

SUMMARY STATEMENT
(Privileged Communication)

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Release Date: 06/18/2014
Revised Date: 06/20/2014

Application Number: 1 K99 HG007076-01A1

Principal Investigator

YU, JOON-HO

Applicant Organization: UNIVERSITY OF WASHINGTON

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

Meeting Date: 06/11/2014
Council: OCT 2014
Requested Start: 09/01/2014

RFA/PA: PA14-042
PCC: X5JM

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

SRG Action: Impact Score:

Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm

Human Subjects: 30-Human subjects involved - Certified, no SRG concerns

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

Gender: 1A-Both genders, scientifically acceptable

Minority: 2A-Only minorities, scientifically acceptable

Children: 1A-Both Children and Adults, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	92,437	<input type="text" value="Estimated Costs"/>
2	93,736	
3	161,165	
4	161,165	
5	161,165	
TOTAL	669,668	

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

REVISION NOTE

1K99HG007076-01A1 Yu, Joon-Ho

REVISED: June 20, 2014

RESUME AND SUMMARY OF DISCUSSION: This is a Pathway to Independence application from an outstanding, productive candidate with strong letters of support. The purpose is to extend the candidate's training and expertise in understanding preferences of under-represented populations with returning of results from exome and whole genome sequencing. The candidate has an extensive record working with ethnic minority populations and the training plan is well developed with specific goals for both the mentored and independent research phases. The candidate will focus on survey methods, cultural competency, and bioethics. The mentors are outstanding with complementary expertise and the reviewers noted a strong commitment to the development of the candidate. The mentor team is augmented by an outstanding group of advisors who are also leaders in their field and who will provide supplemental support for the two proposed studies. The candidate has been very responsive to the previous review and has addressed the concerns. The reviewers all agreed that this is an outstanding candidate with a high likelihood of a productive independent research career.

DESCRIPTION (provided by applicant): 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 American 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.

CRITIQUE 1:

Candidate: 1

Career Development Plan/Career Goals /Plan to Provide Mentoring: 2

Research Plan: 2

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1

Environment Commitment to the Candidate: 1

Overall Impact: This resubmission is extremely responsive to the initial critique, clearly addressing its major concerns. My strong support of this application stems from several factors: 1) Dr. Yu brings key experience and demonstrated commitment working with ethnic minority populations; 2) From his doctoral studies and his subsequent work, Dr. Yu is brings a strong foundation in ELSI research and is uniquely situated to conduct the inter-disciplinary work he proposes; 3) The team of mentors is outstanding and offers complementary expertise that will support Dr. Yu's transition to independence; and 4) the proposed research is of great significance and leverages existing tools and studies in probing patient preferences for ES/WGS return of results.

1. Candidate:

Strengths

- The candidate has an extensive track record working with ethnic minority populations and is well poised to conduct community based research as demonstrated by his long-standing commitment to serving the very local communities he plans to work with as part of this K99.
- Since the original submission, the candidate has published five articles as first and second author in high impact, highly regarded journals in his proposed area of research – AJOB Pm Res, Am J of Med Gen and Genet Med. This level of productivity rivals many established ELSI researchers.
- The candidate has extensive research experience in ELSI of genetic research and public health genetics, and will build on this foundation to develop an independent research program.

Weaknesses

- None noted.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:

Strengths

- In response to the initial critique, it is clear that the research training components have been expanded to include two rigorously designed studies to develop qualitative skills.

Weaknesses

- The candidate has planned a robust training program that includes coursework, mentored training and extensive "training" research projects for the first two K00 years. I have some concerns that this may be overly ambitious given the timeline. Scaling back on the two extensive research components might be necessary to complete the K portion within the two years.

- The training projects focus on qualitative research methods with which Yu appears to have a fairly strong foundation already. Development of quantitative research methods and in particular, survey development, would seem to a better training opportunity in light of the proposed R00 research.

3. Research Plan:

Strengths

- The research plan of investigating patient preferences for ES/WGS return of results addresses an important issue with immediate policy relevance.
- The research builds on the candidate's previous experience with the online platform My46 and leverages his understanding and knowledge of the tools available through this website.
- Research builds directly from the finding of the training research components in creating culturally relevant approaches to returning ES/WGS results and to probing participants on their views and preferences.

Weaknesses

- None noted.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- Drs. Wylie Burke and Mike Bamshad are outstanding primary mentors for this candidate and will bring complementary expertise and very strong track records for mentorship to his development.
- Additional mentorship from Drs. Holly Tabor, Charmaine Royal, and Deborah Bowen, all of whom are key ELSI researchers, will provide an outstanding team for the candidate's development as an independent ELSI researcher.
- As indicated by the strong letters of support, the candidate's experience working with a broad representation of community based organizations in the Seattle area suggest a strong network of potential collaborators directly relevant for his proposed research and future career plans.

Weaknesses

- None noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Excellent institutional support with a strong record for ELSI training and research.
- Letters of support indicate a high level of commitment to the development of the candidate.
- Outstanding resources are available to the candidate that specifically address the goals outlined for training and independent research.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children and not IRB Exemption #4.

- Sex/Gender: Distribution justified scientifically
- Race/Ethnicity: Distribution justified scientifically
- Inclusion/Exclusion of Children under 21: Excluding ages < 21 justified scientifically

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Resubmission:

- This application is extremely responsive to the initial review and has addressed concerns through extensive revisions.

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- excellent

Comments on Subject Matter (Required):

- appropriate

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- excellent

Comments on Duration (Required):

- appropriate

Comments on Frequency (Required):

- appropriate

Resource Sharing Plans:

Acceptable

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Candidate: 2

Career Development Plan/Career Goals /Plan to Provide Mentoring: 3

Research Plan: 3

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1

Environment Commitment to the Candidate: 1

Overall Impact: This K99/R00 focuses on examination of minority perspectives on ES/WGS and return of results to these communities who are historically underrepresented in genomic research. This is a highly significant focus. The candidate has been responsive to most concerns from previous review except for the lack of experience with African American communities in terms of research. The primary mentors are exceptional and have made documented commitment to mentoring and development of career independence. Institutional commitment is also outstanding. An excellent group of advisors supplement mentoring and will provide input on accessing minorities, design and outcome measure development. A major omission from the training and career development plan is training on career development of bidirectional and sustained community collaborations for research. This is essential to meet the investigator aim to become a leading researcher in assuring participation of minorities in genetic research. The research plan aims are acceptable.

1. Candidate:

Strengths

- A highly trained investigator, Dr. Joon-Ho Yu is an academically prepared candidate with dedication to scholarly advancement and commitment to address the genomic research participation issues involving minority populations.
- The training plan, the mentoring plans, and the candidate statement are excellent except for the weakness noted.
- It is clear that candidate is on a trajectory toward research independence with the two mentors and group of advisors assembled.

Weaknesses

- None noted.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:

Strengths

- Career goals are clearly articulated and are of high significance and are laudable. The mentoring from the two primary mentors is well planned to support eventual independence of this investigator.
- The advisors are excellent and will provide supplemental support for conduct of the two proposed studies as well as provide practical experience in meeting study aims and recruitment of the priority populations.
- The letter of support from the Asian Pacific Islander Coalition Advocating Together (APICAT) for Healthy Communities is excellent and documents previous collaborative relationship with this organization

Weaknesses

- The goal to develop skills in collaborative research WITH culturally diverse and underserved communities is not supported by the advisors nor listing of planned trainings.

- A series of trainings with community organizations and individuals representing the priority populations, especially African Americans and Latinos is as essential as the formal traditional research courses planned.
- While the advisors listed are outstanding scientists, there is no plan for mentoring/training on building bidirectional and sustained relationships with underserved communities to support collaborative research. This should be a critical component of the career development for this investigator who wants to make a long term career commitment to increasing participation of minority populations in genomic research.

3. Research Plan:

Strengths

- Mixed methods approach is proposed and is acceptable
- This is stated as first study to systematically assess attitudes on return of ES/WGS results and conduct comparative analysis between minority populations.

Weaknesses

- While use of the survey firm to collect online survey data is acceptable from a research standpoint, there is limited information about the experience of the firm with these populations proposed and use of a firm does not assist the candidate in development of their own community relationships to develop collaborative research in the future.
- The candidate has experience collaborating with API and Asian but no direct experience working with African American and Latinos. The advisors will assist in providing access to these communities for the candidates but there is no plan on how the candidate will develop their own collaborations with these priority populations. The letters from the advisors do not address this need.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- The primary mentor is Dr. Wylie Burke who is an exceptional scientist and has provided an exemplary letter detailing the mentoring process. She is Professor Department of Bioethics and Humanities. Dr. Michael Bamshad is Professor and Chief, Division of Genetic Medicine, Department of Pediatrics, University of Washington. Each has committed significant time and mentoring to support the career development and ultimate independence of this candidate.
- A group of advisors area also included for this candidate with scientific aspects of the proposed research including providing access to design support, outcome measurement and recruitment of minorities.

Weaknesses

- There is no community advisor(s) representing the priority populations of focus for this candidate.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Documented institutional commitment is exceptional in letters of support

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M2A - Only Minority, Acceptable

C3A - No Children Included, Acceptable

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

CRITIQUE 3:

Candidate: 3

Career Development Plan/Career Goals /Plan to Provide Mentoring: 3

Research Plan: 3

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1

Environment Commitment to the Candidate: 1

Overall Impact: This is a resubmitted application. The proposed career development plan and research is focused on understanding preferences and responses of underrepresented populations with regard to results of exome and genome sequencing. This is a well-written application that has been very responsive to the prior critique. The candidate has addressed previously noted deficits in regard to his scholarly productivity, experience with the populations of interest, and the research and training plans. Strong mentoring and advisory teams, and other collaborations, have been proposed. In general, there is enthusiasm for the candidate, the significance of the research.

1. Candidate:

Strengths

- The candidate is very highly recommended by the referees, who comment favorably on his potential for becoming a successful independent investigator and his scientific expertise and accomplishments. Referees are leading experts in genetics and bioethics, and several have had first-hand experience working with Dr. Yu.
- In response to comments from the prior review, the candidate has published 5 manuscripts with 2 as first author, which augments his scholarly productivity.
- The candidate has experience as a collaborator on studies involving genetics, bioethics and genomics, which will provide useful background for the proposed research and training.

- Also in response to prior critiques, Dr. Yu has completed coursework in qualitative research and has conducted preliminary research that informed the development of this proposal.

Weaknesses

- Limited plans for manuscript preparation during the training phase may make the candidate less competitive for transitioning to an independent faculty position.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:

Strengths

- Training plans outlines coursework and local training activities focused on survey methods, cultural competency and bioethics.
- Appropriate involvement and engagement with mentors.
- Inclusion of an expert advisory group is a strength. The advisory group is comprised of very solid and well-regarded experts in genetics and genomics.

Weaknesses

- The candidate's prior training in statistical methods is not known. The training plan would be strengthened with the inclusion of training in this area, given the focus on developing quantitative research skills.
- The applicant has prior experience with the mentors, thus, the extent of new training or knowledge to be gained during the training phase is unclear.

3. Research Plan:

Strengths

- The research plan is consistent with stated career and training goals.
- Candidate has the skills to conduct the qualitative components of the proposed research.
- The focus groups with individuals of diverse ethnic/minority groups is expected to inform the proposed R00 survey.

Weaknesses

- Development of the national survey for providers may be an ambitious goal for the training research phase, given the lack of quantitative training to date.
- Lack of experience with administering surveys to professionals is a weakness.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- Very strong mentoring and advisory team. Primary mentors are leaders in bioethics and genetics, with exceptional records as mentors and investigators. The advisory team is strong and complements the mentoring team, and Drs Bowen, Tabor and Royal.

Weaknesses

- Mentor letters contain some overlapping text.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Outstanding.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- No concerns.

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M2A - Only Minority, Acceptable

C1A - Children and Adults, Acceptable

- No concerns.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Budget and Period of Support:

Recommend as Requested

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

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

REVISION NOTE: Updated roster

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html>.

The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.