including their expectations and motivations for receiving different types of results. Data from AS, NHPI, and HL participants will be compared to similar previously collected data from AA and EA.

Aim 3: Evaluate the outcome of returning ES/WGS incidental findings to AA. One hundred AA adults from the Minority Health Genomics and Translational Bio-repository Database (MH-GRID) Study at Morehouse School of Medicine who have undergone ES will be offered the opportunity to receive incidental findings. Participants will complete surveys and be interviewed, both before and after receiving results to assess short-term outcomes including changes in health care utilization, behavioral and lifestyle changes, sharing genetic information, psychosocial impacts such as anxiety and depression, and attitudes toward receiving genetic results. Results will be compared to data I recently collected from EA.

2. RESEARCH STRATEGY

2.1 Significance

Minority perspectives on the risks and benefits of ES/WGS, and the implications for return of ES/WGS results for participation in genomic research, are largely unknown. Information about returning individual genetic results to racial and ethnic minorities is limited, but it is clear that knowledge and attitudes toward genetic tests vary among racial and ethnic populations,[1; 4; 21; 23; 49; 69-74] and this can impact test utilization and willingness to participate in research.[75] I have shown that AA focus group participants identify a broader set of possible risks and benefits from ES/WGS than EAs, extending to families, AA communities, and society.[6] Moreover, despite evidence of greater than average interest in genetic testing in some minority populations,[48; 58] minorities are less knowledgeable about genetics and genetic testing,[22; 76] and frequently hold misperceptions of genetic risk.[77] **A major deliverable of this proposal is a quantitative assessment of the perceptions of the benefits/risks of receiving ES/WGS results in minority populations and a comparison of these perspectives to those of EAs.**

Factors that influence decision-making in minorities about receiving ES/WGS results are poorly understood. Key factors in the utilization of individual tests include financial access to healthcare,[78] socioeconomic status,[68] trust in medicine,[22; 66; 79] and cultural acceptability of genetic services.[80; 81] The impact of each of these factors may differ in the context of returning ES/WGS results to minority research participants.[4; 82] Focus groups with AA highlight how mistrust in healthcare may preclude sharing results with healthcare providers and the importance of community social supports in results decision-making.[6] The meaning and clinical utility of genetic test results (such as *BRCA1* testing) are known to vary across different cultural contexts;[83-85] and orientations to family, time, and spirituality are known to differ and impact utilization of genetic tests.[86-88] **A second major deliverable of this proposal is the identification of the range of views, compared to EA, that influence decisions about receiving ES/WGS results.**

No data exist on whether the ES/WGS results return preferences of minorities vary by result type (e.g., carrier status, altered risk for complex disease, etc.) and predicted impact on health, or change over time. An analysis of results return preferences from WGS in an EA family with a Mendelian disorder suggested that preferences vary across result types and can change over time.[89] Preliminary data suggest that AA participants' preferences for results may vary more than those of EA participants; more broadly, differing cultural contexts may be important to preferences for results.[70] The results from the studies I propose will provide important guidance to researchers and clinicians as there is robust debate about: (1) the best way(s) to categorize ES/WGS results for return, (2) whether unanticipated results should be returned, and (3) whether result type will influence preferences for return.[62; 63; 90-98] **A major deliverable herein is to provide data about minority preferences for results, by result type; and guidance on whether different or more flexible strategies for ES/WGS results return are necessary when minority participants are included.**

No one has conducted a study of outcomes of selecting and receiving ES/WGS results focused on racial and ethnic minorities. Outcomes may differ because genetic information has different cultural significance and responses to genetic information are contingent on prior expectations. **This study will assess whether outcomes of receiving ES/WGS results may differ for AA as compared to EA. Study results will advance research on return of results with AA by assessing if commonly studied outcomes capture AA participants' experiences in receiving results and inform the reliability of instruments to measure outcomes among AA participants.**

2.2 Innovation

Studies of minority group attitudes toward return of genetic results have focused on whether individuals are interested in receiving results and if they recognize commonly held concerns (e.g., privacy, genetic discrimination).[99-101] Further, the heterogeneity of studies and study populations have precluded comparative analysis of attitudes between populations. Preliminary data from my own work on ES/WGS and that of others on return of results[5; 6; 47; 58; 102] indicates minority research participants are likely interested in receiving ES/WGS results, as seen in EA populations, but that concerns about potential harms may differ than among EA participants.[11; 12; 103-105] **This will be the first study to my knowledge to systematically assess attitudes on return of ES/WGS results and conduct comparative analysis between minority populations. I will therefore be uniquely positioned to develop and test models for offering and returning ES/WGS results in minority populations.**

While the information disparity between minority populations about return of results is a fundamental problem in translational genomics, research on AA participants' attitudes toward and responses to genetic testing and

research is most developed. For instance, recent studies suggest that disparity in willingness and utilization of genetic testing may more accurately reflect an informed difference than the effects of on-going inequality[106], in other words, a choice. **With this in mind, I will be the first to test how AAs respond to a preference-driven return of ES/WGS results.**

2.3 Approach

Project overview. This project utilizes both qualitative and quantitative behavioral research methods to study attitudes toward return of ES/WGS results, both in general and as a factor in participation in genomic research, preferences for specific types of results, and outcomes of receiving results among members of racial and ethnic minority groups. By working within and across multiple populations, I will study issues specific to the experiences of a particular group and understand factors common to all groups (e.g., fear of racial discrimination). **Aim 1** uses a cross-sectional online survey to solicit AA, HL, AS, and NHPI participants' attitudes toward receiving results, characterize constructs hypothesized to predict these attitudes (e.g., distrust in medicine), and evaluate the relationship between these attitudes and constructs. **Aim 2** solicits preferences from HL, NHPI, and AS participants and uses in-depth semi-structured pre- and post-preference setting interviews to characterize motivations and concerns about receiving ES/WGS results, the experience of deciding results preferences, and how to improve this process. These data will also provide an opportunity to explore reasoning behind main outcomes of survey. **Aim 3** returns ES/WGS results to a cohort of AA participants, based on their preferences for different kinds of results, and uses a mixed methods approach including surveys and in-depth interviews to assess outcomes of receiving results over at least a 6 month period. Aims 2 and 3 utilize a secure web-based tool for return of ES/WGS results, My46 [www.My46.org] (*see Dr. Tabor's letter*). My46 has three modules relevant to this proposal: (1) a Participant Preference Tool (PPT); (2) a Results Management Tool (RMT); and (3) a Survey and Assessment Tool (SAT). Each participant profile is linked to a consecutive usage log of participant navigation on the site, including access data (log-in, log-out), order, and duration of information resources visited on the site. Therefore, I will be able to collect and analyze data about participant usage of My46, including when participants change their preferences.

2.3.1 Aim 1: Characterize and describe attitudes of underserved populations toward return of ES/WGS results in research and clinical settings.

Research questions. While individuals broadly recognize the potential for clinical/personal benefits and express interest in receiving genetic test results, underserved populations have been shown to differ in their interest in individual tests compared to EAs.[48] I seek to learn how cultural and social forms of identity influence (1) individuals' understandings of the risks and benefits of receiving ES/WGS results, especially consideration of group harms and benefits; (2) whether or not ES/WGS results are desired; and (3) attitudes toward choice, method of return, sharing results, and other related issues. Facilitators and barriers to receiving results may depend on interpersonal obligations that originate from intersecting family contexts, community contexts, and racial/ethnic identity. To explore the effects of these factors on attitudes toward return of ES/WGS results, I will address four specific questions:

- What are AA, HL, AS, and NHPI attitudes toward receiving ES/WGS results (i.e., perceived benefits and risks, expectations, concerns) and do these attitudes differ by population?
- Do attitudes toward return of results differ in the context of research versus healthcare?
- How important are genetic knowledge and experience, and psychosocial constructs such as temporal orientation, spirituality/religiosity, family centeredness, distrust of research/healthcare/medicine, racial/ethnic identity (solidarity/centricism), to attitudes about return of ES/WGS results?
- Do relationships between attitudes and constructs differ among populations?

Participants & recruitment. Building on the formative research proposed in K-Research Aim 2, I will conduct an online survey of 800 AA, HL, AS, and NHPI working with Lake Research Partners (LRP), a national survey research company that specializes in research with racial and ethnic minorities *(see Dr. Celinda Lake's letter)*. Adults will be recruited from a commercial research panel that includes over 2.1 million active members accrued through online marketing with over 300 diverse affiliate partner organizations. The panel includes ~678,000 individuals from minority populations (168,000 AA, 210,000 HL, 168,000 AS, 10,500 NHPI, 16,800 AIAN, 147,000 other). LRP report an overall 40% response rate using this research panel that will require inviting approximately 500 individuals from each racial/ethnic group. The target of 800 respondents across four underrepresented groups will allow for generalizability within and comparisons between these groups (to detect a 15% difference in survey response proportions between two groups assuming .80 power).

Survey Development and Validation. Building on K-Research Aim 2, survey domains will include attitudes toward receiving results, in general, and as a factor in participation in genomic research, including the role of choice, expected benefits and harms of receiving results, and preferences for different types of results; method of return; and sharing results. Items about attitudes will include those regarding respondents' own genetic information. The instrument will include items to assess distrust of research/healthcare/medicine[107-109], racial/ethnic identity (solidarity/centricism)[110; 111], temporal orientation[112], spirituality/religiosity, family centeredness, genetic knowledge/experience, genetic numeracy/literacy, and standard demographic items (gender, age, race, ethnicity, education, income, occupation, perceived social status). Items from validated instruments (e.g., Healthcare System Distrust Scale, Multigroup Ethnic Identity Measure, Zimbardo Time Orientation Inventory) will be used when available for predictive constructs, recognizing that validity and reliability have not been evaluated in multiple languages or in a survey on return of results. Items for remaining constructs will be developed in-house. The instrument will be pilot tested with at least 5 individuals from each population and cognitive interviews will be conducted with participants to improve face validity. The survey will be translated from English to Spanish, Mandarin/Cantonese, Korean, Tagalog, and Vietnamese. Iterations of back translation and rewording will be conducted to ensure validity and comparability.

Survey implementation. A link to the online survey will be sent to adults who self-identify as AA, HL, AS or NHPI to obtain a total of 800 responses (~200 for each AA, HL, AS, and NHPI group). Two email reminders will be sent to those who have not completed the survey to remind them of the link and to complete by the stated deadline. Adults who complete the survey will receive a thank you reward such as digital coupons.

Analysis. Univariate statistical analysis will be conducted to characterize participant responses overall and within racial/ethnic subgroups. A subset of demographic items and items to capture reasons for survey refusal will be used to compare non-responders. Bivariate analysis will be conducted to characterize attitudes toward return of results and to assess differences between racial/ethnic groups. Differences will be tested statistically using chi-squared or other comparable test. As a cross sectional survey focusing on characterizing group differences in attitudes, power is limited to detect differences between groups, whereas I expect to have sufficient power to evaluate selected attitude-construct associations in the overall sample. Therefore, associations between selected construct measures and selected outcomes will be evaluated by regression analysis overall, stratified by race/ethnicity, and adjusted for select demographic variables.

Deliverables. Three major deliverables will compare similarities and differences in group perspectives toward return of ES/WGS results: (1) attitudes toward receiving ES/WGS results, including potential benefits and harms; (2) relationship between attitudes toward receiving ES/WGS results and participation in ES/WGS research; and (3) factors associated with attitudes toward receiving ES/WGS results.

Anticipated challenges. To assess potential responder bias, which may threaten generalizability of findings[113], I will query non-responders on selected demographic items for comparison to responders and reasons for refusal. Establishing construct validity of psychometric measure items and genetic terms in different languages and cultures threatens comparabilty of findings between groups. To address this I will work with LRP to conduct iterative translation and back translation of in-language versions, and conduct in-language pilot testing and associated cognitive interviews to improve construct validity. Finally, generalizability of findings will be limited because lower SES respondents to an online study are likely to differ in other ways, for instance, to lower SES patients seen in a community clinic.

2.3.2 Aim 2: Characterize individual preferences for receiving ES/WGS incidental findings.

Research questions. Recent studies of preferences and public attitudes toward genetic information suggest that most individuals seek all available genetic result information, do not distinguish between primary and secondary results from research, and are motivated by the potential for both clinical and personal utility.[47; 59; 60; 114-119] Yet many of these studies have been conducted among high SES, European-American "early adopters"[120; 121] enrolled in studies of direct-to-consumer genetic testing, and studies of research participants and the public have focused on attitudes toward results, in general. In contrast, Unpublished

Unpublished

Unpublished In this context, I plan to ask the following research questions:

- Do underserved minorities' preferences for genetic results from participation in ES/WGS research differ from those of "early adopting EAs" and if so, how and why?
- Do particular orientations to time, family, cultural identity, and spirituality impact preferences for results?

Recruitment. I will use the same existing collaborative relationships to recruit adult study participants as described in K-Research Aim 2. Adults from underrepresented minority groups (n=90; approximately 30 AS, 30 NHPI, and 30 HL) will be recruited from the UW Pediatric Care Center (UWPCC) and via local public health clinics and organizations including Odessa Brown Children's Clinic (OBCC), Meredith Mathews YMCA (YMCA), and the Asian Pacific Islander Coalition Acting Together (APICAT) for Healthy Communities. Recruitment will include a mixture of phone, email, and flyer-based recruitment. I do not anticipate difficulty recruiting 90 study participants and will provide a $50 giftcard as incentive. During the K-phase I will explore options for recruiting AIAN with the Seattle Indian Health Board and adjust participant numbers accordingly.

Preference Setting Sessions. Sessions will be modeled on my preliminary study with AAs. Adults will be presented a hypothetical research scenario where they have undergone WGS and are asked to set preferences for receiving results using My46. They will be given the choice to receive results for conditions organized by categories: disease risk, carrier status, genetic syndromes, medication response, and ACMG recommended conditions. Preferences will be recorded in My46. Using the survey functionality of My46, they will take a baseline survey before setting preferences to characterize demographics; experience with genetic and numeracy; health status, healthcare utilization and insurance status; self-efficacy; and orientations to time, family, cultural identity, and spirituality. After setting their preferences, they will take a survey to describe their motivations and concerns about receiving genetic results. All participants will be interviewed before and after selecting preferences to better understand their preference decisions in the context of their expectations and concerns, specifically what motivated their preference decisions. Interviews will be audio-recorded.

Analysis: Frequencies of participant preferences for results overall and by subgroup will be tabulated for all results, results by category, and individual conditions. These data will be directly compared, both quantitatively and qualitatively, to those from AA and EA in previous studies. Associations between preferences and hypothesized predictors (e.g., experience with genetics) will be assessed in the overall sample of responses. Motivations and concerns from surveys will be described for each group. Survey analysis will be conducted in consultation with the Center for Biomedical Statistics at the UW. Qualitative themes about motivations and concerns will be identified from interview transcripts through content analysis using standard coding, notation, and memoing.[45] Themes from the qualitative analysis and survey results will be compared between racial and ethnic groups to identify similarities and differences. These data will be compared to those previously collected among EAs and AAs (*see Dr. Tabor's letter*). Group level survey analyses will be descriptive, due to limited sample size, however, when combined with qualitative session data they will provide critical data for generating hypotheses about how minorities think about receiving genetic results from ES/WGS.

Deliverables. Two major deliverables will characterize group perspectives on return of ES/WGS: 1) Analysis of preferences for managing results across racial and ethnic strata; and 2) factors that may affect preference decisions including informational needs, demographic characteristics, psychometrics (self efficacy, ethnic centricism, temporal orientation, religiosity), motivations and concerns about receiving genetic information.

Anticipated challenges. A key challenge will be an ascertainment bias of participants who are predominantly of higher SES or of lower SES. To obtain a balanced sample, I plan to recruit from a wide variety of clinical and community setting and will include SES as an inclusion/selection criteria.

2.3.3 Aim 3: Evaluate the outcome of returning ES/WGS incidental findings to AA.

Research questions. Several potential outcomes are expected from return of ES/WGS results including medical treatment/prevention; psychological outcomes that may positively or adversely affect health-related behaviors and lifestyle changes; sharing of genetic information with family members leading to cascade testing; sharing results with healthcare providers expected to yield personalized healthcare; and changes in healthcare utilization. Receiving results may also impact interest and willingness to receive additional genetic information in the future and even participation in genetic research. In this aim, I address two main questions:

- What short-term outcomes do AAs experience from receiving ES/WGS results?
- Do outcomes differ between EA and AA research participants?

Return of ES/WGS results through genetic counselor and My46. AA adults enrolled in ES/WGS studies (n=100) will be recruited to receive ES/WGS results through a combination of genetic counseling and online return of results tool My46. Time course analyses require a minimum of 75 participants at 0.80 power to detect

a measurable difference of ≥1.97 points for the PHQ-9 and ≥1.5 points for the PAGIS overall scores (described below). Recruiting ~25% of available MH-GRID participants is likely and will provide a sample size of 100 to protect against individuals who may withdraw or may not have a returnable result. Mirroring the procedures in Aim 2, AA adults will communicate their results preferences to study staff using My46. These preferences will be used to filter results offered for return. I will utilize an existing UW Variant Review Board (VRB) comprised of 12 medical/clinical geneticists, genetic counselors, genome scientists and ethicists, chaired by Drs. Bamshad and Burke to (1) decide which specific genes to assess for returnable results; (2) adjudicate returnable results in light of participant preferences; (3) provide guidance about what counseling should be provided with each result. Each result will be validated (i.e., confirm that a result is not a false positive) in the molecular diagnostics service lab of the UW Department of Laboratory Medicine and offered for return by a certified genetic counselor using My46. Ms. Seema M. Jamal, My46 staff genetic counselor, will return ES/WGS results with the aid of My46. Ms. Jamal has extensive experience as a genetic counselor and, prior to her current position at the UW, was an assistant professor in the genetic counseling program at Boston University. Ms. Jamal also has extensive experience returning ES results, specifically secondary results as staff genetic counselor for a current study on returning ES research results (Tabor R01). Outcomes of receiving results will be assessed among all 100 participants using psychometric, behavioral, and attitudinal surveys, and qualitative interviews with a subset of 50 participants.

Study population. AA participants will be recruited through the Minority Health Genomics and Translational Research bio-repository Database (MH-GRID) housed at Morehouse School of Medicine, a historically black medical school, which includes >435 self-identified AA adults with annotated ES/WGS variant data. Additional AA adults may be recruited from other studies housed at Morehouse who would undergo prospective sequencing at UW (*see letter of collaboration from Drs. Quarells and Royal*).

Evaluation of existing annotated exome sequencing data. Because of the costs associated with CLIA testing, I will concentrate on returning results from existing clinical genetic tests. The VRB will select for review 50 to 100 genes and associated phenotypes, including those recommended by the ACMG,[50] representing a range of possible kinds of results that may be returned in ES/WGS studies. These will be largely based on recommendations of NHGRI-funded projects studying return of results[63] and supplemented with conditions of public health priority among the AA population (e.g., Type 2 diabetes, sudden death, Alzheimer's Disease).

Assess outcomes through participant surveys. I will collect responses at 4 time points using My46: at baseline prior to choosing preferences (T1), directly after setting preferences (T2), directly following receipt of results (T3), and 6 months after receipt of results (T4). My46 standard surveys include both paper validated and non-validated items for corresponding domains listed in Table 6. Outcome measures will include the following:

Table 6. Selected My46 Surveys

Domain	Instrument(s)/ Sources	T1	T2	T3	T4
Your Health (Anxiety/Depression)	PHQ-9	X		X	X
Health Care Use	NHANES/PhenX	X		X	X
Insurance Information	NHANES/PhenX	X		X	X
About You (demographics)	In-house/multiple	X			
Motivations/concerns about results	In-house		X		X
Satisfaction Receiving Results	In-house			X	X
Plans for Sharing Results	In-house	X		X	
Response to your results	PAGIS			X	X
Sharing genetic research results	In-house			X	X
Future Results	In-house				X

(1) Psychological impact of receiving results (T1/T3/T4). I will assess psychological measures such as depression and anxiety, and the psychological impacts of genetic results using validated instruments such as the PHQ-9[122] and the Psychological Adaptation to Genetic Information Scale (PAGIS)[123] before and after receiving results to assess changes in depression and anxiety.[124; 125] **(2) Insurance/Healthcare utilization outcomes (T1/T3/T4).** Before and after receiving results, I will ask participants how often they see their healthcare provider and about their health, disability, longterm care, and life insurance status. After results, I will ask if they have visited or spoken to a healthcare provider since receiving results, if so, the kind of care-provider contacted (e.g., genetic counselor, clinical geneticist), if they spoke about results, and what, if any, tests or evaluations were performed. **(3) Health-related behaviors and lifestyle (T1/T3/T4).** Before and after receiving results, I will ask about common behaviors such as tobacco use, exercise, and nutrition; and include items to assess atttitudes toward those behaviors. **(4) Sharing results (T1/T3/T4).** Before receiving results, I will ask participants their intentions to share results. I will compare these intentions to post-results sharing of results and query reasons for sharing or not sharing different kinds of results, and if and why they changed their plans about sharing. **(5) Expectations for future results (T4).** To assess if receiving genetic results either positively or negatively impacts preferences for additional results in the future, I will assess changes in

preferences for up to 6 months after initial results disclosure and ask participants their preferences for receiving future updates on results that have been returned and their interest in receiving results in the future.

The Clinical Sequencing Exploratory Research consortium Outcomes & Measures Workgroup has collected commonly used measures under important domains and will be available to me for final measures selection.

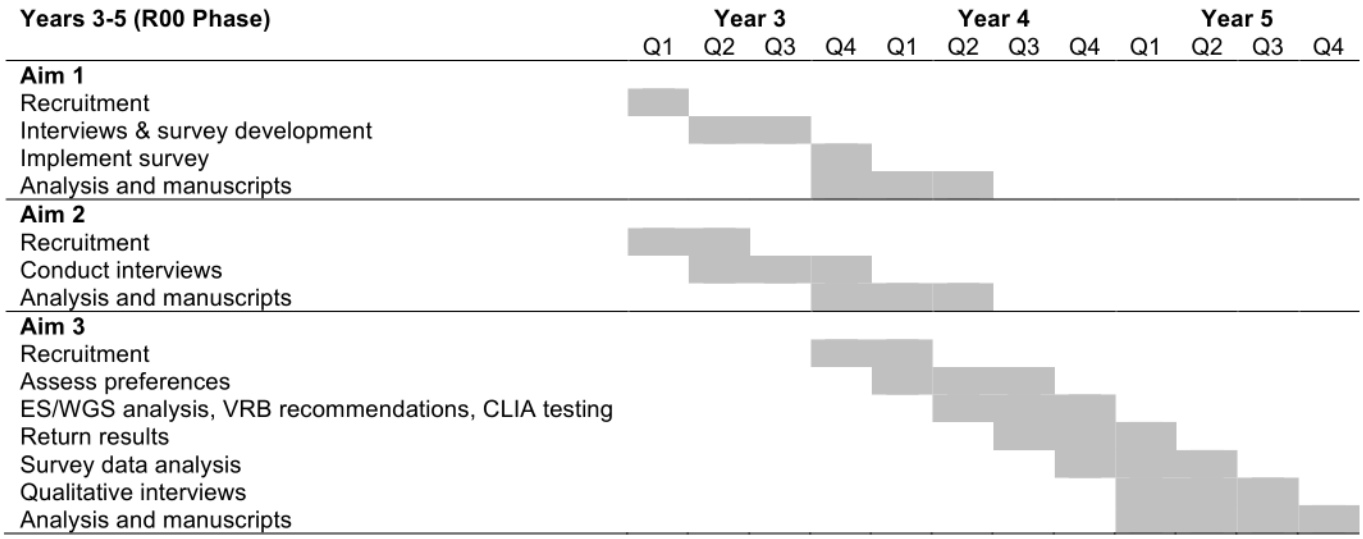
Qualitative experience. I will conduct semi-structured qualitative interviews with a sub-sample of 50 AA participants prior to receiving results, and 2-4 weeks and 6 months after participants have reviewed results to assess their experience and outcomes of receiving results. Interviews before results return will focus on participants' expectations about receiving results. Interviews after results return will focus on learning how participants have responded to results (e.g., impacted their health-related behaviors and attitudes) and whether the surveys adequately captured their response to results.

Analysis. Survey data will be analyzed to generate summary statistics. Responses to validated scales will be summarized following published practices. Outcome survey data from AAs will be directly compared to similar, existing data from EAs (n=150) who have received ES/WGS results using My46 or a genetic counselor. Following Table 6, I will (1) calculate differences in measures before and after receipt of results to assess impact of results, (2) calculate differences in outcomes measures between 2-4 weeks and 6 months after receipt of results to assess if outcomes are sustained over time, (3) summarize remaining single time point measures and (4) compare data from AAs and EAs to test for differences in impact of receiving results, changes overtime, and other single time point measures between AAs and EAs. I will evaluate effects of SES variables such as income, education, occupation, perceived social status, as well as health literacy and numeracy all of which have been shown to impact outcomes. Qualitative thematic analysis from interviews will be conducted and results compared to interviews previously conducted with EAs *(see Dr. Tabor's letter).*

Deliverables. Through this study, I will (1) characterize the short term outcomes of receiving ES/WGS results among AA adults and determine if these outcomes are sustained over a 6 month period and (2) produce a comparison of outcomes between AA and EA cohorts. Through a comparison of qualitative interview data and survey assessments of outcomes, I will (3) assess whether selected outcomes accurately capture/reflect those deemed important by AA participants and whether additional constructs need to be explored in future studies involving AA participants.

Anticipated challenges. Retention of study participants to study completion is a challenge I will address by providing incentives for completing each phase of the study including surveys and interviews. Some participants might not have results eligible for return. Given that ES/WGS data will be available from each individual, I will supplement the number of genes assessed in any particular individual so as to capture at least one result for return. Prior survey research with early adopters has reported measurement ceiling effects.[117] Items will be pretested and response categories revised as needed to reduce this possibility in the field. Outcomes may not develop or be observable over the 6-month period of follow up and is a practical limit of this study. Finally, comparison of outcome data in AAs to those previously collected in EAs may be limited due to the passage of time. This study will provide a foundation for future longitudinal studies of outcomes with AAs and other minority populations.

2.4 Timeline



PROTECTION OF HUMAN SUBJECTS

If any research herein is determined non-exempt, we will then submit an appropriate human subjects research application based on guidance from the UW IRB. Research projects proposed in this K99R00 include both exempt and non-exempt research.

K-Research Aim 1 and 2, and R00-Specific Aim 1

This human subjects' research falls under exemption category 2. These projects and aims use focus group, cognitive interview, and survey methodologies to conduct qualitative and quantitative research on attitudes toward genetic research and return of ES/WGS results. None of these require completion of a task or conduct of an intervention.

Risk to Subjects

Human Subjects Involvement and Characteristics
A total of n=1240 (40 participants for interviews in K-Research Aim 1; 200 survey respondents in K-Research Aim 1; 200 focus group participants in K-Research Aim 2; and 800 survey respondents in R00-Specific Aim 1) subjects ages 18 and over will be recruited for focus groups, interviews, or survey. Subjects for K-Research Aim 2 and R00 Aim 1 will be recruited who self-identify as African American (AA), Hispanic/Latino American (HL), Native Hawaiian Pacific Islander (NHPI) or Asian American (AS). Subjects for K-Research Aim 1 will be recruited from community health clinics and community-based organizations that serve African American (AA), Hispanic/Latino American (HL), Native Hawaiian Pacific Islander (NHPI) or Asian American (AS) populations. Preferrably, individuals who self-identify as members of these racial and ethnic groups will be recruited as interview participants in the K-Research Aim 1.

Source of Materials
Subjects for K-Research Aim 1 interviews and surveys will be from Federally Funded Federally Qualified Health Centers, commonly referred to as community health centers (CHCs), and from community-based organizations (including federally recognized tribal facilities) identified from public directories from national minority health organizations. Subjects for K-Research Aim 2 focus groups will be recruited from the University of Washington Pediatric Care Center (see Dr. Jeffry Wright's letter of commitment), Odessa Brown Children's Clinic (see Dr. Ben Danielson letter of commitment), Meredith Mathews YMCA of Greater Seattle (see Chip Byrne's letter of commitment), APICAT (see Elaine Ishihara's letter of commitment) and existing studies involving Hispanic Latino(s) Americans (see Dr. Beti Thompson letter of commitment). Subjects for the R00-Research Aim 1 survey will be recruited through Lake Research Partners and their online vendors (see Celinda Lake's letter of commitment). Although, I will receive those data as anonymous data, I will review their recruitment protocols and data collection methods to ensure that they are following human subjects regulations appropriate for research.

Potential Risks
Participants may experience discomfort when answering focus group, interview or survey questions about their own experiences or feelings. Although we will ask participants to keep what is said in focus group discussions in confidence, participants may repeat things said during the focus group to others. All the procedures that will be carried out during this study are believed to represent very low risks or have no known medical risks to date.

Adequacy of Protections Against Risks

Recruitment and Informed Consent
Recruitment for K-Research Aim 1 of individuals identified from publicly available lists will be conducted by email, if available, or by letter. A maximum of three attempts by phone or email will be made to encourage participation in the interview and or survey. Focus group recruitment (K-Research Aim 2) will involve a mixture of direct phone solicitation of eligible adults when lists are available, electronic and paper directed advertising (i.e., study flyer and study postcards) when eligible individuals visit the UWPCC, and if necessary onsite face-to-face recruitment. Study flyers will be posted on public bulletin boards at community organizations with the organization's approval. I will either contact eligible adults from call lists or respond to inquiries by phone. During the phone call, staff will explain the content of the study and assess their eligibility and availability for specific focus group dates and times. A letter describing the study and directions to the focus group or interview will be mailed to those interested in participating. Study staff will follow up by phone to answer questions about the study and confirm the date and time. Recruitment for R00-Research Aim 1 will involve sending an invitation to participate in an online survey via email. Up to three reminder emails will be sent to encourage participation.

As exempt research, subjects will be provided a written statement describing the study purpose, procedures, risks and benefits, human subject protections, confidentiality, and alternatives to participation; and will not undergo a written consent procedure.

Protections Against Risk
When study staff contact eligible individuals by phone, no more than 3 call attempts will be made for recruitment. Subjects will be informed that they do not have to answer any questions and are free to withdraw from the study at any time. At the start focus groups, the moderator will reiterate that our discussion is confidential and that we ask participants to be respectful of each other. All personal information will be kept in locked cabinets and on password-secured computers. Although we will have access and collect contact information for the purposes of recruitment, that information will not be linked to audio files or transcripts. Any inadvertently captured personally identifiable information will be redacted from transcripts. Audio-recordings will be destroyed within 2 years of the completion of the study.

Potential Benefits of the Proposed Research to Human Subjects and Others
The focus group, interview, and survey data will help investigators better understand attitudes toward return of ES/WGS results. While there are minimal risks involved in participating in this study, there are no direct benefits to subjects. The risk benefit ratio for individual subjects is very low.

Importance of the Knowledge to be Gained
The proposed research will benefit researchers in genome science and ethics, as well as policy makers and IRBs, by providing empirical data about how to discuss and return the kinds of results that will be identified from exome and whole genome sequencing research in a range of racial and ethnic populations. This will facilitate the ethical conduct of this research in a way that benefits participants in the future.

R00-Specific Aim 2

This research is non-exempt because the potential to link study data with personal identifiable information will be maintained and because participants will be asked to set their preferences for results and complete surveys using the online tool My46.

Risk to Subjects

Human Subjects Involvement and Characteristics
A total of n=90 subjects ages 18 and over will be recruited for interviews. Subjects R00 Aim 2 will be recruited who self-identify as Hispanic/Latino American (HL), Native Hawaiian Pacific Islander (NA) or Asian American (AS).

Source of Materials
Subjects for R00-Research Aim 2 interviews will be recruited from the University of Washington Pediatric Care Center (see Dr. Jeffry Wright's letter of commitment), Odessa Brown Children's Clinic (see Dr. Ben Danielson letter of commitment), Meredith Mathews YMCA of Greater Seattle (see Chip Byrne's letter of commitment), APICAT (see Elaine Ishihara's letter of commitment) and existing studies involving Hispanic Latino(s) Americans (see Dr. Beti Thompson letter of commitment).

Potential Risks
Participants may experience discomfort when answering interview and survey questions about their own experiences or feelings. All the procedures that will be carried out during this study are believed to represent very low risks or have no known medical risks to date.

Adequacy of Protections Against Risks

Recruitment and Informed Consent
Preference study recruiment for R00-Specific Aim 2 will involve a mixture of direct phone solicitation of eligible adults when lists are available, distribution of electronic and paper directed advertising (i.e., study flyer and study postcards) through institutional lists, and if necessary onsite face-to-face recruitment. Study flyers will be posted on public bulletin boards at community organizations with the organization's approval. I will either contact eligible adults from call lists or respond to inquiries by phone. During the phone call, staff will explain the content of the study and assess their eligibility and availability for study participation. A letter describing the study, directions, and consent form, will be mailed to those interested in participating. Study staff will follow up by phone to answer questions about the study and confirm scheduling a date and time.

Upon arrive at the University of Washington for the interview, subjects will be provided a consent form and study flyer describing the study purpose, procedures, risks and benefits, human subject protections, confidentiality, and alternatives to participation for the study; and will undergo a written consent procedure. Study staff will review the consent form, solicit and answer any questions, and document consent.

Protections Against Risk
When study staff contact eligible individuals by phone, no more than 3 call attempts will be made for recruitment. Subjects will be informed that they do not have to answer any questions and are free to withdraw from the study at any time. At the start of the interview, the interviewer will reiterate that the discussion is confidential, explain that all personal information will be kept in locked cabinets and on password-secured computers, explain that a link between data and personally identifying will be maintained by a code which will only be available to study staff, describe that any inadvertently captured personally identifiable information will be redacted from transcripts, and that audio-recordings will be destroyed within 2 years of the completion of the study.

Potential Benefits of the Proposed Research to Human Subjects and Others

These interview data will help investigators better understand attitudes toward return of ES/WGS results, specifically the role of preferences for receiving results and its importance to participation in genomic research. While there are minimal risks involved in participating in this study, there are no direct benefits to subjects. The risk benefit ratio for individual subjects is very low.

Importance of the Knowledge to be Gained
The proposed research will benefit researchers in genome science and ethics, as well as policy makers and IRBs, by providing empirical data about how to discuss and return the kinds of results that will be identified from exome and whole genome sequencing research in a range of racial and ethnic populations. This will facilitate the ethical conduct of this research in a way that benefits participants in the future.

R00-Specific Aim 3

This human subjects' research is non-exempt because of the potential to link study data with personal identifiable information will be maintained and because participants will receive ES/WGS results through a genetic counselor in conjunction with the online tool My46.

Risk to Subjects

Human Subjects Involvement and Characteristics
This research will be conducted with African American subjects (n=100), ages 18 years old or over, recruited from existing studies involving whole genome or exome sequencing. Original studies will either have ongoing contact with subjects or have IRB approval for re-contact and consent for other projects. Written information and biological samples (blood, buccal cells, saliva) will be collected from each study subject for CLIA-validation of results to be returned.

Sources of Materials
Human subjects enrolling in the research outlined in this proposal will be ascertained from on-going exome or whole genome sequencing studies, specifically MH-GRID (see Dr. Rakale Quarell and Dr. Charmaine Royal's letter of commitment). Samples of blood, saliva, or buccal cells from which DNA is to be extracted (for validation of results to be returned) will be shipped directly to a CLIA approved laboratory at the University of Washington for CLIA validation. Qualitative and quantitative data from subjects will be collected from interviews and online surveys and validated tools, including data about psychological, social and health-related responses to receiving results.

Potential Risks
Potential physical risks of this project include discomfort, mild pain and slight bruising at the phlebotomy site for the blood draw for the CLIA validation of returnable results. This project is explicitly designed to study genetic information about individuals that may be revealed by the analysis of the whole genome and exome sequencing data, information that may sometimes be unexpected. This includes potential results both related and unrelated to the disease that was the original focus of investigation. Participants will be given the option to not receive some or all offered results at the beginning of the study. They will also be able to decline participation in this study, while still participating in the original studies. A Variant Review Board (led by Drs. Bamshad and Burke) composed of bioethicists, geneticists and genetic counselors, and experts in regulatory issues, will carefully review possible results of clinical significance and utility that should be considered for return to individual participants. The Variant Review Board and the

research team will develop protocols for the return of results tool and genetics counseling to provide individuals with information about the meaning of possible results and options for next steps. Additional genetic counseling will be available to all participants after they have received results and thereafter for the duration of the study. One possible risk to subjects involves potential compromised confidentiality and potential psychological harm if unexpected genetic findings are determined appropriate to return to individual subjects. Loss of confidentiality will be mitigated by strict adherence to secure data practices. Result information will not be incorporated into participants' medical records.

Adequacy of Protection Against Risks

Recruitment and Informed Consent
I will work closely with the Principal Investigators of the original studies, and their institutional IRBs, to coordinate recruitment and informed consent of subjects for this study. Only subjects from original studies that have permission in their consent forms to re-contact participants about additional research will be included in this study. The recruitment and informed consent process will take place in four steps. First, the original study principal investigators will obtain IRB modifications, if needed, from their institutional IRBs to approach participants about participation in this study. Once approved, participants will be re-contacted by letter or by phone to either obtain permission for us to contact them directly, or to allow them the option to opt-out if they do not wish to be contacted. Second, our study coordinator will contact the participants by letter, e-mail or phone to recruit them. The coordinator will screen individuals by having them complete complete a baseline Patient Health Questionnaire nine-item scale (PHQ-9) assessment.[68] Individuals who score over 15 will be excluded to avoid enrolling participants who may be more likely to suffer adverse psychological responses to results. Participants will be excluded if they are not willing to obtain a confirmatory blood/buccal sample for CLIA validation of samples. Informed consent will take place by video chat or phone, and participants will return signed consent/assent forms to study staff. The Bamshad lab has been using this informed consent protocol for several years for other studies. Following receipt of the informed consent documents, participants will be sent kits for blood/buccal sample collection that will be shipped for CLIA certified testing.

The Bamshad lab has developed informed consent materials and forms that describe: 1) exome and whole genome sequencing (ES/WGS), 2) the kinds of results that can be identified from ES/WGS, 3) the limitations on the interpretations of those results, and that meaning of these results may change over time, 4) the need for CLIA validation of any genetic results with an additional DNA sample, 5) potential risks and benefits from different kinds of genetic results to individuals and to their family members/children.

Protections Against Risk
To minimize discomfort to participants an effort is made to obtain biological samples from procedures carried out as part of a participant's routine clinical care. Every effort is made to protect confidentiality. All clinical information and biological samples will be labeled with a coded number without any reference to individual identity. All identifiers will be stored in a protected database isolated from the network and a back-up will be made on a separate encrypted storage device that will be kept in a locked file cabinet in the locked study coordinator office. Access to the clinical data will be available only to approved staff. The identity of subjects will not be revealed in any publications, slides, presentations or other materials. Our current IRB approval is in compliance with HIPAA regulations. All research planned in this application will be performed at the University of Washington. Electronic data captured by the My46 has been configured to ensure access is secure in compliance with HIPAA regulations.

Potential Benefits of the Proposed Research to Human Subjects and Others
Participants will potentially benefit by having the opportunity to learn about genetic results from exome or whole genome sequencing that are of clinical or personal utility, and that may affect their health or life planning in a positive way. These results may be about the disease that they or someone else in their family has, and they may also be about other conditions. It is also possible that some participants may not have any returnable findings among the genes studied.

Importance of the Knowledge to be Gained
The proposed research on returning results will benefit researchers in genome science and ethics, as well as policy makers and IRBs, by providing empirical data about how to discuss and return the kinds of results that will be identified from exome and whole genome sequencing research with underrepresented minorities.

INCLUSION OF WOMEN AND MINORITIES

Recruitment of female participants will be included in all research activities. Based on prior experience recruiting parents for research studies, women are more likely than men to be interested in participating in focus groups about genetics. Women are included in the research studies from which subjects will be recruited for returning results. We have an expectation for 50% female participation.

The purpose of this research plan is to learn the perspectives of underserved racial and ethnic minorities on participation in genetic research and the return of result from exome and whole genome sequencing. These populations are well represented in the recruitment sites, study cohorts contributing to this protocol, and specific aims of this proposal.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Returning Exome and Whole Genome Results To Underserved Minority Populations

Domestic/Foreign: Domestic

Comments: The overall sample target is underserved/underrepresented racial and ethnic minorities from populations who experience higher rates of health disparities. Racial and ethnic sampling numbers are appoximations. Explicit inclusion/exclusion of specific racial and ethnic populations varies depending on specific purpose of each specific aim. Additional AI/AN participants may be recruited depending on outcomes and timing of mentored conversations with AI/AN community leaders.

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	4	4	0	0	**8**
Asian	169	169	0	0	**338**
Native Hawaiian or Other Pacific Islander	169	169	0	0	**338**
Black or African American	204	204	0	0	**408**
White	0	0	169	169	**338**
More than One Race	0	0	0	0	**0**
Total	**546**	**546**	**169**	**169**	**1430**

Study 1 of 1

Funding Opportunity Number: PA-14-042. Received Date: 2014-03-12T12:47:13.000-04:00

INCLUSION OF CHILDREN

Subjects age 18 years or over will be recruited into this study. No one under 18 years of age will be recruited into this study.