SUMMARY STATEMENT

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Release Date: **03/05/2015**

Application Number: **1 K99 HG008689-01**
Formerly: **1K99MH107865-01**

Principal Investigator

LAZARO-MUNOZ, GABRIEL JD, PHD

Applicant Organization: UNIV OF NORTH CAROLINA CHAPEL HILL

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

Meeting Date: **02/18/2015**
Council: **MAY 2015**
Requested Start: **07/01/2015**

RFA/PA: **PA14-042**
PCC: **X5JM**
Dual PCC: **8K-RT**
Dual IC(s): **MH**

Project Title: **Ethical Legal and Social Implications of Translational Psychiatric Genomics Research**

SRG Action: **Impact Score:** Priority Score

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

Human Subjects:
Animal Subjects:
Gender:
Minority:
Children:

reviewers' comments

Project Year	Direct Costs Requested	Estimated Total Cost
1	84,474	Estimated Costs
2	86,710	
3	163,816	
4	163,816	
5	163,816	
TOTAL	662,632	

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.

1K99HG008689-01 Lazaro-Munoz, Gabriel

RESUME AND SUMMARY OF DISCUSSION: This is a Pathway to Independence application from an outstanding productive candidate with a strong academic record and supportive letters of reference. The candidate has expertise in neuroscience, law and bioethics and the goal of this application is to extend the candidate's training and expertise into qualitative research methods. The research project will address the ethical issues of the methods for securing consent for both participation and return of results of genomic variants for mentally ill patients. The project is significant and innovative as it involves an extremely vulnerable group, those that are institutionalized and seriously mentally ill. The sponsors are outstanding and an excellent fit and committed to the candidate's interests and training plan. A minor concern for some reviewers is that the investigator needs to consider whether and what information from the secondary findings should be provided to legal guardians. The reviewers all agreed that the strengths outweigh any minor weaknesses in this application from an outstanding candidate who will have a high likelihood of an independent research career.

DESCRIPTION (provided by applicant): This project employs a multi-method, transdisciplinary approach that combines ethnographic participant- observation, interview research methods, ethical, legal, and public policy analyses. The two goals of the present project are 1) to identify the ethical, legal, and policy challenges that the field of psychiatric genomics will face when trying to translate the findings of large-scale GWAS into clinically useful information, and 2) to make evidence-based recommendations about how to address these challenges. To achieve these goals, I will use, as a case study, one of the first attempts to translate large-scale psychiatric genomics GWAS findings, the Genomics of Treatment-Resistant Psychosis (GTRP) study. GTRP will perform whole exome sequencing (WES) in a sample of 1,000 institutionalized patients who suffer from treatment-resistant psychosis (TRP). GTRP's goals are to identify genomic variants associated with TRP, and ascertain whether any clinically actionable information emerges from these genomic tests that could help improve mental health care for particular patient-participants. I propose to study GTRP's experience to address three research aims critical to understanding the challenges faced in translational psychiatric genomics research with severely mentally ill patients. Aim 1 will be the mentored research phase of the project, and Aims 2 and 3 will be the independent research phases. Aim 1a employs ethnographic participant-observation and interview methods to study the factors that influence GTRP researchers' decision-making process while designing and conducting the WES consent process and the return of results (RoR) components of their study. Aim 1b employs ethical analysis to evaluate the design of the GTRP study, including the WES consent process and RoR components. Aim 1c employs legal and policy analyses to examine the regulatory framework currently in place to protect institutionalized severely mentally ill patients who participate in translational psychiatric WES research. Aim 2a is an empirical examination informed by Aim 1 that employs interview methods to study the views and preferences of GTRP patient-participants, patient-participants' legal guardians or authorized representatives (LG/AR), patient-participants' mental health clinicians, and officials of the mental health institutions in which GTRP will take place. The interviews will assess their perspectives regarding how to handle the WES consent process, selection of results to return, RoR consent process, actual RoR procedure, and the Post-RoR management of WES findings. Aim 2b employs legal analysis to examine what kind of legal responsibility, if any, LG/ARs, clinicians, and mental health institutions, assume regarding the management of WES findings once these are returned by researchers (Post-RoR management). Aim 3 employs ethical and legal analyses to explore the implications of applying a legal Fiduciary Relationship Model (FRM) for defining the ethical responsibilities that different parties hold towards patient-participants in translational psychiatric genomics research. This work will be informed by the data collected in Aims 1 and 2.

PUBLIC HEALTH RELEVANCE: This project will identify the ethical, legal, and policy challenges that genomic scientists face when attempting to convert the identification of genes associated with mental health disorders into information and technologies that can improve treatment and prevention. The

identification and analysis of these challenges will allow this project to generate evidence-based recommendations about how to protect the interests of the mentally ill patients who participate in these studies. The protection of vulnerable populations that participate in research is a fundamental requirement of any study. Therefore, this project will advance psychiatric genomics medicine by providing guidance to scientists and other relevant parties involved in translational psychiatric genomics research.

CRITIQUE 1:

Candidate: 2
Career Development Plan/Career Goals /Plan to Provide Mentoring: 2
Research Plan: 2
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment Commitment to the Candidate: 1

Overall Impact: This is a very strong K99R00 application from an already productive candidate who combines a background in neuroscience, law, bioethics to first train in (primarily) qualitative research methods during the K99 period to address ethical issues in genome sequencing in treatment resistant psychosis. The institutional setting is superb and the mentoring team is stellar, with an excellent fit between the candidate's background and interest and the mentors' expertise and institutional resources. The only potential gap is the absence of a psychiatric expert, someone who can help guide the project's mental health and ethics angle. The R00 project is significant because it takes the return of results debate to a difficult and unexplored area. The method of ethical, legal, and ethnographic analysis seems well suited for this project. Perhaps the only weakness is the very ambitious scope of the project, but one expects adjustments as the project planning progresses during first two years and it seems likely important findings will be made. Overall, this is a very strong candidate with an excellent plan for mentored phase and research phase. The package is very well put together.

1. Candidate:

Strengths

- Excellent educational background, and top institutions, in interdisciplinary training—neuroscience, law, bioethics.
- He graduated in 2013 from his JD and MBE, and during first 10 months of his fellowship, has published a law review article (lead author), a multi-authored paper on intellectual property in genetics, an accepted single authored paper in JLME on a fiduciary model for analyzing IFs, and has submitted another piece as lead author. There are good signs that he will continue to be creative and productive.
- The package is well put together, reflecting the candidate's ability to think logically, and potential to plan, organize, and execute a research study.

Weaknesses

- None noted.

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

Strengths

- Although the candidate is superbly trained in key fields, to develop into an independent investigator, he does need some formal and experiential empirical research training. He has

chosen to focus on qualitative methods mostly, which seems reasonable in that given his bench science background, picking up the quantitative side may be easier.

Weaknesses

- None noted.

3. Research Plan:

Strengths

- The topic is significant and novel—i.e., WES and RoR gets plenty of press and debate but the candidate has chosen a niche that is ethically novel, i.e., the issues as they arise when the subjects are institutionalized, seriously mentally ill.
- An actual study has been identified and the candidate has obtained collaboration agreements for conducting an ethnographic study.

Weaknesses

- There is insufficient discussion of how the normative and descriptive aspects of the projects are to be combined or integrated. Also, the plan is very ambitious, but given the nature of the project, it is likely that important products can still be obtained.

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

Strengths

- Eric Juengst is a well-respected scholar in ELSI in genetics. Conley is both a social scientist and a lawyer, and Skinner is an anthropologist—with these and others at the CGC and bioethics center at UNC, there is an outstanding team of primary mentor and co-mentors. There is an excellent fit between the candidate's interest, background, and the mentors.

Weaknesses

- The only potential gap is a mentor who really understands psychiatric illnesses and bioethical and regulatory issues in psychiatric research.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- UNC's Dept. of Social Med, the Center for Genomics and Society, the Bioethics Center, law school and med school—these all add up to excellent intellectual resources for the candidate.
- Letters of support are strong.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- Candidate has thoughtfully addressed all relevant risk benefit and privacy concerns, and have proposed plans to minimize risks.

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Although only 18 and over will be recruited, all justified.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Multiple formats provided which seem appropriate to candidate's background and plans

Comments on Subject Matter (Required):

- Courses, lectures, and mentors all address relevant topics.

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

- Described adequately by the candidate.

Comments on Duration (Required):

- During mentored phase, each year: 4 x 5hours, plus 2 days per year. Plus research ethics grand rounds, online courses (but not specified), and mentoring.

Comments on Frequency (Required):

- See above. Adequate

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Candidate: 1
Career Development Plan/Career Goals /Plan to Provide Mentoring: 5
Research Plan: 4
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment Commitment to the Candidate: 1

Overall Impact: Dr. Lázaro-Muñoz is a neuroscientist, lawyer, and bioethicist, currently doing a post-doctoral fellowship at UNC working with Eric Juengst and other esteemed mentors; institutional commitments and his letters of support and recommendation are uniformly very strong; Dr. Lázaro-

Muñoz's training program appears to be directed to his proposed project, focused on coursework and research experience in qualitative research methods and public policy analysis, but the proposed public policy training appears thin and not well justified, and the focus on qualitative methods seems to be at odds with his stated long term goals of having skills relevant to assessment of evidence-based policies; the application proposes a significant and innovative qualitative study of the design and implementation of consent and return of results aspects of a whole exome sequencing study in hospitalized patients suffering from treatment resistant psychoses, drawing on a wide range of skills that Dr. Lázaro-Muñoz possesses or will develop; while there are several minor issues with the methods, the most significant concern is that the proposed ethnographic study of researchers' discussions and decision-making about design issues and choices about how to manage RoR seems to be timed poorly, given that the project appears to have been preliminarily approved by Drexel's IRB and approved by at least one of 6 hospital sites at the time of application submission, suggesting that protocol design issues have all been resolved.

1. Candidate:

Strengths

- Dr. Lázaro-Muñoz is a neuroscientist (NYU PhD 2010) and lawyer (UPenn 2013), with a Masters in Bioethics (UPenn 2013);
- He currently is a post-doctoral researcher in UNC's Center for Genomics and Society, working on various issues at the intersection of ethics, society, law, and genomics;
- He has been very productive throughout his relatively short career, and his writings reflect his transition from neuroscience to ELSI topics;
- Recommendation letters are very strong.

Weaknesses

- None.

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

Strengths

- Dr. Lázaro-Muñoz intends to develop qualitative research skills by taking two courses and performing the proposed participant observer and interview study with close mentorship by experienced researchers;
- He also wants to further develop public policy analysis skills by taking a single class and by focal experience with the proposed project;
- These skills will help him transition to be an independent investigator.

Weaknesses

- It's unclear what the precise goal is from the proposed coursework in both qualitative research methods (2) and public policy (1), plus the proposed project, which will involve at the most 36 days of participant observer, interviews, and other observations during the K99 portion of the project – the choice of qualitative methods appears driven by the proposed research instead of any deeper goal to develop sociological or anthropological expertise, and a single policy course doesn't translate into public policy expertise (or appear to add that much to the applicant's law and bioethics training)
- Long-term goals include the desire to "promote evidence-based public policies", but the focus on qualitative methods skills is perhaps too narrow, and – without disparaging the

generalizability and utility of ethnographic methods - there is no mention of quantitative methods in the application.

3. Research Plan:

Strengths

- The research plan proposes a mixed-methods assessment of decision-making and practices involved in a large (N=1000) translational genomics project involving seriously ill, hospitalized patients suffering from treatment resistant psychoses, a legal and ethical analysis of the methods for securing consent (and permissions and assent) for both participation and return of results, and the outcomes of returning results, with a summative normative analysis developed around the applicant's use of fiduciary law to assess ethical obligations of investigators, clinicians, and others to this population;
- This is a significant application, in that it involves an extremely vulnerable population for whom translational whole exome sequencing might hold out some prospect of help directly related to their intransigent mental health problem as well as for incidental findings for which RoR will be considered, and the methods are appropriately drawn and access appears to be in place to provide the applicant with broad exposure to the research team, subjects, subjects' family or other legal representatives; clinicians, and others;
- The population to be studied and the access to the entire research enterprise described above makes this an innovative application;
- Methods appear appropriate.

Weaknesses

- It may be that ethical return of results mandates that post-RoR management (p.92) includes assessment (and clinical services, if appropriate) of genetic relatives, particularly those involved in a patient subject's care who are likely to be part of the decision-making about RoR, and may well be more directly affected by various findings;
- The PI may want to get involved in data collection earlier in the recruitment process than merely attending any WES consent sessions, as such sessions may come at the tail end of a set of communications between the researchers and the family and patient that fix expectations and diminish the spontaneity of the actual consent session;
- The application states that researcher decision-making about return of results and choices of consent processes are to be assessed by ethnographic participant observer methods, but it appears that these decisions must have already been made, given that Drexel's IRB has granted preliminary approval, as has Norristown State Hospital, to the protocol (see Dr. Josiassen's letter, p.87), thus it is unclear that the applicant will have any opportunity to observe, for example, meetings and discussions about the design of the project;
- The application states at p.94 that "a consensus has emerged" that researchers "should" return results to subjects, but at p.91 this was stated more tentatively, "there is an emerging consensus", even though p.94 admits that "there is no standard for RoR" and researchers are free to return "no results of any type", all of which points to the fact that there is no consensus;
- Regarding interviews with institutional officials, it might be desirable to standardize the focus to truly reach individuals who can speak on behalf of the institution, such as CEOs or medical directors, as it is unlikely that IRB or HEC committee members – absent other qualifications – would be qualified to do so.

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

Strengths

- Primary mentors Juengst (philosophy, bioethics, genetics policy), Skinner (medical anthropology), and Conley (law, linguistic anthropology) are excellent and fully committed to their mentoring roles for Dr. Lázaro-Muñoz;
- Advisors Henderson, Cook-Deegan, Evans, and Stroup, as well as collaborators Josiassen and Sullivan are all excellent and fully supportive of the proposed training program and research plan.

Weaknesses

- None noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The PI and mentors are located in the UNC Center for Genomics and Society (CGS), an NIH P50-funded “Center of Excellence in ELSI Research” affiliated with the Department of Social Medicine, which is excellent;
- Institutional commitment is strong and supportive.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- It is stated near the top of p.99 that "GTRP patient-participants will have already been considered to have sufficient decision-making capacity to consent for participation in GTRP", and that patients will be approached after their clinician gives permission to solicit them for the proposed ethnographic study, but the next paragraph and the paragraph at the end of the page both clarify that some patients had permission given by a LG/AR with assent (see p.98, as well), so there should be a plan to get LG/AR permission and appropriate assent for the instant study's procedures, as well.

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Minors 18-21 who otherwise meet criteria for participation will be included.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- Includes various courses, workshops, and seminars, plus CITI.

Comments on Subject Matter (Required):

- All relevant RCR and HSR topics to be comprehensively addressed.

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

- All courses appear appropriately staffed by UNC faculty.

Comments on Duration (Required):

- More than 40 hrs./year, which is more than adequate.

Comments on Frequency (Required):

- Exposure will be continuous over the 2 training years.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Candidate: 1
Career Development Plan/Career Goals /Plan to Provide Mentoring: 1
Research Plan: 5
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment Commitment to the Candidate: 1

Overall Impact: Plans to study the ELSI issues faced by genomic scientists when attempting to identify genes associated with serious mental health disorders which can be then translated into improved treatment and prevention. Using Genomics of Treatment Resistant Psychosis (GTRP) as a case study. Goal is to generate evidence-based recommendations about return of results to patient-participants or their legal guardians regarding sequencing findings and secondary findings. One concern not adequately addressed focuses on the return of results to legal guardians when the patient-participant cannot consent for him- or herself, and whether the PIs have given adequate consideration regarding the protections of the privacy of the participant-patient.

1. Candidate:

Strengths

- Excellent mix of ethics, legal and neuroscience credentials
- Has proven his ability to publish in the field rather quickly

Weaknesses

- Does not adequately discuss the difference between returning results to individuals and surrogates. There are significant differences between children (and their parents who are their

legal guardians) and adults (whose parents, but also whose siblings or the state may be their legal guardians).

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

Strengths

- Excellent career development plan
- Dr. Lazaro-Munoz has proven his ability to succeed in a variety of academic areas
- Dr. Lazaro-Munoz is committed to working with underrepresented minorities in mentorship

Weaknesses

- None noted.

3. Research Plan:

Strengths

- Access to a vulnerable population with mentorship from thoughtful providers and researchers.

Weaknesses

- Aim 1b plans to analyze the ethics of GTRP's research design. Given that this is a funded project, what is the plan if the PI decides that the design is unethical (e.g., that it does not minimize risks)?
- I am a bit nervous about what information should be given to Legal guardians with respect to secondary findings, particularly when the legal guardian may be a relative who wants the information for interests beyond the patient-participant? I hope that the research team will consider whether there is some information that should only be reported to the individual him or herself.
- Lazaro-Munoz writes: "Even though a consensus has emerged that genomic researchers should return or offer to return results to participants, currently there is no standard for RoR in genomics research." It is not the case that there is consensus about RoR to participants, let alone to surrogates in the clinical setting. While less settled in the research setting, it is also the case that most RoR occurs in a setting in which these lines are blurred. This suggests that the PI has already decided the answer to some of the questions he seeks to answer.
- Need to evaluate therapeutic misconception in the researchers (and not just in the patient-participants and their legal representatives
- Concern about the rights of the non-physicians to refuse to participate in the ethnographic participant-observer component of this grant. The PI says he will not inform anyone about who has agreed to participate and who has not. He will tape everyone but only transcribe those who agree. I find this not fully adequate particularly since those who may not want to be transcribed--particularly staff or non-physicians (i.e., those with less job security)—that is more vulnerable employees who may feel constrained in talking but whose viewpoint may be important. He seems to ignore that these individuals are vulnerable in a different way than the participant-patients.

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

Strengths

- Conley and Juengst and Skinner are a powerful mentorship team

- Dr. P. Sullivan's willingness to train him " so you can develop the skills necessary to conduct interviews With patients who suffer from TRP during the R00 phase of your grant

Weaknesses

- The team members do not seem to consider the rights and vulnerabilities of non-physician members (e.g. staff) who may not want to participate in ethnography.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Strong institutional commitment.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and Adequate Protections

- I do not think the PI has given adequate attention to questions of what rights surrogates have about getting secondary findings. I hope this will be part of the process and that this will be addressed prospectively.
- Concern about the rights of the non-physicians to refuse to participate in the ethnographic participant-observer component of this grant.

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- There is a possibility that either the patient-participant or the legal guardian is a minor (Younger than 21 years), but they are appropriately limiting to over 18 years (legal for consent in most jurisdictions). Plans for bilingual participation. Men and women appropriate.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- in person training

Comments on Subject Matter (Required):

- covers policies regarding human subjects research; conflict of interest; mentor/mentee relationships; peer review; authorship and publication; data acquisition, management, sharing, ownership; research misconduct; collaborative research; contemporary issues biomedical research; and discussion sessions using case studies
- will attend the Research Ethics Grand Rounds (REGR), which is a monthly seminar series of local and invited speakers, addressing current ethical, legal and social issues in the design and conduct of biomedical research involving human subjects. REGR is offered by the UNC Center for Bioethics in collaboration with the NC TraCS Institute and the UNC Office of Research Ethics

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

- the Research ethics grand rounds will clearly be taught by faculty

Comments on Duration (Required):

- Took a 2 day program; will continue with 4 hours annually throughout entire training

Comments on Frequency (Required):

- 4 hours annually through the 5 years

Budget and Period of Support:

Recommend as Requested

- Appropriate.

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWER'S WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.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.