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.

Copyright Information

The text of the grant applications is copyrighted. Text from these applications can only be used for nonprofit, educational purposes. When using text from these applications for nonprofit, educational purposes, the text cannot be changed and the respective Principal Investigator, institution, and NHGRI must be appropriately cited and credited.

PI: **Lazaro-Munoz, Gabriel**	Title: Ethical Legal and Social Implications of Translational Psychiatric Genomics Research	
Received: 10/23/2014	FOA: PA14-042	Council: 05/2015
Competition ID: FORMS-C	FOA Title: NIH PATHWAY TO INDEPENDENCE AWARD (PARENT K99/R00)	
1 K99 HG008689-01	Dual: MH	Accession Number: 3753980
IPF: 578206	Organization: UNIV OF NORTH CAROLINA CHAPEL HILL	
Former Number: 1K99MH107865-01	Department: Social Medicine	
IRG/SRG: SEIR	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 84,474 Year 2: 86,710 Year 3: 163,816 Year 4: 163,816 Year 5: 163,816	Animals: N Humans: Y Clinical Trial: N Current HS Code: Evaluative Info HESC: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Gabriel Lazaro-Munoz Ph.D	The University of North Carolina at Chapel Hill	PD/PI
Eric Juengst Ph.D	The University of North Carolina at Chapel Hill	Other Professional-Mentor
John Conley JD	The University of North Carolina at Chapel Hill	Other Professional-Co-Mentor
Debra Skinner Ph.D	The University of North Carolina at Chapel Hill	Other Professional-Co-Mentor
Gail Henderson Ph.D	The University of North Carolina at Chapel Hill	Other Professional-Advisory Committee Member
Patrick Sullivan M.D.	The University of North Carolina at Chapel Hill	Other Professional-Collaborator

Reference Letters

[redacted]

Additions for Review

Accepted Publication new accepted 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

b. Agency Routing Number

2. DATE SUBMITTED | **Application Identifier**

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational DUNS*: 608195277

Legal Name*: The University of North Carolina at Chapel Hill
Department: Office of Sponsored Research
Division: Research
Street1*: 104 Airport Drive, suite 2200, CB#1350
Street2:
City*: Chapel Hill
County: Orange
State*: NC: North Carolina
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 27599-1350

Person to be contacted on matters involving this application
Prefix: First Name*: Kim Middle Name: Last Name*: Jones Suffix:
Position/Title: Grants Analyst, Sponsored Programs Office
Street1*: 1140-C Bioinformatics Bldg., CB 9525
Street2: 130 Mason Farm Road
City*: Chapel Hill
County: Orange
State*: NC: North Carolina
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 27599-9525
Phone Number*: 919-962-3950 Fax Number: Email: grants@unc.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 1566001393A1

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*
Ethical Legal and Social Implications of Translational Psychiatric Genomics Research

12. PROPOSED PROJECT
Start Date* 07/01/2015
Ending Date* 06/30/2020

13. CONGRESSIONAL DISTRICTS OF APPLICANT
NC-004

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: Gabriel Middle Name: Last Name*: Lazaro-Munoz Suffix: Ph.D

Position/Title: Postdoctoral Research Fellow
Organization Name*: The University of North Carolina at Chapel Hill
Department: Social Medicine
Division: School of Medicine
Street1*: 333 South Columbia Street
Street2: 343 MacNider Hall
City*: Chapel Hill
County: Orange
State*: NC: North Carolina
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 27599-1350
Phone Number*: 919-962-8493 Fax Number: 919-966-7499 Email*: gabriel_lazaro@med.unc.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$931,879.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$931,879.00
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: Dr. First Name*: Barbara Middle Name: Last Name*: Entwisle Suffix: Ph.D

Position/Title*: Vice Chancellor for Research
Organization Name*: The University of North Carolina at Chapel Hill
Department: Office of Sponsored Research
Division: Research
Street1*: 104 Airport Drive, Suite 2200, CB# 1350
Street2:
City*: Chapel Hill
County: Orange
State*: NC: North Carolina
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 27599-1350
Phone Number*: 919-966-3411 Fax Number: 919-966-3352 Email*: resadminosr@unc.edu

Signature of Authorized Representative*
Kim Jones

Date Signed*
10/23/2014

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:1252-Cover_Letter_Lazaro-Munoz_K99.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:	The University of North Carolina at Chapel Hill
Duns Number:	6081952770000
Street1*:	104 Airport Drive, Suite 2200, CB#1350
Street2:	
City*:	Chapel Hill
County:	Orange
State*:	NC: North Carolina
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	27599-1350
Project/Performance Site Congressional District*:	NC-004

	File Name
Additional Location(s)	

Funding Opportunity Number: PA-14-042. Received Date: 2014-10-23T16:52:09.000-04:00

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

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*	1245-7_Project_Summary_Abstract_GLM.pdf
8. Project Narrative*	1246-8_Project_Narrative_GLM.pdf
9. Bibliography & References Cited	1247-9_Bibliography_and_References_Cited_GLM.pdf
10.Facilities & Other Resources	1248-10_Facilities_and_Other_Resources_GLM.pdf
11.Equipment	1249-11_Equipment_GLM.pdf
12. Other Attachments	1250-List_of_Referees_GLM.pdf 1251-Medical_Director_PA_Dept_Public_Welfare_LoS_for_GTRP.pdf

Funding Opportunity Number: PA-14-042. Received Date: 2014-10-23T16:52:09.000-04:00

PROJECT SUMMARY/ABSTRACT

Ethical, Legal, and Social Implications of Translational Psychiatric Genomics Research

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.

PROJECT NARRATIVE

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.

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Unpublished

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FACILITIES AND RESOURCES

THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

Founded in 1792, the University of North Carolina is the oldest public university in the United States. The University of North Carolina at Chapel Hill (UNC) is the flagship campus for the 16-campus University of North Carolina system with more than 29,000 students, six professional schools, and five health affairs schools. These include Business, Law, Education, Journalism, Social Work, Information and Library Sciences, and the Schools of Dentistry, Medicine, Nursing, Pharmacy and Public Health. UNC is a research-intensive institution and consistently ranks among the top U.S. public universities in research support. In fiscal 2014 its researchers attracted more than $792 million, a direct reflection of the quality of the research the faculty are conducting and the excellence of the infrastructure that supports their research. UNC has spearheaded a commitment to expanding and enriching resources available to researchers while emphasizing the collaborative links between basic scientists at the bench, clinicians in the hospital, and social science and bioethical researchers. This general atmosphere, and specific resources provided by departments and research centers make UNC an exhilarating place to conduct science.

The following is a list of relevant resources that will be available to this K99/R00, **"Ethical, Legal, and Social Implications of Translational Psychiatric Genomics Research."** The UNC web site (www.unc.edu) provides a rich description of virtually every resource on campus.

SCHOOL OF MEDICINE

The UNC School of Medicine has a record of maintaining its commitment to education and health services for the people of its state, while building a steadily growing and diverse environment for medical research. The School of Medicine remains the University's largest source of contract and grant funding, with faculty bringing in $431 million in 2014. The School of Medicine houses the Department of Social Medicine, the Center for Genomics and Society, and the Center for Bioethics, which will play a key role in this K99/R00.

DEPARTMENT OF SOCIAL MEDICINE

The Department of Social Medicine, chaired by **Dr. Gail E. Henderson**, is an academic unit that incorporates the long-standing interest of the University of North Carolina and the School of Medicine in community medicine and health care delivery systems. The mission of the Department is to inform the work and thought of physicians on: (1) the social conditions and characteristics of patients, the social causes of illness and the social barriers to effective care; and (2) the social responsibilities of the medical profession. Members of the faculty apply their various disciplines to problems of the poor, elderly, chronically ill, and other categories of people with special health and medical care needs like those who are severely mentally ill; questions of allocation, distribution, organization and financing of health resources; and health and medical care problems in North Carolina.

The Department carries out its mission through a variety of educational, research, and service activities in several venues and almost always in interdisciplinary collaboration throughout the UNC campus. Though not an exclusive list, the following areas are those in which the Department has active research and ongoing interests: cultural anthropology and medical anthropology, epidemiology, health economics, history of medicine and public health, literature and medicine, medical care organization, medical ethics, medical sociology, medicine and the law, preventive medicine, public policy in health and medical care.

The Department of Social Medicine, unlike other departments in the University, serves as an interdisciplinary department, and employs faculty and researchers from across the campus and beyond to accomplish its mission. This means that the administrative staff in the department is exceptional in terms of their ability to comprehend and coordinate activities across the wide array of constituencies served by the department. Social Medicine is a bridge between medicine and public health, and between medicine and the arts and humanities disciplines, and those who work in Social Medicine must have strong skills in translation and organization.

CENTER FOR GENOMICS AND SOCIETY

The training component of this K99/R00 will be based in the UNC Center for Genomics and Society (CGS),

an NIH P50-funded “Center of Excellence in ELSI Research” housed within the Department of Social Medicine at UNC’s School of Medicine. **Dr. Henderson** is the Director of the CGS and an Advisor on this K99/R00. In addition, the three Co-Mentors (**Drs. Eric T. Juengst, Debra Skinner, and John M. Conley**) are all Co-investigators within CGS, which is now entering its seventh year of funding and is supported until 2018. CGS provides a rich learning and research environment for trainees because it brings together investigators from numerous fields such as medical genetics, genetic counseling, bioethics, sociology, anthropology, law, public health, philosophy, and nursing. CGS’s goal is to carry out an integrated set of transdisciplinary research, training, and policy activities addressing ethical, legal and social issues involved in the application of genomics to the general public. To create a real-world context in which to study this application of genomics, CGS investigators are designing and conducting a trial protocol informed by ELSI perspectives, recruiting 1,000 individuals within a controlled setting, focusing on highly penetrant rare mutations that place people at risk for potentially preventable conditions.

UNC CENTER FOR BIOETHICS

The UNC Center for Bioethics will be a valuable resource for this K99/R00. **Dr. Juengst,** the Primary Mentor on this proposal directs this Center. Larry Churchill, Ph.D. and Laura Hanson, M.D. originally proposed the UNC Center for Bioethics as the “Center for Health Ethics and Policy” in 1999. They served as its founding Co-Directors when the University established it as a unit of the School of Medicine in 2001. The Center was active under their leadership until 2004. In 2008, Dr. Etta Pisano, then Vice Dean for the School of Medicine, revitalized the Center and initiated the search that brought Dr. Juengst to direct the Center in 2010.The mission of the UNC Center for Bioethics is to provide a core facility for collaborative capacity-building in bioethics at UNC. Today, the work at the Center for Bioethics is supported by funding from: UNC School of Medicine Dean’s Office, UNC Department of Social Medicine, UNC Health System, North Carolina Translational and Clinical Sciences Institute (NC TraCS), NC Center for AIDS Research, the Center for Genomics and Society at UNC, Fogarty International Center, National Institutes for Health, National Human Genome Research Institute, and the Private Source

DEPARTMENT OF GENETICS

The Department of Genetics, chaired by Dr. Terry Magnuson, provides basic and applied genetic/genomic research, education and training at the interface between biology, chemistry, physics, computer science, mathematics, the social sciences, public health and medicine in order to have a profound effect on how medicine will be practiced in the future. The Department includes a clinical arm focused on medical genetics, which covers the broad spectrum of clinical genetic research from disease prevention to diagnosis and treatment. The Department is home to a distinguished group of genomics investigators, which includes psychiatric genomics researcher, **Dr. Patrick F. Sullivan**, a Collaborator on this grant, and **Dr. James P. Evans** who will serve as an Advisor. Drs. Sullivan and Evans are co-investigators on the Genomics of Treatment-Resistant Psychosis (GTRP) study.

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

The Gillings School of Global Public Health (SPH) at UNC was established in 1940 as the fourth school of public health in the US and the first to be created at a state university. The SPH at UNC is ranked first among schools of public health at public universities by *U.S. News & World Report* (last ranked in 2011), and second among all schools of public health. The departments within the SPH include: Biostatistics; Environmental Science and Engineering; Epidemiology; Health Behavior; Health Policy and Management; Maternal and Child Health; and Nutrition. SPH faculty members such as Drs. Christine Rini and Dan E. Jonas are extensively involved in collaborative research with CGS and will also serve as useful resources for this K99/R00.

SCHOOL OF LAW

Established in 1845, the UNC School of Law is among the oldest law schools in the nation and has played influential roles in the state, the south, and throughout the nation. **Dr. Conley**, Co-Mentor on this K99/R00, is the William Rand Kenan Jr. Professor at UNC Law. The Law School will enrich Dr. Lázaro-Muñoz’s training during this K99/R00 grant. For example, Dr. Conley will invite Dr. Lázaro-Muñoz to be a guest lecturer in the *Biotechnology and the Law* course. Recently, Dr. Conley gave Dr. Lázaro-Muñoz the opportunity to speak at

meetings that are relevant to this K99/R00 grant such as a UNC Law Symposium “Gene Patents after Myriad” and the Blue Ridge Health Law Professors Meeting.

In addition to Dr. Conley, UNC Law faculty includes world-class scholars, award-winning teachers, and noted practitioners. An impressive new series of externship and clinical programs—combining academic rigor with essential professional practice—has invigorated the second- and third-year learning experience. Rigorous joint degree programs in business, public policy, planning, social work and public administration assure diverse methods of inquiry. Forty-seven full-time professors conduct classes in a range of specialties. Many of the faculty come to UNC Law from public and private practice; others have combined the study of law with such disciplines as computer science, anthropology, history, theology, psychiatry, and philosophy. Research conducted within the School of Law produces a rich body of publications - books, monographs, manuals, and articles in law reviews and other professional publications. Faculty members also participate in various local, regional, and national programs on continuing legal education sponsored by the School of Law and other organizations.

FRANK PORTER GRAHAM CHILD DEVELOPMENT INSTITUTE (FPG)

FPG was founded in 1966 by a small group of scientists who had a vision to conduct research that would make a difference in children's lives, support families, and inform public policy. Today FPG is one of the nation's oldest and largest multidisciplinary centers devoted to the study of young children and their families. FPG has a long history of obtaining federal funding to conduct training and research projects to address the health and education of young children. With approximately 280 employees, research and training projects are conducted by an interdisciplinary faculty with backgrounds in anthropology, education, maternal and child health, pediatrics, nursing, psychology, social work, speech and hearing sciences, and related fields. Research projects focus on genetic disorders; developmental disabilities; early care and education; physical and social health; professional development, technical assistance, and implementation science; public policy and evaluation; and racial, ethnic, linguistic, cultural, and socioeconomic diversity. Core units within FPG offer support for the successful implementation of grants. These include the Publications Office, the Data Management and Analysis Center, and Qualitative/Ethnographic Methods & Analysis Core (QMAC). QMAC, directed by **Dr. Skinner,** Co-Mentor on this K99/R00, will be a particularly useful resource for the qualitative research planned in this proposal. It will provide an experienced staff and resources to assist in all aspects of qualitative/ethnographic research, including research design, training, implementation, data management, collection, and analysis.

ODUM INSTITUTE FOR RESEARCH IN SOCIAL SCIENCES

The Odum Institute will also be an important resource for this K99/R00 because it provides training in empirical social science research methods and qualitative data analysis. The Odum Institute houses one of the nation’s largest social science and census data archives, maintains a state-of-the-art Geographic Information System (GIS) and computing lab. It also provides advanced statistical software and consulting support for social science and survey research design and analysis, offers short courses and seminars on research and related topics, and sponsors 16 ongoing faculty work groups.

The Institute’s services are available to faculty and graduate students, undergraduate students and faculty mentors, academic departments, UNC centers and institutes, university staff and administrators, other research groups and partners, government officials and the public. The Institute is staffed by experts in quantitative and qualitative research methods, statistics, survey research, and social science and census data archives. Its short course faculty draws from leading national and international experts throughout the Triangle’s research community. The Institute supports multidisciplinary social science research in a variety of ways. The Institute’s Survey Research Group supports the university’s only Certificate Program in Survey Methodology for social scientists and graduate students. In addition to the Institute’s upgraded survey research capability, the Survey Research Group offers consultation and services on questionnaire design and pre-testing, data collection (including telephone and Web surveys), sample design, data analysis, and focus group research.

LIBRARY RESOURCES

The UNC Library system comprises nearly three dozen libraries, including the Walter Royal Davis Library, which is the main Academic Affairs library, the House Undergraduate Library, and the Health Sciences Library, which is the main Health Affairs library. Campus libraries have more than three hundred staff, and the library's combined holdings exceed 5,000,000 volumes, 4,000,000 microforms, 2,000,000 printed government publications, 16,000,000 manuscripts, hundreds of thousands of audiovisuals, maps and photographs, and thousands of electronic titles. In scope, campus libraries cover most areas of the fine arts, biomedical and physical sciences, humanities, law, and social sciences.

THE UNC HEALTH SCIENCES LIBRARY (HSL)

The HSL, part of the UNC Library system, has superb staff, facilities, and collections and is considered to be among the best medical school libraries in the United States and Canada. The six-story building has seating capacity for 713 users. The HSL has over 328,000 volumes, and 3,950 journals (about 3,000 of these are also available electronically). The HSL and the School of Medicine's Office of Information Services jointly support the University of North Carolina Literature Exchange (UNCLE), a locally mounted, networked version of MEDLINE, the major bibliographic database in the biomedical sciences and clinical medicine. This Web-based system is available free of charge to all members of the University health affairs community and is easily accessible from any location on or off campus. In addition, HSL has an online system that provides information about material available at the other area institutions of higher learning. Information about other resources and databases can be obtained at the library's Internet Desk, which is staffed on a full-time basis by technical experts. The HSL is also a participant in faculty and student education related to the retrieval of electronic information and use of specialized computer applications.

EQUIPMENT

No item of property that has an acquisition cost of $5,000 or more will be necessary for this project.

BUDGET JUSTIFICATION

Personnel

Gabriel Lázaro-Muñoz, PhD, JD, MBE, Principal Investigator (PI) (EFFORT months in Years 1-2). Dr. Lázaro-Muñoz is a Post-Doctoral Research Fellow at the University of North Carolina Center for Genomics and Society (CGS) and will be the principal investigator on this proposal. During years 1 and 2, he will conduct an ethnographic examination (participant-observation and interviews) of a group of psychiatric genomics researchers as they design and conduct a genomics study (Genomics of Treatment-Resistant Psychosis; GTRP) in patients with treatment-resistant psychosis (TRP). During the mentored phase of the grant, Dr. Lázaro-Muñoz will also attend courses and seminars on ethnography, interview methods, and qualitative data analysis. He will also train in ethnography by working in some of his co-mentors' studies.

Benefits

Benefit support is requested for the PI at the University rate of 8.968%, plus $3,6852/FTE per year for health insurance. A 3% increase in salaries and benefits are requested in all subsequent years of the proposal.

Supplies

In year 1, we request **$2,200** for a laptop computer and software to be used by the PI. Dr. Lázaro-Muñoz will use these exclusively for this project and for his work off-site collecting data and note-taking at meetings. We also request **$500** for an educational license for NVivo 10 software, which will be used for qualitative data analysis. We are also requesting **$300** for a digital tape recorder to be used for participant-observation and interviews.

Travel

In year 1, Dr. Lázaro-Muñoz will travel to Pennsylvania for ethnographic data collection about the recruitment and consent process followed by the Genomics of Treatment-Resistant Psychosis (GTRP) researchers as they conduct their study. This data collection will take place at different state psychiatric hospitals and facilities that are operated by the Pennsylvania Department of Public Welfare (DPW). Each trip will be for 4 days and he will make 4 trips per year. (Roundtrip airfare = $300 x 4 = $1,200, hotel =$180/night x 3 nights = $540 x 4 = $2,160, car rental = $50/day x 16 days = $800, food =$40/day x 16 days = $640) total **= $4,800**.

In order to disseminate his work and be informed of the latest research on psychiatric genomics, Dr. Lázaro-Muñoz will attend the World Congress of Psychiatric Genetics Conference, in Toronto (registration fee = $900 plus transportation and lodging =$1,500) **= $2,400**. Dr. Lázaro-Muñoz will also attend the American Society for Bioethics and Humanities conference in Houston Texas (registration =$400, transportation and lodging = $1,500) **= $1,900**.

In year 2, Dr. Lázaro-Muñoz will continue to travel to Pennsylvania for ethnographic data collection about the recruitment and consent process followed by GTRP researchers. During year 2, Dr. Lázaro-Muñoz will also need to travel to the hospitals to begin coordinating the interviews that he will conduct in year 3 of this project. Each trip will be for 4 days and he will make 5 trips in year 2. (Roundtrip airfare = $300 x 5 = $1,500, hotel =$180/night x 3 nights = $540 x 5 = $2,700, car rental = $50/day x 20 days = $1,000, food =$40/day x 20 days = $800) total **= $6,000**.

In order to disseminate his work and be informed of the latest research on psychiatric genomics, Dr. Lázaro-Muñoz will attend the World Congress of Psychiatric Genetics, Location TBD (registration fee = $900 plus transportation and lodging =$1,500) **= $2,400**. Dr. Lázaro-Muñoz will also attend the American Society for Bioethics and Humanities conference, Location TBD (registration =$400,

transportation and lodging = $1,500) **=$1,900**; and the American Society of Human Genetics conference Location TBD (registration = 900, transportation and lodging = $1,500) **=$2,400**.

Other Expenses

In year 1, WestlawNext will be purchased for research access to law reviews and federal and state case law and statutes. This is a necessary resource for the kind of legal and public policy research and analysis that will be conducted in this project. The UNC School of Medicine does not have access to this legal database; therefore funds are required to help offset the cost for access **= $3,600**.

Transcription service will be needed for the recorded interactions between researchers and participants, and researchers' discussions and interviews about the project's consent process and the return of results. There will be an estimated 30 hours of audio recordings. (30 hours of audio x 6 hours of transcribing per hour of audio = 180 hours x $35/hr.) **= $6,300**.

A critical component of Dr. Lázaro-Muñoz's proposal is his training in empirical social science research methods. As part of this training, Dr. Lázaro-Muñoz will take the following two courses, ResearchTalk Summer Intensive **= $1,500** and UNC's School of Nursing Qualitative Analysis Institute **= $1,500**.

In year 2, Dr. Lázaro-Muñoz will continue to use WestlawNext to conduct legal and policy research **= $3,600**.

Transcription service will also be needed for the recorded interactions between GTRP researchers and participants, researchers' discussions during meetings, and individual interviews with the researchers about the project's consent process and the return of results. There will be an estimated 30 hours of audio recordings. (30 hours of audio x 6 hours of transcribing per hour of audio = 180 hours x $35/hr.) **= $6,300**.

Dr. Lázaro-Muñoz's training in qualitative research methods will continue during year 2 in which he will take a number of courses and seminars offered by the Odum Institute and others on interview methods and qualitative data analysis **= $1,900**.

Finally, in year 2 Dr. Lázaro-Muñoz will be applying to positions in medical schools and law schools in order to fulfill the purpose of the K99/R00 proposal to promote the transition of scholars from mentored to independent research positions. Applications to law school faculty positions are managed through the Association of American Law Schools (AALS), which charges a fee for this service **= $500**.

Indirect Costs

The Facilities and Administration (F&A) Cost Rate Agreement for the University of North Carolina at Chapel Hill is dated May 16, 2012. The indirect cost rate for Year 1-2 of the contract that begins 7/1/15 and ends 6/30/17 is 8%.

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OMB Number: 0925-0001

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

Prefix: Dr.
First Name*: Gabriel
Middle Name:
Last Name*: Lazaro-Munoz
Suffix: Ph.D

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: 2014-10-23T16:52:09.000-04:00

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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)	
Candidate Information	
2. Candidate's Background	1253-Candidate_Background_GLM.pdf
3. Career Goals and Objectives	1254-Career_Goals_Objectives_GLM.pdf
4. Career Development/Training Activities During Award Period	1255-Candidate_Plan_Career_Development_Training_GLM.pdf
5. Training in the Responsible Conduct of Research	1256-Training_Responsible_Conduct_Research_GLM.pdf
6.Candidate's Plan to Provide Mentoring (as applicable)	
Statements of Support	
7. Plans and Statements of Mentor and Co-Mentor(s)	1257-Plan_and_Statement_of_Mentors.pdf
8. Letters of Support from Collaborators, Contributors, and Consultants	1258-Letters_of_Support.pdf
Environment and Institutional Commitment to Candidate	
9. Description of Institutional Environment	1259-Description_Institutional_Environment_GLM.pdf
10. Institutional Commitment to Candidate's Research Career Development	1260-Institutional_Commitment_to_Candidate_GLM.pdf
Research Plan	
11. Specific Aims	1261-Specific_Aims_GLM.pdf
12. Research Strategy*	1262-Research_Strategy_GLM.pdf
13. Progress Report Publication List (for RENEWAL applications only)	
Human Subject Sections	
14. Protection of Human Subjects	1263-Protection_Human_Subjects_GLM.pdf
15. Inclusion of Women and Minorities	1264-Inclusion_Women_Minorities_GLM.pdf
16. Inclusion of Children	1265-Inclusion_Children_GLM.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*:

- ● U.S. Citizen or noncitizen national
- Non-U.S. Citizen with temporary U.S. visa
- Permanent Resident of U.S. (If a permanent resident of the U.S., a notarized statement must be provided by the time of award)
- Permanent Resident of U.S. Pending

CANDIDATE'S BACKGROUND

My background reflects both my interest and commitment to a career investigating the ethical, legal, and social (ELSI) implications of emerging technologies (i.e., genomics and neuroscience). My career as an investigator began as an undergraduate student at the University of Puerto Rico (UPR), where I was a fellow of the NIMH's Career Opportunities in Research (COR) program. COR's goal was to train and promote interest in research among underrepresented minority students and it certainly worked in my case. During my four years at UPR, I worked in research projects related to mental health and neurobiology. My participation in this program led me to pursue a PhD in Neuroscience at New York University (NYU), where I studied the amygdala, a brain region that plays an key role in processing and storing fear memories. The goal of my research was to understand the neurobiological underpinnings of anxiety disorders such as post-traumatic stress disorder (PTSD). As a doctoral researcher, I received funding from two NIMH fellowship programs: 1) F31 NRSA Predoctoral fellowship (2009-2010); and 2) American Psychological Association's Diversity Program in Neuroscience fellowship (T32 grant) (2005-2008).

My interest in ELSI of scientific developments is in great part inspired by my experience as a neuroscientist. A couple of years before I arrived to Professor Joseph LeDoux's laboratory at NYU, the lab had demonstrated a method for erasing fear memories in rats. Numerous laboratories quickly began working on ways to erase traumatic memories to help patients with PTSD. However, whenever a colleague from the lab presented research about this work to the general public, audiences often asked about the ethics and potential social implications of developing memory erasure techniques. I remember being surprised by these concerns; however, this experience helped me realize how sometimes individuals can get so focused on figuring out how to achieve a scientific or clinical goal that they may forget or not realize their work may have unintended consequences that need to be anticipated and managed.

After I obtained my PhD in Neuroscience, a growing interest in science public policy and the regulation of emerging technologies led me to pursue a JD and a Master of Bioethics at the University of Pennsylvania. My experience at Penn confirmed my interest in working in the intersection of science and society. As I studied for the bar (PR attorney ID #19-882), an opportunity emerged to work as a postdoctoral fellow at the NHGRI-funded Center for Genomics and Society (CGS) at the University of North Carolina. Accepting this position has proven to be a very rewarding decision. The field of ELSI genomics has allowed me to combine my interests in science, law, bioethics, and public policy. This K99/R00 will even allow me to incorporate my interests in mental health and neuroscience into my work in ELSI genomics. I enjoy this work and I am committed to career as an ELSI researcher.

I also believe that, with the guidance of my mentors, I am developing the necessary tools to become a successful independent ELSI genomics investigator. My background in neuroscience, together with my postdoctoral training in ELSI genomics, helps me understand the technical and scientific aspects of genomics. My training in law, and bioethics allow me to tackle the legal and ethical implications of developments in genomics. My training in empirical social science research methods during the K99 will allow me to generate empirical data that can inform my ethical and legal analyses of problems in genomics. This training will also help me better understand the way empirical social science studies are designed, performed, and interpreted in ELSI genomics. Finally, my training in public policy analysis during the K99 will hopefully help me translate my research into public policy recommendations that can help maximize the benefits and minimize the harms of genomic technologies.

During the past year at CGS, I have had the opportunity to employ my background in science, law, and bioethics to tackle diverse ethical and legal problems in genomics. The support of my mentors, Professors Eric T. Juengst, Debra Skinner, John M. Conley, numerous other CGS investigators, and my enthusiasm for investigating ELSI genomics issues, have helped me produce three first author manuscripts, one co-authorship, this K99/R00 proposal, and presentations in a number of different forums. This K99/R00 will be instrumental in allowing me to become a more complete ELSI investigator; equipped to help my colleagues in the field tackle the most complex upcoming challenges in ELSI genomics.

CAREER GOALS AND OBJECTIVES

I have a long-standing interest in the development and implementation of medical technologies to help treat and prevent disease, particularly psychiatric disorders. As an undergraduate and doctoral student, I worked on building scientific knowledge to develop medical technologies that could eventually help treat and prevent drug addiction, and psychiatric disorders. As a law and bioethics student, and during my postdoc in ELSI genomics, my work has focused on examining ethical and legally sound ways of implementing medical technologies in order to maximize their social benefits and minimize their harms.

As a postdoc at the Center for Genomics and Society (CGS), I have worked under the mentorship of Professors Eric T. Juengst, Debra Skinner, and John M. Conley to explore the ethical and legal implications of genomic sequencing research, and attempts to use genomic technologies to treat and minimize the risk for certain diseases. During my first 6 months at CGS, I examined ethical and legal challenges associated with: the use of gene patents and trade secret law by genomic testing companies; managing genomic secondary target findings; and implementing a preventive genomic sequencing program in the general population.

At the beginning of the summer, I met with my CGS mentoring committee (Professors Juengst, Skinner, and Conley) to discuss my progress and ways to advance my career as an independent ELSI investigator. We decided that gaining research skills in empirical social science methods would help me become a more complete and competitive ELSI investigator. This is how the idea for pursuing a K99/R00 to train in these methods originated. However, while I knew I wanted to pursue a K99/R00 to learn these methods, I was also determined to look for ways to begin incorporating my interests in neuroscience and psychiatric disorders into my ELSI genomics work. In this pursuit, two great opportunities emerged.

First, Professor Juengst invited me to be the lead author on a manuscript about the use of genomics in the U.S. military. We decided to focus this article on the scientific, ethical, and legal challenges of establishing a preventive genomic sequencing program for post-traumatic stress disorder (PTSD) in the military. Predictive genomic testing for PTSD is an idea that has been recently discussed in military circles, and the work on that paper allowed me to analyze the state of the science in psychiatric genetics and genomics as well as the ethical issues involved in working with individuals in decisionally constraining institutional circumstances.

The second opportunity emerged after I discussed my interest in writing a K99/R00 on psychiatric genomics with Professors Gail E. Henderson and James P. Evans. They both suggested that I talk to one of our UNC colleagues, Professor Patrick F. Sullivan, who is a leading expert on psychiatric genomics. Fortunately, Professor Sullivan happened to be initiating a collaboration (Genomics of Treatment-Resistant Psychosis; GTRP) to try to translate the recent identification of more than 130 genomic loci implicated in psychotic disorders into clinically useful information for patients who suffer from treatment-resistant psychosis (TRP). The novelty of these translational efforts in psychiatric genomics and the population under study makes this a project with numerous challenging ethical and legal questions. Professor Sullivan and his collaborators where happy to help incorporate my K99/R00 plans into their study.

During the K99 phase of this project my goals are to: 1) gain formal training and experience in participant-observation, interview methods, and qualitative data analysis; 2) gain training and experience in public policy analysis; 3) enhance my skills in ethical and legal analyses related to problems in genomics and psychiatric research; 4) publish ethnographic research about the factors that influenced GTRP researchers' decision-making when designing and conducting the consent and return of results components of their study; 5) publish an ethical analysis of the research design and conduct of GTRP; and 6) publish legal analyses and public policy analyses and recommendations regarding the current regulatory framework in place to protect severely mentally ill individuals who participate in translational psychiatric genomics research.

During the R00 phase my goals are to: 1) conduct interviews to study the perspectives of the different parties involved in GTRP; 2) study and develop a framework, the Fiduciary Relationship Model (FRM), to help guide the ethical management of genomics testing and return of results in research with mentally ill patients; 3) submit an R01 to examine how patient-participants and the parties involved in protecting their best interests, interpreted and managed the genomic findings returned by GTRP researchers. Finally, **my long-term goals are to**: 1) establish myself as an independent ELSI investigator with a focus on psychiatric genomics; 2) develop programs to train and motivate underrepresented ethnic minorities in ELSI genomics research; and 3) promote evidence-based public policies regarding genomic technologies.

CANDIDATE'S PLAN FOR CAREER DEVELOPMENT/TRAINING ACTIVITIES DURING AWARD PERIOD

I. Justification for Training

During my postdoctoral work at UNC's Center for Genomics and Society (CGS), I have gained valuable training and experience performing theoretically grounded analyses of the ethical and legal implications of developments in genomics. My experience at UNC, together with my formal training background in neuroscience, law, and bioethics, has helped me address diverse issues in genomics. These include the ethical and legal implications of 1) gene patents and the use of trade secret law for the protection of medical information relevant to the interpretation of genomic variants; 2) clinicians' fiduciary duties to patients when managing genomic incidental findings in the clinic; 3) preventive genomic sequencing programs in the general population; and 4) preventive genomic sequencing programs for post-traumatic stress disorder (PTSD) in the U.S. military.

However, balanced ethical and legal analyses are in many ways dependent on the nuanced perspectives of those who will be involved in and impacted by genomic technologies. Often, unexpected factors, concerns, hopes, and misconceptions influence the way individuals perceive and experience the benefits and burdens of genomic technologies. Empirical social science research methods such as participant observation and semi-structured interviews are valuable and proven research tools for capturing individuals' perspectives. To inform the ethical and legal analyses of my research and to more comprehensively tackle ELSI problems in genomics, my plan is to acquire research skills in participant-observation and interview methods during the mentored phase of this proposal.

The career development and training plan that I have crafted with my mentors will allow me to gain formal training and mentored research experience with empirical social science data collection techniques. These techniques will be a valuable complement to my training and research experience in ELSI genomics, neuroscience, law, and bioethics. They should also make me a more competitive candidate in the academic job market and provide the skills needed to develop transdisciplinary projects as an independent ELSI researcher.

II. Team

My two-year career development and training plan will be supervised and supported by a team of accomplished and experienced mentors Eric T. Juengst, Debra Skinner, and John M. Conley (See Biosketches and Mentor Statements); advisors Gail E. Henderson, James P. Evans, Robert Cook-Deegan, and T. Scott Stroup; and collaborators Patrick F. Sullivan and Richard C. Josiassen. (See Letters of Support).

Mentors

- **Eric T. Juengst, PhD.** Dr. Juengst is a philosopher with many years of NIH-supported experience in the multi-disciplinary analysis of the ethical, legal, and social implications of genomic research. As my principal mentor, he will provide conceptual frames and research leads for my continued exploration of ethical issues in psychiatric genomic research through regular discussions aimed at clarifying issues, constructing arguments, and making connections between my ethnographic and interview findings and the larger research ethics literature.

- **Debra Skinner, PhD.** Dr. Skinner is a cultural and medical anthropologist with many years experience conducting ethnographic and mixed methods studies focused on how parents of children with disabilities and adult patients understand and use genetic information, and on the production of expert knowledge in the field of genomic medicine. As a co-mentor, Dr. Skinner will provide hands-on experience in ethnographic methods and analysis, relevant sociological/anthropological theories, and research design related to my topic of interest.

- **John M. Conley, JD, PhD.** Dr. Conley is a lawyer as well as a legal and linguistic anthropologist with extensive experience using the methods of ethnography and sociolinguistics to conduct research in a variety of institutional settings, including law, business and finance, and medical science. He has also written extensively on gene patents and other intellectual property issues. As a co-mentor, Dr. Conley will provide guidance on ethnographic methods and analysis, particularly where linguistic data are involved, and will be available to assist and advise on legal issues that may arise.

Throughout the mentored phase, I will meet individually with each of my mentors at least once a week. We will also meet as a group quarterly, and maintain continuous communication through email. I have had the opportunity to work with Professors Juengst, Skinner, and Conley over the past year, and they have provided continuous feedback and guidance on my work at CGS. They have also opened many doors for me in terms of projects, publications, and networking. I look forward to working with them as I begin my training in empirical social science research methods with this K99/R00, and continue enhancing my ethical and legal analysis skills, which are key components of my research.

III. Training Goals and Plan

I have three main goals for the mentored phase of this project (years 1 and 2; See **Table 1,** below), which I will achieve through a combination of working directly with my mentors to gain experience in social science research methods and participating in formal coursework, workshops, and mentored research.

1) Formal training and research experience with empirical research methods (e.g., participant-observation, interview methods, and qualitative data analysis). To attain this goal, I will work with Drs. Skinner and Conley on their current ethnographic studies examining the translation of genomics to clinical medicine as a participant observer and interviewer. I will be involved in the data analysis from these projects, and gain valuable hands-on experience of different approaches to qualitative data analysis and theoretical perspectives that inform those methods.

I will also take the following courses offered at UNC's Department of Anthropology: *809 ANTH Ethnographic Methods*, a course that explores theories and methods of ethnographic research and *750 Seminar in Medical Anthropology*, a course that examines medicine as a part of culture, anthropological theories of medicine, and research methods for studying medical arenas. In addition, I will take short courses and workshops on interview methods, qualitative data analysis, and software programs (e.g., NVivo10, MaxQDA) that facilitate qualitative data analysis, offered at UNC's Odum Institute, UNC's School of Nursing, and through ResearchTalk's summer intensive program held in Chapel Hill.

I will gain further experience with ethnographic/qualitative methods and analysis during the research proposed in ***Aim1a*** of this project. Under the mentorship of Drs. Skinner and Conley, I will work as participant-observer with a group of psychiatric genomics researchers conducting a translational genomics study (Genomics of Treatment-Resistant Psychosis; GTRP) in a sample of institutionalized patients with treatment-resistant psychosis (TRP). As part of ***Aim 1a***, I will also conduct semi-structured interviews with GTRP researchers, and I will perform qualitative data analysis of the observation and interview data collected.

During the mentored phase, I will also gain experience with interview methods by designing and piloting the semi-structured interviews I will use during part of the independent phase of this proposal (***Aim 2a***). Piloting these interviews during the mentored phase will serve as valuable training and experience in qualitative research methods, and will help facilitate my transition as an independent researcher. Furthermore, in order to strengthen my preparation for the independent research phase, Professor Patrick F. Sullivan has agreed to provide training on how to conduct interviews with patients who suffer from TRP, which will be an important component of Aim 2. (See Letter of Support)

2) ***Formal training and experience in policy analysis***, I will take *710 PLCY Public Policy Analysis* offered at UNC's Department of Public Policy. In addition, I will work under the guidance of Drs. Conley and Cook-Deegan in ***Aim 1c*** to analyze and make policy recommendations about the current regulatory framework for the protection of institutionalized severely mentally ill patients who participate in translational genomics research.

3) ***Enhance my ethical and legal analysis skills***. I will work under the mentorship of Dr. Juengst to conduct ethical analysis (***Aim 1b***) of the design and implementation of the GTRP study that I will examine as part of ***Aim 1a***. This will include individualized problem-based learning sessions to explore perspectives in the literature relevant to designing and conducting research with institutionalized populations who may lack decision-making capacity, as well as practical opportunities to work through real issues as a member of the research ethics consultation service that Dr. Juengst directs at the North Carolina Translational & Clinical Sciences Institute (NC TraCS). To enhance my legal analysis skills, I will work under the mentorship of Dr. Conley (***Aim 1c***) to examine relevant cases and evaluate the laws and regulations currently in place to protect

institutionalized severely mentally ill patients who participate in translational genomics research. Dr. Conley has also offered to invite me as a guest lecturer in some of his relevant courses at UNC School of Law such as *Biotechnology and the Law*, to allow me to gain more experience teaching about these topics.

IV. Other Training

Throughout the mentored phase of this proposal, I will also participate in career development and training seminars offered by the CGS. Specifically, I will participate in the monthly *ELSI Reading Group*, a journal club on ELSI issues led by Dr. Skinner for CGS trainees; the monthly *CGS Trainees Writing Group*, also led by Dr. Skinner, in which CGS trainees get the opportunity to submit works in progress for feedback; and monthly *Professional Development Seminars* in which CGS investigators and others present topics relevant for a professional academic career, such as grant writing, research ethics, and developing an independent research program. In addition, I will participate in the career development training programs offered by UNC's Office of Postdoctoral Affairs.

Finally, as part of my training and career development I plan to present my research in meetings such as the World Congress of Psychiatric Genetics, the American Society for Bioethics and Humanities (ASBH) Meeting, the American Society of Human Genetics (ASHG), and the Law and Society Association Meeting.

Note: Please see next page for **Table 1 Training and Research Activities During K99 Mentored Phase**

Table 1 Training and Research Activities During K99 Mentored Phase

Years 1-2: K99 Mentored Phase	Year 1												Year 2											
Career Development Plan	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
809 ANTH Ethnographic Methods																								
750 ANTH Medical Anthropology																								
710 PLCY Public Policy Analysis																								
ResearchTalk Qualitative Methods Summer Intensive																								
Qualitative Analysis Summer Institute (UNC's School of Nursing)																								
Odum Institute Qualitative Methods (e.g., NVivo 10)																								
ELSI Reading Group																								
CGS Trainees Writing Group																								
CGS Professional Development Seminars																								
Clinical and Research Ethics Training (CEGR; REGR)																								
Ethnographic Practicum Dr. Skinner NCGENES																								
Meetings with Mentor Team																								
Individual Meetings Dr. Juengst (Bioethics)																								
Individual Meetings Dr. Skinner (Ethnography)																								
Individual Meetings Dr. Conley (Ethnography and Law)																								
Presentation at Research Conferences																								
Design and Pilot Interviews for Aim 2a																								
Research Plan	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Aim 1a: Ethnographic Examination of GTRP researchers' Design and Conduct of WES Consent and RoR																								
Ethnography of GTRP Researchers Discussions																								
Ethnography of Consent Process in Psychiatric Hospitals																								
Interviews with GTRP Researchers																								
Data Analysis																								
Preparation of Manuscripts																								
Aim 1b: Ethical Analysis of GTRP Project's Design and Conduct of WES Consent and RoR																								
Research and Manuscript Preparation																								
Aim 1c: Legal and Public Policy Analysis of Regulatory Framework for the Protection of Mentally Ill Patients in Genomics Research																								
Legal and Regulatory Research																								
Public Policy Analysis and Recommendations																								
Preparation of Manuscripts																								

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH

Prior Training in the Responsible Conduct of Research (RCR)

As an undergraduate student in psychology and a doctoral student in neuroscience, I was involved in NIH-funded research, and NIH-training programs (2001-2010), which involved RCR training in the protection of human subjects (I worked with human subjects research from 2001-2003), and animal use (2003-2010). This training included issues related to conflict of interest, authorship, data management, laboratory safety, research misconduct, research ethics, and confidentiality. As a law and master of bioethics student (2010-2013), I continued my training in the history, theory, and significance of conducting human research in a way that is respectful of participants and maximizes the protection of their best interests.

My RCR education continued during my postdoctoral training in the ethical, legal, and social implications of genomics at the University of North Carolina Center for Genomics and Society (CGS). When I arrived at CGS, I took the Collaborative Institutional Training Initiative (CITI) Human Research Curriculum for Social and Behavioral Research (December 13, 2013), which included the following modules: 1) History and Ethical Principles; 2) Defining Research with Human Subjects; 3) The Regulations; 4) Assessing Risk; 5) Informed Consent; 6) Privacy and Confidentiality; 7) Records-Based Research; 8) Research With Protected Populations - Vulnerable Subjects: An Overview; 9) Avoiding Group Harms - U.S. Research Perspectives; 10) Research and HIPAA Privacy Protections; 11) Vulnerable Subjects - Research Involving Workers/Employees; and 12) Conflicts of Interest in Research Involving Human Subjects.

As part of my research training at CGS and in order to become a member of UNC's Hospital Ethics Committee, I also took HIPAA training on January 25, 2014 and July 1, 2014. This training included modules in: 1) Guidelines for Contacting Patients; 2) Patients Right to Accounting of Disclosure; 3) Patients Rights; 4) Patients Right to Object to Disclosures; and 5) General Privacy & Information Security.

In addition, I took a two-day training (July 14-15, 2014) on RCR Human Subjects Research sponsored by the North Carolina Translational and Clinical Sciences Institute (NC TraCS Institute). I will also take a two-day (October 28-29, 2014) RCR Training for Postdoctoral Scholars offered by UNC's Office of Postdoctoral Affairs.

RCR Training During the Award Period

I will continue my RCR training through a combination of methods. 1) During each year of the mentored phase, I will attend an RCR course (five, 4hr sessions) offered by the NC TraCS Institute, which 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. 2) During each year of the mentored phase, I will also attend a two-day RCR course offered by UNC's Office of Postdoctoral Affairs. This course covers many of the issues mentioned above, but with a particular emphasis on matters that are relevant to postdoctoral scholars. 3) In addition, I 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. 4) I will strengthen my RCR training by taking relevant online courses, and 5) through regular meetings with my research mentors, Professors Eric T. Juengst (Director of UNC's Center for Bioethics, and Director of NC TraCS Institute's Research Ethics Consultation Service), Debra Skinner, and John M. Conley, in which we will discuss RCR issues related to my project and the Genomics of Treatment-Resistant Psychosis (GTRP) study.

DESCRIPTION OF INSTITUTIONAL ENVIRONMENT

The training component of this K99 award will be based 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 at the University of North Carolina at Chapel Hill. Dr. Lázaro-Muñoz's three Co-Mentors are all Co-investigators within the CGS, which is entering its seventh year of funding. Additional career development opportunities will also come to Dr. Lázaro-Muñoz through the UNC Center for Bioethics, which the Primary Mentor, Dr. Juengst, directs.

Since its inception, CGS has integrated a postdoctoral training program into its mission to conduct transdisciplinary research on emerging ethical, legal and social issues in genomics. The goals of the CGS's Training Program are to enable the trainees to: 1) acquire knowledge and skills needed to conduct ELSI research and translational work; 2) learn to work and communicate across disciplines; and 3) learn to communicate and disseminate ideas and findings effectively to academic, policy, and law audiences. The CGS has fully funded 8 post-docs as formal CGS trainees, 5 of whom are women, 3 of whom are African American and one of whom is Latino. It has trained or is currently training 10 graduate students, 6 of whom received assistantships or developmental awards through the CGS, and of these, 3 are African American. It has also trained 4 undergraduates or recent graduates, two of whom are African American and one who is Latino. In addition, the CGS has involved 15 other post-docs, graduate students, medical students, and law students in CGS research and training. All have gone to independent research and policy careers in their fields.

The CGS's postdoctoral scholars develop individualized training plans with their mentors, engage in research projects with the faculty co-investigators, conduct independent analyses and projects, and participate in a formal curriculum of professional development seminars, journal club discussions, and paper-writing groups. In addition, most trainees have enrolled in courses on quantitative or qualitative methods through the Odum Institute for Social Science Research. Trainees have been funded to travel to national professional conferences and training workshops that provide networking and learning opportunities in their areas of interest.

The training environment at CGS is further enhanced by its affiliation with the Department of Social Medicine, an interdisciplinary department within the School of Medicine that also houses the UNC Center for Bioethics and the UNC Center for Health Equity Research. Each of these other Centers can offer training experiences, such as opportunities for fellows to become involved with the "Research Ethics Consultation Service" and the "Community Engagement Core" of the UNC CTSA, the UNC Hospital Ethics Committee, and the "Bioethics at UNC" cross-campus faculty research group. Both of these other Centers also host post-doctoral fellows, which gives the Department a combined cohort of 8-10 fellows at any one time, ranging across multiple disciplines.

Of particular relevance to this application is the CGS's involvement with the NCGENES project, an NIH-funded "Clinical Sequencing Exploratory Research" study at UNC, studying the use of whole exome sequencing in the clinical setting. It is in the context of this study that co-mentor Debra Skinner has conducted an ethnographic study of the actual decision-making processes and production of scientific knowledge. In conjunction with other studies at UNC, such as NCNEXUS that explores issues in using sequencing technologies in newborn screening, CGS has a wealth of experience with the issues that this application addresses.

SPECIFIC AIMS

Recent large-scale genome-wide association studies (GWAS) and GWAS mega-analyses have identified more than 130 genomic loci implicated in psychotic disorders (i.e., schizophrenia, and to a lesser extent bipolar disorder). The challenge now is to use genomic sequencing to translate GWAS findings into clinically useful information that can help improve patient care. However, translational genomics research with patients who suffer from psychotic disorders will be ethically and legally challenging. Depending on the severity of their condition and response to treatment, these patients may have diminished decision-making capacity and may even be involuntarily committed in long-term psychiatric care institutions. This raises questions about patients' ability to freely volunteer for translational genomic research, especially when the research aims to produce information useful to their clinical care.

Complicating things further, there is an emerging consensus within the genomics community that researchers have an ethical responsibility to provide individual research participants any clinically relevant results generated when conducting genomic testing for research purposes, including secondary findings unrelated to the purpose of the study. To fulfill this responsibility, translational genomics researchers who work with patients with psychotic disorders will have to identify ethical, but practical ways to manage the return of results (RoR). In turn, to protect patient-participants' best medical and overall interests, it will be necessary for their legal guardians or authorized representatives (LG/AR), mental health clinicians, and mental health institutions to develop protocols for managing patients' clinically relevant WES findings once returned by researchers (Post-RoR management).

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: Examine the factors that influence GTRP researchers' decision-making when designing and conducting the WES consent process and RoR components of their study. Using ethnographic participant-observation techniques and key informant interviews, I will identify the processes and factors that play a role in psychiatric genomic researchers' determinations when designing and conducting the: 1) WES consent process, 2) selection of results to return, 3) RoR consent process, and 4) actual RoR procedure with institutionalized patients who suffer from TRP.

Aim 2: Examine stakeholders' perspectives regarding how to handle the WES consent process, RoR, and Post-RoR management of WES findings with institutionalized patients who suffer from TRP. Using interview methods, I will examine the views and preferences of GTRP patient-participants, patient-participants' LG/ARs, patient-participants' mental health clinicians, and officials of the mental health institutions where GTRP will take place regarding how the: 1) WES consent process, 2) selection of results to return, 3) RoR consent process, 4) actual RoR procedure, and 5) Post-RoR management of WES findings should occur.

Aim 3: Explore the Fiduciary Relationship Model (FRM) for guiding the ethical use of WES in translational psychiatric genomics research with institutionalized patients. Using ethical analysis, I will examine the implications of applying legal fiduciary principles *taken from trusts and agency law* (e.g., duty of care, duty of loyalty, duty to inform, and duty to act within the scope of authority) to define ethical responsibilities in translational WES research with this population. Specifically, I will apply FRM to help define the ethical responsibilities that researchers, LG/ARs, mental health clinicians, and mental health institutions hold towards these patient-participants in different components of translational psychiatric genomics studies (e.g., WES consent process, RoR, and Post-RoR management).

RESEARCH STRATEGY

A. Significance

Psychotic disorders (e.g., schizophrenia and bipolar disorder) are major contributors to the biopsychosocial and financial burdens of mental health disorders.[1, 2] Psychotic disorders involve debilitating symptoms such as delusions and hallucinations,[3] generally begin early in adulthood, and treatment options are frequently ineffective or have intolerable side effects.[4-7] Approximately 30% of patients who suffer from psychosis are considered treatment-resistant.[5-8] Due to the disruptive effect of psychosis on patients' lives and decision-making capacity,[1] those who suffer from treatment-resistant psychosis (TRP) are often involuntarily committed in psychiatric care institutions.[8] Involuntary long-term care helps protect patients with TRP, and manage some of their symptoms, but offers few prospects for improving their psychotic symptoms.

Recent large-scale genome-wide association studies (GWAS) and GWAS mega-analyses[9,10] ***have identified more than 130 genomic loci implicated in psychotic disorders.***[9-16] Because of their lack of response to available treatments, patients with TRP stand to gain from the translation of these GWAS findings into clinically useful information (e.g., improved risk prediction, diagnosis, treatment, pharmacogenetic guidance, and identification of drug targets). One of the first efforts to translate large-scale GWAS findings into improved clinical management for patients with TRP is the Genomics of Treatment-Resistant Psychosis (GTRP) study. GTRP will conduct whole-exome sequencing (WES) in a sample of 1,000 institutionalized patients with TRP who have not responded to antipsychotics after at least 5 years of treatment.

Translational psychiatric WES studies such as GTRP aim to help translate large-scale GWAS findings into clinically useful information for the management of TRP, but they generate challenging ethical and legal questions.[17-19] GTRP will recruit patients with TRP who are involuntarily committed in long-term psychiatric care institutions and who may often lack decision-making capacity due to their condition.[20-23] These characteristics raise questions about the ability of GTRP participants to freely volunteer for the study and how to ensure the protection of their best interests.[20-29]

Five key aspects of translational WES research are largely unexplored with institutionalized severely mentally ill patients, and require careful attention in order to conduct studies like GTRP in an ethically and legally responsible manner. First, how should genomic researchers manage the consent to WES process with this population (***WES consent process***)?[17-30] Second, what kind of WES findings, if any, should researchers return to participants (***selection of results to return***)?[31-41] Third, which of the four models, currently proposed, should researchers follow to obtain informed consent for the return of results (***RoR consent process***)?[30, 42, 43] Fourth, in this context, how can researchers return results to patient-participants in an ethical, but practical way (***actual RoR procedure***)?[17,19,31] Fifth, how should legal guardians or authorized representatives (LG/AR), mental health clinicians, and mental health institutions manage WES findings once returned by researchers (***Post-RoR management***). A plan for the Post-RoR management of patients' WES findings is essential for the protection of their best medical and overall interests.

This project will advance the ethical and legal conduct of translational WES research with institutionalized severely mentally ill patients. Since 2010 there has been widespread interest in research on the best ways to utilize translational genomic technologies like WES in the clinical setting, yielding an ongoing national consortium of NIH-funded Clinical Sequencing Exploratory Research (CSER) studies, a large literature on the challenges involved in consent and RoR in both research and clinical settings, and a variety of professional policy statements[44] and federal guidance documents.[35] While some of this work has addressed challenges facing WES in pediatric settings, none of it has contemplated the use of these technologies with decisionally-impaired adults in institutionalized settings. Similarly, while there is literature and policy guidance on conducting biomedical research with psychiatric patients in general,[20-29] only a few articles have begun to address the special issues of translational genomic research,[17, 19, 31] such as the complexities of obtaining consent for WES and returning results in institutionalized settings. This project attempts to bridge that gap, in order to advance the ethical and legal conduct of translational WES research with institutionalized severely mentally ill patients.

B. Innovation

This study is innovative in a number of ways. It builds on UNC's record of translational genomic sequencing studies in clinical and public health settings to tackle a ***novel problem in this domain:*** how to conduct responsible WES studies in order to translate the findings of large-scale psychiatric GWAS with

institutionalized severely mentally ill patients. It employs a ***novel transdisciplinary approach*** to generate empirically-based proposals to address this problem. This transdisciplinary approach involves an embedded ethnographic study of GTRP researchers' decision-making during the design and conduct of their study, which will then inform an empirical study of stakeholders' perspectives, and the ethical, legal, and policy analyses of the problem. Furthermore, drawing from my legal training, I will explore the utility of a ***novel analytical model in ELSI research***, the Fiduciary Relationship Model (FRM),[45] to guide the ethical use of WES in psychiatric genomics research and care. FRM involves the application of fiduciary principles *as defined in trusts*[85] *and agency law*[86] (e.g., duty of care, duty of loyalty, duty to inform, duty to act within the scope of authority) to help delineate ethical responsibilities between parties. Specifically, this project will explore how FRM can help define ethical responsibilities that researchers, LG/ARs, clinicians, and mental health institutions hold towards patient-participants in translational psychiatric genomics research.

C. Approach

Summary

The research plan (See **Tables 1 & 2**) employs a multi-method, transdisciplinary approach that combines ethnographic participant-observation, interview research methods, ethical, legal, and policy analyses to examine and provide recommendations to some of the most challenging aspects of conducting translational psychiatric WES research with institutionalized severely mentally ill populations. 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 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, participants' LG/ARs, 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 the 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.

Aim 1: Methods and Analysis (Mentored Research Phase)

Aim 1a. *Ethnographic methods (participant-observation and key informant interviews) will be used to identify the expected and unexpected factors that impact psychiatric genomic researchers' decision-making process when designing and conducting their studies.* Ethnographic methods are widely used in medical anthropology, sociology, and public health research because they are conducive to examining complex and dynamic social processes, understandings, and experiences.[46-49]

Specifically, ethnographic methods will be employed to study the GTRP project conducted by Professors Richard C. Josiassen, Patrick F. Sullivan, and James P. Evans (See Letters of Support). GTRP will perform WES with institutionalized patients who suffer from TRP, and have not responded to antipsychotic medications after at least 5 years of treatment. These patients will be recruited from long-term psychiatric care hospitals and structured residences. Like the CSER studies,[41, 50] GTRP has both research and clinical goals. Its principal research goal is to use WES to identify genomic variants associated with TRP. Its principal clinical goal is to use WES to examine if any genomic variant suggests there is a genetic origin to a patient's symptoms and evaluate whether these variants could generate clinically useful information that can help improve the patient's mental health care.

GTRP researchers have agreed to allow me to collect ethnographic data from their project via: 1) full access as a participant-observer to every aspect of the project, including team meetings, discussions about the

design and progress of the project, calls with collaborators, email exchanges, and IRB submissions; 2) periodic semi-structured, individual interviews with the researchers; and 3) visits to the hospitals where GTRP patient-participants will be recruited to observe how GTRP researchers interact with participants and conduct the WES consent process. All meetings and interviews where the design and conduct of the WES consent process and RoR components of the study are discussed will be digitally recorded, transcribed, and analyzed using standard content analysis and discourse analysis with the aid of NVivo 10 software.[51-53]

Areas of Focus for Ethnography (Aim 1a)

This ethnographic examination will focus on identifying the factors that influence GTRP researchers' decision-making process about four components of genomics research:

The ***first*** component to be examined is the ***WES consent process***: the process followed by researchers to provide the information necessary to allow patient-participants or their authorized representatives to make an informed decision about whether to undergo WES. The consent process with severely mentally ill patients can be complex[17-25] and involves a number of questions that are largely unexplored in the translational psychiatric WES context.

For example, 1) how will GTRP researchers assess decision-making capacity of potential participants?[20-25, 54-56] 2) How will GTRP researchers safeguard participants' understanding of the goals of this translational WES study, and its risks and benefits? It may be particularly difficult to avoid therapeutic misconception in a study like GTRP given that patient-participants may have impaired decision-making capacity; the study will be conducted in the clinical setting where patients generally receive their mental health care; and results may be returned—all of which could lead to unreasonable expectations about the potential clinical benefit of participating in GTRP or to the belief that participation in GTRP is part of their treatment.[30, 57-61] 3) Should GTRP researchers exclude patients who cannot provide informed consent or should they allow legal guardians to provide consent, together with patients' assent?[20, 23-25] 4) Not all institutionalized patients with TRP will have a legal guardian; therefore, should GTRP researchers exclude these patients?[24, 25] If not, who should researchers consider an authorized representative to consent incapacitated patients for WES?[20, 23-25] Finally, 5) given participants' foreseeably transient decision-making capacity due to their TRP, should LG/ARs always provide consent, and/or be involved during the entire study? [20, 23-25] Some have suggested that this may help ensure the protection of participants' best interests including their right to freely withdraw from the study at any point.[20, 23-25]

The ***second*** component for which GTRP researchers' decision-making process will be examined is the ***selection of results to return***.[31-41, 62] 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.[33-35] This means that GTRP researchers will likely have the difficult task of determining which genomic results, if any, could be returned to their patient-participants. RoR alternatives could range from the return of no results of any type to the return of: a) primary target variants, in this case, WES findings related to psychotic symptoms, and/or b) secondary target findings, which may include WES findings related to other psychiatric disorders, medically actionable conditions such as hereditary breast and ovarian cancer,[44, 63] or even non-actionable diseases such as Huntington's or risk for Alzheimer's.[31, 39-41, 64, 65]

The ***third*** component to be examined is GTRP researchers' decision-making about the ***RoR consent process***: if GTRP researchers decide to return or offer any WES results, how will they conduct the RoR consent process? [42, 43] There is no standard RoR consent process in genomics research, and this process has not been explored in the context of WES research with the population GTRP will study.[33-35, 42, 43] This means that GTRP researchers will have the challenging task of selecting the most ethically sound, but practical model for obtaining RoR consent from their vulnerable participants or participants' LG/ARs.

Four RoR consent models are used in genomic research or have recently been proposed:[42] One option is to follow a *traditional consent model*, where participants make a determination regarding which results they want returned when they enroll in the study.[42] Another option is to follow a *staged consent model*, where participants are simply briefly informed about RoR and possible secondary target findings at the time of enrollment.[42] However, if researchers find reportable results, participants receive a more comprehensive discussion and are given the option whether to consent to RoR. A third alternative is to use an *outsourced model*, where participants receive all of their genomic raw data.[42] Then, it is up to them or their LG/ARs to decide whether to pursue analysis of this genomic data, at their own cost, and through some service provider independent of the study. Finally, a fourth option is to use a *mandatory return model*. Under this approach

participants are asked—at the time of enrollment—to consent to RoR of specific findings as a condition for participating in the study.[42]

The ***fourth*** component for which GTRP researchers' decision-making process will be examined is the ***actual RoR procedure***: if results will be returned, how will researchers do this in an ethical, but practical way? The dual clinical-research goals of translational studies, like GTRP, make this a particularly complex issue.[57-60] Some of the issues that will be explored include: 1) who should receive the results (e.g., patients, clinicians, LG/ARs, others, a combination of these); 2) will results be included in the patient-participant's medical record; 3) how will the results be delivered; 4) should genetic counselors explain the results or at least be made available; and 5) what role should participants' mental illness and decisional-capacity play in these decisions?[17, 19, 31]

Aim 1b. *Ethical analysis of GTRP's research design and conduct will be performed.* Using the criteria proposed by Emanuel et al., (2000)[66] to examine the ethics of clinical research, and the last authoritative federal guidance on doing research with persons with mental disorders[24, 25] as starting points, I will examine the design of the GTRP study. This analytic process will involve the iterative writing and revising of assessment reports in dialogue with my primary mentor, other research ethics faculty in the UNC Center for Bioethics and CGS co-investigators. It will also be informed by new research literature as required. I will also conduct a more specific ethical analysis of GTRP's approach to the consent to research process and RoR components of their study compared to the approaches followed by other researchers who work with vulnerable populations, for example, antipsychotic medication trials for patients with schizophrenia who are unresponsive to treatment, research with other patients who may lack decisional capacity (e.g., Alzheimer's patients or children),[27, 67-73] and research with prisoners.[74-77] Information about the consent and RoR methods used by other researchers will be obtained by examining relevant studies identified on Pubmed and clinicaltrials.gov.

Aim 1c. *Legal and policy analyses will be performed to examine if the current human subjects research regulatory framework offers adequate protection for institutionalized severely mentally ill patients who participate in translational WES studies*. Applicable federal (e.g., Common Rule)[78] and state regulations, legal actions related to these, and guidelines proposed by professional organizations or government advisory groups[24, 25] will be identified and examined using WestlawNext (legal research search engine) and Pubmed. In order to systematically analyze and make public policy recommendations about the regulatory framework, I will take a course on public policy analysis at UNC (See Training Plan, **Table 1)** and I will work with John M. Conley and Robert Cook-Deegan, who have experience in legal and policy analysis (See Letters of Support).

Aim 2: Methods and Analysis (Independent Research Phase)

Aim 2a. *Semi-structured interviews will be conducted with patient-participants, LG/ARs, mental health clinicians, and officials of the mental health institutions involved in the GTRP study*. The data and analyses performed in Aim 1 will inform the design of these interviews. These groups will be interviewed after the consent process and collection of samples for WES, but before the return of results. In the last year of this K99/R00 grant, I plan to submit an R01 proposal to conduct another wave of interviews following the return of results. The interviews in ***Aim2a*** will empirically examine these groups' views and preferences regarding how the WES consent process, RoR components, and the Post-RoR management of WES findings should be handled in translational psychiatric research. The interviews will be piloted with mental health providers and students at my training institution, UNC. All interviews will be conducted in person and the audio will be digitally recorded and transcribed. Responses will be analyzed using standard content analysis and NVivo10.[51-53]

Areas of Focus for Interviews (Aim 2a)

- understanding of GTRP research and clinical goals
- understanding of the risks and benefits of participating in GTRP
- knowledge about genomics
- attitudes about psychiatric genomics research and genomic testing for mental health care
- views and preferences about the design and conduct of the WES consent process, selection of results to return, RoR consent process, and actual RoR procedure
- perceived readiness to understand and manage WES findings returned by GTRP
- views about how different categories of WES findings should be handled during Post-RoR management

Interview Groups (Aim 2a)

Patient-Participants (n = 30) Upon obtaining clinician's approval and informed consent, patients who are eligible to participate in GTRP will be recruited for in-person interviews. Due to their TRP, a number of participants may not be able to participate in these interviews, but GTRP aims to recruit 1,000 participants. Therefore, after discussing this with researchers who have worked with similar populations, I expect to be able to meet the goal of interviewing 30 GTRP participants. The views of patient-participants are essential because they are the ones most likely to benefit or be harmed by WES findings in mental health research and care.

Legal Guardians or Authorized Representatives (n = 30) LG/ARs will be recruited from those involved in the consent and participation of patients in GTRP. GTRP involves patients who suffer from TRP; therefore, it is likely that a significant number of potential participants will lack decisional capacity to consent to WES or RoR. In those cases, it is the LG/ARs who will weigh the risks and benefits of participation and provide informed consent, together with patients' assent.[20, 23-25] The perspectives of LG/ARs are also important because they are tasked with protecting the well being of, and making certain decisions for, many of these patients; therefore, they will likely play a key role in the Post-RoR management of WES findings returned by GTRP.[24, 25]

Mental Health Clinicians (psychiatrists n = 20; clinical psychologists n = 20) Both psychiatrists and clinical psychologists who care for the participants in the GTRP study will be interviewed because they have markedly different training backgrounds and approaches to the treatment of mental health disorders, which likely influences their perspectives on genomic research and clinical applications of genomic information. Furthermore, while psychiatrists' attitudes towards genomic testing have received some attention, there is a lack of research about clinical psychologists' perspectives regarding genomics research and the use of genomics for mental health care and prevention.[79-84]

Mental Health Institution Officials (n = 30) Officials (e.g., medical directors, hospital administrators, IRB members, hospital ethics committee members) who represent the mental health institutions where GTRP will take place will be interviewed to obtain institutional perspectives regarding translational genomics research and the Post-RoR management of their patients' WES findings.

Aim 2b. *Legal analysis will be performed to examine what kind of legal responsibility, if any, emerges during the Post-RoR management of WES findings.* WES findings generated and returned by GTRP may have important implications for participants' mental health care, or they may contain actionable health risk information, which, for example, could be used to prevent or minimize patient-participants' risks for different types of cancer or heart disease. Yet, participants who suffer from TRP may not have the cognitive capacity necessary to understand these results or to act upon them. This means that it is up to patients' LG/ARs, clinicians, and/or their mental health institutions to protect their best interests and decide how to manage patients' WES findings. I will conduct legal analyses to examine what responsibilities, if any, these parties have towards patient-participants during Post-RoR management of WES findings. I will use Pubmed to search and review applicable medical literature and WestlawNext to examine applicable laws, regulations, and legal cases.

Aim 3: Methods and Analysis

Goal. *Aim 3 will explore the Fiduciary Relationship Model (FRM)[45] as a framework for guiding the ethical design and conduct of translational genomics research with severely mentally ill patients.* FRM involves the application of fiduciary principles *as defined in trusts*[85] *and agency law*[86] (e.g., duty of care, duty of loyalty, duty to inform, duty to act within the scope of authority). FRM uses these principles to help define ethical responsibilities between parties. The goal of this aim is not to use FRM to make claims about the legal obligations that researchers, LG/ARs, clinicians, and mental health institutions have towards patient-participants, but to help define their ethical responsibilities.

Problem. Outside of the legal arena fiduciary principles are often invoked—including in genomic medicine and research—to make claims about the ethical responsibilities that parties in positions of power hold towards others who in some ways depend on them (e.g., physicians-patients, researchers-participants).[35, 44] The problem is that fiduciary principles are often not applied in a theoretically grounded way, or some principles are applied without considering the role of other relevant fiduciary principles.[45]

Potential Solution. For years, trusts and agency law have used fiduciary principles to define the responsibilities that trustees and agents hold towards beneficiaries and principals, respectively.[45, 87] ***FRM tries to avoid incomplete or biased appeals to fiduciary principles by grounding its application of these principles in the rich body of literature and precedents that trusts and agency law has developed***.[45]

This grounding allows FRM to generate more theoretically coherent definitions of the ethical responsibilities held by fiduciaries in the genomics research and clinical contexts.[45]

I recently explored how FRM can help define clinicians' ethical duties towards patients regarding the management of genomic incidental or secondary target findings in the clinic.[45] In this work, I argued that a comprehensive application of the principles of fiduciary law is necessary in order to use fiduciary principles as a reliable framework for defining clinicians' duties. For example, clinicians have a fiduciary duty of care to act in the best interest of their patients. This may suggest that clinicians have a duty to warn patients about clinically relevant incidental or secondary target findings, regardless of patients' preferences for knowing this information. However, as fiduciaries, clinicians have other duties, such as the duty of loyalty to the interests of the patient, that argue strongly against returning secondary target genomic results without considering patients' preferences.

FRM could also be a useful framework for guiding the ethical use of WES and the management of WES findings in translational psychiatric genomics research. These studies involve a combination of clinical and research goals, and numerous parties that are key to protecting the interests of patient-participants. Therefore, any framework that could help anticipate ethical challenges and generate potential solutions in this context must be able to adapt and apply to different relationships and interests. In the legal arena, fiduciary principles have proven to be adaptable to different contexts and relationships (e.g., physicians-patients, researchers-participants, parents-children, employers-employees, directors-shareholders).[87-91] I will examine the utility of FRM to help define ethical responsibilities in the translational psychiatric genomics research context.

Deliverables. I will prepare at least two manuscripts in which I will apply FRM to examine ethical responsibilities in this context. First, I will apply FRM to examine the ethical responsibilities that researchers may hold towards patient-participants when designing and conducting the WES consent process, the selection of results to return, the RoR consent process, and the actual RoR procedure. Second, I will use FRM to examine the ethical responsibilities that clinicians, LG/ARs, and mental health institutions may hold towards patients regarding the Post-RoR management of WES findings. I will also identify other relevant relationships and scenarios for which FRM may be useful throughout my ethnographic examination of GTRP and the interviews conducted with groups involved in the study.

Table 2 Research Activities During R00 Independent Phase

Years 3-5: R00 Independent Phase	Year 3											
Research Plan	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Aim 2a: Examine Stakeholders' Perspectives about How to Handle WES Consent, RoR, and Post-RoR Management												
IRB Submissions												
Recruitment for Interviews with Groups Involved in GTRP												
Interviews with Groups Involved in GTRP												
Data Analysis												
Presentation at Research Conferences												
	Year 4											
Research Plan	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Aim 2a: Examine stakeholders' perspectives about how to handle WES consent, RoR, and Post-RoR management												
Recruitment for Interviews with Groups Involved in GTRP												
Interviews with Groups Involved in GTRP												
Data Analysis												
Preparation of Manuscripts												
Aim 2b: Legal Analysis of Post-RoR Management												
Legal Research												
Preparation of Manuscripts												
Presentation at Research Conferences												
	Year 5											
Research Plan	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul
Aim 3: Explore the Fiduciary Relationship Model for Guiding the Ethical Use of WES in Psychiatric Research												
Legal Research on Fiduciary Law												
Application of FRM to Psychiatric Genomics Researchers when Designing and Conducting WES Consent and RoR												
Application of FRM to Clinicians, LG/ARs, and Mental Health Institutions During Post-RoR Management												
Application of FRM to Other Relevant Scenarios												
Preparation of Manuscripts												
Presentation at Research Conferences												
Prepare and Submit R01 Proposal to Explore the Use of Genomics in Mental Health Clinical Care (Including Post-RoR Interviews with GTRP Participants and Clinicians)												

PROTECTION OF HUMAN SUBJECTS

Point 4.1.1 RISKS TO HUMAN SUBJECTS

a. Human Subjects Involvement, Characteristics, and Design

Description of Human Subjects Involvement

This project explores the ethical and legal challenges of using whole exome sequencing (WES) in research studies with the goals of identifying genomic variants associated with severe mental illness (treatment-resistant psychosis; TRP), and potentially helping to guide the care of patient-participants who suffer from TRP. In order to examine these challenges, this project will use the Genomics of Treatment-Resistant Psychosis (GTRP) study as a case study.

Human subject involvement in this project is necessary given the nature of the questions that are being addressed. Inherent in the study design is a consideration of the ethical and legal issues involved in using genomic sequencing for patients with TRP. The study tries to examine the factors that influence researchers' decision-making process when designing and implementing the WES consent process and the Return of Results (RoR) component of their study. Furthermore, the study aims to examine the views and perspectives of the parties involved in translational psychiatric genomics studies like GTRP regarding the WES consent process, and the RoR. In order to make an informed analysis of the ethical, legal, and public policy issues related to psychiatric genomics studies, it is essential to study the perspectives of many of the groups involved and directly affected by these studies.

Five kinds of participants will be involved in this study: 1) **GTRP researchers** involved in designing and implementing the GTRP study, 2) the **GTRP patient-participants**, 3) **patient-participants' legal guardian or authorized representatives (LG/AR)**, 4) **mental health clinicians** involved in caring for the GTRP study participants, and 5) **officials** of the mental health institution where GTRP will be conducted. Each set of participants will be provided with an extensive description of the study protocol and design, including the rationale and background of the study, the observational and interview procedures, risks and benefits of participation, and the voluntary nature of their participation. All study participants will be consented under the guidelines of a project-specific IRB approved protocol that will be provided as JIT if this proposal is funded.

Characteristics of the Study Participants

Five different populations are involved with this study: 1) **GTRP researchers** are approximately 20 English-speaking adult volunteers, who will be observed in GTRP team meetings and interviewed in person or by telephone about their perceptions of challenges in the design and implementation of the GTRP project. GTRP researchers will also be observed as they interact with GTRP patient-participants during the WES consent process. These researchers are academic and medical professionals employed by UNC and the collaborating GTRP sites. We will obtain consent from them as research subjects.

The following parties involved in the GTRP study will be recruited for interviews *about their experience with the GTRP study, their perspectives on the WES consent and RoR components of the study, their views about psychiatric genomics research, and the use of genomics in mental health care.* 2) **GTRP patient-participants** will be recruited for two aspects of this project. First, as part of the ethnographic examination of Aim 1, 20 GTRP patient-participants will be recruited to allow me to be present and digitally audio-record the WES consent process conducted by GTRP researchers. Second, as part of Aim 2, 30 adult patients with TRP will be recruited after GTRP enrollment for in-person interviews. GTRP patient-participants may be either male or female adults, of any race or ethnicity, and fluent in either English of Spanish. The population breakdown is expected to mirror the racial and ethnic characteristics of the general population at the participating recruitment sites. A special effort will be made to identify eligible racial minorities. All participants must be cognitively able to consent. 3) **LG/ARs** will be recruited for in-person or telephone interviews among those LG/ARs who provided consent, together with patients' assent, for the participation of patients with TRP who were considered to lack sufficient decision-making capacity to provide informed consent to participate in the GTRP study. This K99/R00 project will recruit 30 LG/ARs, who may be either male or female adults, of any race or ethnicity, and fluent in either English of Spanish. 4) **Mental health clinicians** recruited for in-person interviews will be 40 English or Spanish-speaking adult volunteers (20 psychiatrists; 20 clinical psychologists) who care for the participants in the GTRP study. These mental health clinicians will be recruited from the mental health

institutions in which GTRP will be conducted. 5) **Officials** of the mental health institutions in which GTRP will take place will be 30 English or Spanish-speaking adults. These officials will be medical directors, hospital administrators, IRB members, hospital ethics committee members, or individuals who hold other positions that can represent the institutions' policies on issues relevant to psychiatric genomics research and care.

Recruitment, and Informed Consent Plan

The **GTRP research team** leadership has already agreed to participate as subjects of the ethnographic observation phase of this study (see letters of support). Additional individual GTRP team members will be recruited at formative team meetings, and individual consent will be obtained.

The **GTRP patient-participants** will have already been considered to have sufficient decision-making capacity to consent for participation in GTRP. However, because the interviews will not be conducted immediately after the patients consented to GTRP, it is possible that some of these patients may not have the lack decision-making capacity by the time of recruitment and consent for interviews. In order to protect the interest of these patients and ensure that they have the capacity to volunteer for interviews, I will contact the clinicians who care for GTRP participants in order to obtain their consent to recruit these patients for interviews. Potential GTRP patient-participants will be approached by their treating psychiatrist, psychologist, nurse, or patient advocate about participation in these interviews.

LG/ARs who provided consent for the participation of GTRP patient-participants will be recruited via direct email, mail, or telephone solicitation. Upon obtaining the appropriate authorization, LG/ARs contact information will be obtained from the GTRP study.

Clinicians and **officials** will be recruited during initial on-site GTRP visits to the institutions and programs providing access to potential patient-participants. Individual members from each of these groups will be recruited for interviews subsequent to their enrollment in the GTRP study, through direct email, mail, telephone or personal solicitations, and through flyers and open announcements in the GTRP sites.

Consent will be obtained from individual members of these five groups in a private setting. If they choose not to participate, their choice will not be known to anyone but the R00 research team. As stated above, each set of participants will be provided with an extensive description of the study protocol and design, including the rationale and background of the study, the observational and interview procedures, risks and benefits of participation, and the voluntary nature of their participation. All study participants will be consented under the guidelines of a project-specific IRB approved protocol that will be provided as JIT if this proposal is funded.

Inclusion/Exclusion Criteria

The inclusion criteria are described above in the section, **Characteristics of the Study Participants**. The study will not exclude any adult based on sex, race or ethnicity. Members from minority populations will be sought for participation since a primary goal of this study is to explore the implementation of genomic approaches in a broad context which includes traditionally medically underserved populations. Adults who are proficient in either English or Spanish will be included.

Involvement of Vulnerable Populations

Patients with TRP, which can affect decision-making capacity, will be specifically recruited for this study. A critical aspect of this study is to assess the perspective of TRP patients regarding psychiatric genomics and how psychiatric genomics research should be conducted. All applicable safeguards to their interests will be obtained, including: initial consent from the patient-participants' clinicians in order to recruit the patient for participation; permission of patient-participants' LG/AR, when applicable; consultation with institutional patient advocacy committees, and local institutional IRB or administrative approvals.

b. Sources of Material

Research Data

The research data for this study will consist of interview transcripts, observational field notes, and transcribed audio recordings from research meetings and the WES consent process. Observations of and interviews with the GTRP researchers will be digitally audio-recorded and transcribed. For the interview participants in Aim 2 (i.e., GTRP patient-participants, LG/ARs, clinicians, and officials), semi-structured

interviews will be conducted either in person or by telephone, and will be digitally audio-recorded with participant's permission and transcribed.

Digital voice files will be stored on a protected server and deleted once transcribed. Transcripts will be de-identified and also stored on a protected server and accessible only to research staff.

Who Will Have Access

Access to the data is limited to IRB approved investigators. All digitally audio-recorded data and study information will be coded with a unique code number. The list linking this code to the participant's name and contact information will be kept in a locked drawer in a locked room by the Principal Investigator. Only those IRB approved study investigators and staff with a "need to know" will have access to specific private information linked to a participant's name. Access to individually identified private information would be denied to all outside parties.

c. **Potential Risks**

Description of Potential Risks to Subjects

Psychological Risks: the chief risk to subjects in this study is to the **GTRP patient-participants** and **LG/ARs**, who may experience anxiety or distress from discussing their participation in GTRP, the possibility of having genomic variants that contribute to their TRP, and their attitudes about genomics in mental health research and care. There is a slight risk that **GTRP researchers** might experience uncomfortable emotional states by knowing that they are part of an ethnographic study that is examining their decision-making during the study or by completing the semi-structured interviews about the GTRP study. There is also a slight risk that **Clinicians** who care for GTRP participants, and hospital **Officials** might experience uncomfortable emotional states by completing the semi-structured interviews about the GTRP study.

Risk: Moderate for GTRP patient-participants and LG/ARs; Rare for GTRP researchers, clinicians, and officials.

Confidentiality Risk: Loss of confidentiality leading to adverse personal psychological or professional impact (**moderate, rare**) or social harm (**moderate, rare**). For **GTRP researchers, GTRP patient-participants, LG/ARs, clinicians, and officials** who are part of the ethnographic observations and/or interviews, there is a small, but unlikely chance of loss of confidentiality. Many precautions are used so that information is de-identified and stored in secure sites. IDs will be used on all data collection material. The only risk would be if RAs were to divulge this confidential information. There is little likelihood that individuals could be identified through the de-identified datasets.

Risk: Rare. As described below, measures will be implemented to assure confidentiality.

Alternative Treatments and Procedures

This study is not a treatment or intervention study and thus there are no alternative treatments or procedures. Participants will be informed in the consent process and during the interviews that they may deny or withdraw consent for any portion of the study, and at any time.

POINT 4.1.2 ADEQUACY OF PROTECTIONS AGAINST RISK

a. Recruitment and Informed Consent

Please see **Recruitment and Informed Consent Plan** under **Point 4.1.1 RISKS TO HUMAN SUBJECTS**

Protections Against Psychological Risks:

GTRP patient-participants. As discussed in the **Recruitment and Informed Consent Plan**, obtaining consent from clinicians before recruiting patients for interviews will minimize psychological risks to patient-participants. The purpose of obtaining consent from clinicians is to ensure that they consider the patient-participant to have the decisional-capacity to consent to participate in the interviews, and to ensure that the clinician believes the interview process does not pose any undue psychological risks to patients. Furthermore, in order to minimize psychological risks to GTRP patient-participants, the interviews will be piloted with mental health clinicians to help ensure that questions are asked in a way that minimizes the risk of anxiety and distress to patient-participants. I will also try to protect patient-participants from psychological risks by obtaining

training on how to approach and conduct interviews with patients who suffer from TRP. A psychiatrist who has ample experience working with this population will provide this training. Finally, if any signs of distress are observed during an interview with any patient-participant, the interview will be terminated and their attending clinician will be notified.

GTRP researchers, LG/ARs, clinicians, and officials. As discussed in the **Recruitment and Informed Consent Plan**, the psychological risks to these participants will be minimized by providing an extensive description of the study protocol and design, including the rationale and background of the study, the observational and interview procedures, risks and benefits of participation, and the voluntary nature of their participation. A careful description of the risks and benefits of participation will help these sets of participants to effectively evaluate whether participation in this study will generate any psychological harm. The consent process will also emphasize on the fact that they can withdraw at any point if they experience any psychological harm or for any other reason. If any signs of psychological distress are noticed during observations or interviews participants will be reminded that they can withdraw from the study at any time, and the study can help them identify any relevant psychological services available.

Effectiveness: likely

Protections Against Confidentiality Risk:

For all ethnographic observations and interviews, I will minimize the risk of any harm from a breach of confidentiality by assigning pseudonyms and ID numbers to the individuals in the study. No notes or transcripts will contain their real names. The linkage file will be kept entirely separate from the observation and interview data. Voicefiles collected during the observations or interviews will be erased after these are transcribed and verified, typically about 1 month after the interview or meeting session. Only those assisting in data analysis (e.g., principal investigator and co-mentors) will have access to the interview or group session data. Results in the form of case studies or future publications will be presented in such a way that would not identify an individual with a particular response.

With regards to the **GTRP researchers**, it is possible that some of them will feel subtle pressure to participate in the interviews or observations that are part of the ethnographic examination of the GTRP study. To minimize that risk, I will inform each individual in an informed consent process that their colleagues will not know who has chosen to participate or not. The group conversation will be digitally recorded, but only comments by those who have consented will be transcribed, and no one else other than the ethnographic research team members will have access to the original recordings or to the transcripts. We will share with these individuals the results in the format that they will be in for publication and if necessary, will revise in a way that would protect their privacy or confidentiality. Individual interviews are scheduled individually and privately; there will be no pressure to do these simply by being a member of the GTRP research team. Of course, most of these researchers know each other very well and might assume they can identify who made a reported remark or stated opinion included in a publication as part of the data collected. We will inform everyone about this possible risk beforehand so he or she can decide to participate or not.

Effectiveness: likely

POINT 4.1.3 POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

The participants in this study are not expected to derive any benefit from the study procedures.

Why Risks are Reasonable in Relation to the Importance of the Knowledge that May Reasonably Be Expected to Result

As described, the risks to individual subjects are relatively small given the risk management strategies employed, and that the potential knowledge expected to be gained from the proposed study will help identify potential ethical, legal, and policy challenges regarding the use of genomic sequencing with institutionalized severely mentally ill patients. Genomic medicine is beginning to be widely applied in both traditional clinical settings and in the general population via direct-to-consumer genetic testing, and there is great interest in psychiatric applications. Thus it is critical to begin to understand the clinical impact of such information and the

potential for harm to future patients. This study is carefully designed to assess both beneficial impact and possible harms and has numerous steps in place to minimize those harms.

POINT 4.1.4 IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Since 2010 there has been widespread interest in research on the best ways to utilize translational genomic technologies like WES in the clinical setting, yielding an ongoing national consortium of NIH-funded studies (the CSER studies), a large literature on the challenges involved in consent and RoR in both research and clinical settings, and a variety of professional policy statements and federal guidance documents. While some of this work has addressed challenges facing WES in pediatric settings, none of it has contemplated the use of these technologies with decisionally-impaired adults in institutionalized settings. Similarly, while there is literature and policy guidance on conducting biomedical research with psychiatric patients in general, only a few articles have begun to address the special issues of translational genomic research, such as the complexities of primary incidental and secondary findings in institutionalized settings. This study attempts to bridge that gap, in order to advance the ethical and legal conduct of translational WES research with institutionalized severely mentally ill patients.

Point 4.1.5 Data and Safety Monitoring Plan/Board

N/A

INCLUSION OF WOMEN AND MINORITIES

This project will make every effort to include women and minorities in every component of the study, including the ethnographic examination of the researchers who will conduct the Genomics of Treatment-Resistant Psychosis (GTRP) study, and the interviews with GTRP researchers, clinicians and officials from the mental health hospitals in which the GTRP study will be conducted. Yet, given the case study nature of the proposed study, there will be no opportunity to enrich the observations and interview samples beyond the existing demographics of these cohorts. Similarly, while the project plans for inclusion of women and minorities that is representative of GTRP enrollment, their inclusion in the interview cohorts for GTRP patient-participants, and legal guardians or authorized representatives (LG/AR) will depend upon their enrollment in the GTRP study. However, given the overall demographics of state mental health care facilities such as the Pennsylvania institutions from which GTRP patient-participants will be recruited we anticipate a higher level of women and minorities than are present in the general population.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Ethical, Legal, and Social Implications of Translational Psychiatric Genomics Research

Domestic/Foreign: Domestic

Comments: Between the participant-observation and interview phases, this project will recruit approximately 170 individuals involved in the Genomics of Treatment-Resistant Psychosis (GTRP) study (i.e., researchers, patient-participants, legal guardians/authorized representatives, clinicians, and hospital officials). The project will strive to enroll a diverse sample of participants that is representative of the U.S. population and the GTRP study population.

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	2	2	0	0	**4**
Asian	4	4	0	0	**8**
Native Hawaiian or Other Pacific Islander	1	1	0	0	**2**
Black or African American	15	15	5	5	**40**
White	40	40	5	5	**90**
More than One Race	3	3	10	10	**26**
Total	**65**	**65**	**20**	**20**	**170**

Study 1 of 1

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INCLUSION OF CHILDREN

Current NIH regulations define children as anyone under the age of 21. The Genomics of Treatment-Resistant Psychosis (GTRP) project that will be used as a case study for this K99/R00 will recruit patients who are 18 years or older. This means that the interviews and observations conducted with GTRP patient-participants as part of this K99/R00 could include children between the ages of 18 and 20, but that would depend on the participants recruited by GTRP. The sample of legal guardians or authorized representatives (LG/ARs) interviewed will likely not include any individuals under the age of 21 due to the responsibilities that these involve. The interviews conducted with clinicians and officials of the mental health institutions in which GTRP will take place will probably not include individuals under the age of 21 due to the academic training requirements to hold these positions (e.g., psychiatrists, clinical psychologists, medical directors, hospital administrators). Finally, GTRP researchers who will participate as part of the ethnographic examination will generally be adults due to the academic training necessary to hold these positions. However, there may be some undergraduate students who work in these research teams as research assistants. If that is the case, they will also be invited to participate in this study.