Overview

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

Acknowledgement

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

PI: **STERN, ALEXANDRA M**	Title: Demographic Patterns of Eugenic Sterilization in California	
Received: 02/12/2015	FOA: PA14-278	Council: 10/2015
Competition ID: FORMS-C	FOA Title: ETHICAL, LEGAL, AND SOCIAL IMPLICATIONS (ELSI) OF GENOMIC RESEARCH EXPLORATORY/DEVELOPMENTAL RESEARCH PROGRAM (R21)	
1 R21 HG009205-01	Dual:	Accession Number: 3789371
IPF: 1506502	Organization: UNIVERSITY OF MICHIGAN AT ANN ARBOR	
Former Number: 1R21HD086419-01	Department: Obstetrics and Gynecology	
IRG/SRG: SEIR	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 125,000 Year 2: 150,000	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:*
Alexandra Stern	Regents of the University of Michigan	PD/PI
Sioban Harlow	Regents of the University of Michigan	Co-Investigator
Sharon Kardia	Regents of the University of Michigan	Co-Investigator

Appendices

appendix

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
15-PAF04671

c. Previous Grants.gov Tracking Number
GRANT11833523

5. APPLICANT INFORMATION

Organizational DUNS*: 073133571

Legal Name*: Regents of the University of Michigan
Department:
Division:
Street1*: 3003 S. State St
Street2:
City*: Ann Arbor
County: Washtenaw
State*: MI: Michigan
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 481091274

Person to be contacted on matters involving this application
Prefix: First Name*: Amy Middle Name: Marie Last Name*: Holihan Suffix:
Position/Title: Project Representative
Street1*: Research & Sponsored Projects, Wolverine Tower
Street2: 3003 S. State St
City*: Ann Arbor
County:
State*: MI: Michigan
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 481090000
Phone Number*: 734-763-2171 Fax Number: Email: aholihan@umich.edu

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 38-6006309

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*
Demographic Patterns of Eugenic Sterilization in California: Quantitative and Qualitative Analysis of Reproductive Control of the "Unfit"

12. PROPOSED PROJECT

Start Date* Ending Date*
09/01/2015 08/31/2017

13. CONGRESSIONAL DISTRICTS OF APPLICANT
MI-012

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Alexandra Middle Name: Last Name*: Stern Suffix:
Position/Title: Professor
Organization Name*: Regents of the University of Michigan
Department: Obstetrics and Gynecology
Division: Medical School
Street1*: 1500 E Medical Ctr Dr Women's L4000
Street2:
City*: Ann Arbor
County:
State*: MI: Michigan
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 481095276
Phone Number*: 734-232-4976 Fax Number: 734-763-1460 Email*: amstern@umich.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$407,618.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$407,618.00
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: Mr. First Name*: Daryl Middle Name: C Last Name*: Weinert Suffix:
Position/Title*: Associate Vice President for Research
Organization Name*: Regents of the University of Michigan
Department: Research & Sponsored Projects
Division:
Street1*: 3003 S. State St
Street2:
City*: Ann Arbor
County: Washtenaw
State*: MI: Michigan
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 481091274
Phone Number*: 734-763-2171 Fax Number: Email*: msgrants@umich.edu

Signature of Authorized Representative*
Daryl.Weinert

Date Signed*
02/12/2015

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Cover_Letter.pdf

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

Number of Attachments in Appendix: 1

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:	Regents of the University of Michigan
Duns Number:	073133571
Street1*:	3003 S. State St
Street2:	
City*:	Ann Arbor
County:	
State*:	MI: Michigan
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	481091274
Project/Performance Site Congressional District*:	MI-012

File Name

Additional Location(s)

Funding Opportunity Number: PA-14-278. Received Date: 2015-02-12T10:38:04.000-05:00

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: 03-11-2014

Human Subject Assurance Number 00004969

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*	Abstract.pdf
8. Project Narrative*	Narrative.pdf
9. Bibliography & References Cited	References.pdf
10.Facilities & Other Resources	Resources.pdf
11.Equipment	

Funding Opportunity Number: PA-14-278. Received Date: 2015-02-12T10:38:04.000-05:00

PROJECT SUMMARY
From the passage of the country's first sterilization law in Indiana in 1907 until the 1960s approximately 60,000 people were sterilized based on eugenic criteria that sought to regulate the reproduction of the "unfit" and mentally deficient. California performed about 20,000, or one-third, of all documented sterilizations nationwide. Few empirical historical analyses of this practice are available. In 2007, while conducting historical research at the Department of Mental Health (now Department of State Hospitals) in Sacramento, Dr. Stern located 19 microfilm reels from this era that contain 15,000 sterilization recommendations along with supplemental letters and forms from nine state hospitals (in total, over 30,000 individual documents). Over the past two years Dr. Stern and her team have created a de-identified HIPAA-compliant data set of these recommendations, which date from 1921 to 1952. We now propose to conduct quantitative analyses with the eugenic sterilization dataset, which contains 212 coded variables, to describe trends in sterilization over time and to describe patterns of sterilization according to gender, age, ethnicity, nationality, diagnosis, institutional home, and many other variables. We propose to link the eugenic sterilization dataset to individual-level census microdata and tract-level census reports, which will allow us to calculate population-based estimates of sterilization rates and test hypotheses about the associations of gender, age, ethnicity, nationality, and diagnosis with the risk of sterilization. For example, we hypothesize that teenagers and Spanish-surnamed patients were disproportionately sterilized in California institutions. In addition, we will analyze qualitative patterns in the data with respect to familial resistance to sterilization, patient refusal, and experiences of institutionalization and sterilization. This study is relevant to contemporary ethical, legal, and social issues in human genomics, as it will provide an empirically-based, richer understanding of how medical paternalism and a particular variant of genetic determinism operated during the eugenics era in the United States, and how eugenic stereotypes about ethnicity, gender, sexual behavior, and intellectual disability influenced the state's intervention into the reproductive lives of institutionalized persons. Furthermore, our findings can inform contemporary conversations about the extent to which societal values of "fitness" and "unfitness," abnormality and normality, can insinuate themselves into the norms of disease prevention and human improvement that guide some genetic technologies and tests.

PROJECT NARRATIVE

We will conduct quantitative and qualitative analysis of 15,000 eugenic sterilization recommendations processed by the state of California from 1921 to 1952. Working with a de-identified HIPAA-compliant dataset we created during the pilot phase of this project, we will describe patterns of sterilization according to over 200 coded variables such as gender, age, ethnicity, nationality, parental status, and diagnosis. We will expand this analysis by linking the eugenic sterilization dataset to individual-level census microdata in order to statistically compare risk of sterilization across demographic groups, and by conducting qualitative analysis to better understand familial resistance to sterilization, patient refusals, the fraught process of consent, as well as individual experiences of institutionalization and sterilization.

FACILITIES AND OTHER RESOURCES:

Scientific Environment: The resources listed below are essential for the completion and success of the proposed work. The vast opportunities for interdisciplinary work available at the University of Michigan are key to the expected success of this planned research. Additionally, the multi-level research support system available to the study team through the respective departments of the investigators, the medical school, and research institutes and centers will help to ensure successful attainment of the research aims.

UNIVERSITY OF MICHIGAN

The University of Michigan Health System (UMHS)

The University of Michigan Health System includes numerous Hospitals, Health Centers and Clinics; the University of Michigan Medical School and its Faculty Group Practice; the clinical activities of the University of Michigan School of Nursing; and the Michigan Health Corporation – the legal entity that allows the Health System to enter into partnerships, affiliations, joint ventures, and other business activities. Linkages with other health care and nonprofit institutions foster better care, research, and education in Michigan and beyond. These affiliations include: MidMichigan Health,Trinity Health - Michigan, VA Ann Arbor Healthcare System, Blue Cross Blue Shield of Michigan, Sparrow Health Systems, Pennant Health Alliance, Physician Organization of Michigan, Radiation Oncology Network, Crittenton Hospital (cardiac surgery), four rehabilitation facilities, Paradigm (international genomics consortium), the Regional Alliance for Healthy Schools (public schools), and Hurley Medical Center (emergency & pediatric care, dialysis).

UMHS is creating health care innovation through discovery. According to the University's Office of Research, the total amount of research expenditures for the Medical School and School of Nursing (both part of UMHS) in FY 2013 was $580,938,652, the vast majority of which is funded by external sponsors. The number of invention disclosures from the medical School during this same time frame was 119.

As a major employer, center for research, and hub for training health and science professionals, UMHS impacts the local, state and U.S. economies in several ways. These include: 22,500 UMHS faculty and staff members who care for patients, conduct research, educate students, and provide support services; more than $1.2 billion estimated total economic impact of UMHS research funding (based in $2.60-per-dollar multiplier by AAAMC/Tripp Umbach); 23 new startup companies generated by UMHS faculty research in the last seven years; and 1.8 million Michigan residents are receiving better and more coordinated care due to the statewide Patient-Centered Medical Home demonstration project led by U-M and funded by the federal government. The University of Michigan hospitals are among the safest and most effective hospitals in the country, according to a national ranking from the Leapfrog Group, a respected independent health care quality rating organization. Only two hospitals in the country, including UMHS, have earned these four quality designations simultaneously: an “A” grade from the Hospital Safety Score system, a place on the Leapfrog Group’s Top Hospitals list, and designation as one of Truven Health’s 100 Top Hospitals. The U-M Health System has 505 physicians named to the *2013 Best Doctors in America* list, compiled by the Boston-based Best Doctors Inc. In 2014 the annual *U.S. News and World Report* survey of hospitals put U-M in the national top tier in 15 different medical specialties for treating patients with everything from joint disorders, cancer and eye conditions to heart disease, kidney failure and ear, nose and throat complaints. UMHS earned the distinction of Best Hospitals in eight specialties. In another seven, U-M’s care was recognized among the nation’s finest. The rankings are based on a compilation of data points that serve as indicators of a hospital’s performance in patient safety, specialty-specific performance, survival of patients, nurse staffing and reputation. This is the 22nd year in a row that UMHS has been recognized for strong across-the-board performance on a national level.

The Health System is located on 128 acres with more than 52 buildings constituting 6.2 million gross square feet of space and is located just north of the University's central campus. Facilities include three hospitals, 40 outpatient locations with more than 120 clinics, and extensive home care operation handle 1.9 million visits, nearly 45,000 hospital stays in 990 beds, and much more each year.

With an operating budget of $2.3B in FY13, the University of Michigan Hospitals and Health Centers (UMHHC) are fully self-supporting and do not receive funding from the State of Michigan’s General Fund. UMHHC's

financial stability also is reflected in its excellent bond ratings with both Moody's Investors Service Inc. and Standard & Poor's. This bond rating is among the highest in health care systems across the industry and reflects a strong and sustainable financial position

The University of Michigan Medical School
The University of Michigan Medical School began in the year 1850 with five faculty members, 90 students, and five physicians seeking additional training. The School has 2,967 faculty members teaching 679 medical students, 1,124 interns and residents, 547 graduate students, and 624 postdoctoral fellows, as well as other groups of learners. The Medical School offers three faculty tracks: Instructional Track (901); Research Track (340); and Clinical Track (985). Additionally, the School has 300 clinical lecturers/lecturers.

Today the Medical School graduates approximately 170 physicians annually and is consistently ranked as one of the top institutions in the nation. In 2013 *US News & World Report* placed the University of Michigan Medical School #8 in its national medical school rankings (in both the research and primary care categories).
The Medical School has 20 clinical and nine basic sciences departments, as well as the Unit for Laboratory Animal Medicine and the Department of Medical Education. Teaching, research, and clinical care often cross traditional departmental boundaries, particularly in the School's impressive interdisciplinary research centers and institutes, including the Comprehensive Cancer Center, the Geriatrics Center, the Cardiovascular Center, and the Michigan Institute for Clinical and Health Research (MICHR) .

Faculty members lead research efforts in a broad scope of basic and clinical science areas. In FY2013, the Medical School received $466.8 in awards from all external sponsors, garnered through 2,401 individual awards. Annual NIH grant funding awarded to the School's clinical researchers and biomedical scientists reached $310.5 million in FY2012, representing 2.68% of the market. This achievement places UMMS in the top ten medical schools in the nation in terms of NIH grants awarded.

In FY 2013, Medical School researchers filed a record breaking 133 reports of new inventions with the U-M Office of Technology Transfer. In addition, the Medical School was awarded 41 new patents and generated 44 new patent applications, obtained 40 new licenses to industry, and created two new start up companies. More than three-quarters of U-M FY2013 revenues from past patents and licensing agreements – $11.1 million of $14.4 million – came from technologies that began in the Medical School.

In 2013 a Fast Forward Medical Innovation initiative, lead by Dr. Kevin Ward, was created to unify Medical School efforts to nurture commercialization and entrepreneurship activity in close collaboration with U-M Technology Transfer. The initiative will integrate activities of the Office of Research's Business Development group and the MTRAC for Life Sciences commercialization fund with partners across campus, such as the College of Engineering's Center for Entrepreneurship and the U-M Business Engagement Center.
http://www.techtransfer.umich.edu/

The Medical School's physical plant is comprised of 80 buildings (including 29 at the North Campus Research Complex) encompassing 4.64 million square feet. This inlcudes 1,076 biomedical research laboratories and 2,316 research support rooms

The Department of Obstetrics and Gynecology at the University of Michigan
The University of Michigan Health Systems (UMHS) Department of Obstetrics and Gynecology encompasses approximately 78 full-time faculty members, 26 residents/interns, 15 fellows and a host of pre-doctoral and postdoctoral students which collectively provide a comprehensive range of services and resources to serve the interests of women while enhancing the research and educational mission of the University of Michigan. The Department is among the select few in the country that offer fellowships in all four Board approved areas: Gynecologic Oncology, Maternal Fetal Medicine, Reproductive Endocrinology and Female Pelvic Medicine and Reconstructive Surgery.

Research that answers questions to advance women's health and disease treatments is a core mission of the Department, of which 40% of all faculty members have research funding from sources outside the Department. In the last 5 years, the UM Obstetrics and Gynecology Department has generated over 23 million dollars in research funding including 12.8 million dollars in NIH grant support and 10 million more in additional grant

funding. In FFY 2013, the department was in 17th place for NIH ranking among OB/GYN departments nationally and the Woman's Health Center held 6th place in the Medical School rankings according to US News and World Report.

Office:
Dr. Stern has over 100 square feet of dedicated office space in the Department of Obstetrics and Gynecology. There is sufficient space for students and her research assistants. She has dedicated departmental support for administrative services, purchasing, and finance/accounting.

Computer:
The University of Michigan maintains a flexible, campus-wide computing system delivered to health system and campus sites via Ethernet-TCP/IP connection to the University's central high-speed network. An extensive network supports all phases of data processing, including electronic mail, text, mathematical, accounting, and data base applications. The system is supported by the University with several full-time individuals responsible for maintaining this network.

The University maintains an on-line charting system for all ambulatory, procedural and in-patient hospital stays. The principal investigator has a Dell PC for her exclusive use, which will be used for data management, and work processing.

School of Public Health Resources
Kardia Research Group, University of Michigan

Laboratory Resources:
Dr. Kardia's lab in the Department of Epidemiology at the University of Michigan, School of Public Health occupies 7 offices, totaling approximately 3000 square feet. A keypad lock system is used to prevent unauthorized access to our computing facilities and data records.

Computing Resources Overview:
The Kardia lab participates in a partnership with the Molecular & Behavioral Neuroscience Institute (MBNI) at the University of Michigan to share computing resources. MBNI.org was started from a basic high performance computing (HPC) system in 2005 and has since grown to accommodate new research groups. Its current features include HPC, storage, backup, communication/collaboration and HIPAA-level security. As of October 8, 2013, it is serving 14 researchers and approximately 100 users across the university.

Computational Capacity
The computing resources of the Kardia Lab and the MBNI cluster are continually fine-tuned and upgraded to meet the growing complexity and volume of statistical and genetic data analysis that we perform. This adaptive strategy is accomplished through our partnership with MBNI which includes: high performance hardware and software, access to additional idle computing from the MBNI cluster, and our expert researchers working with the MBNI's systems administrators to understand the system and write programs that maximize its capacity. The computational resources of the Kardia lab and the MBNI network are meticulously maintained to ensure the top echelon of service availability and to prevent the loss or corruption of data. The computational capacity of the network is regularly monitored to ensure efficient data processing and an error-free analysis environment. A detailed overview of the way that the computing resources of the Kardia Lab at the School of Public Health (SPH), MBNI, and the University of Michigan's Academic ComputingCenter (MACC) interconnect is provided in **Figure 1**.

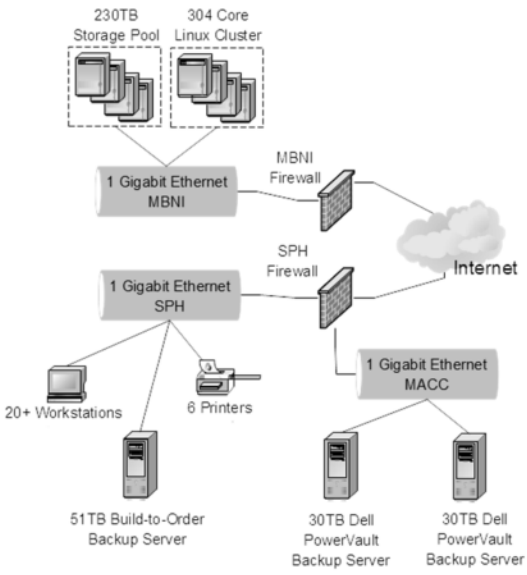

Figure 1: Kardia Lab/MBNI/MACC Network Diagram

Servers
The Kardia lab has added their computing power to the MBNI cluster to offload the system administration of the servers and to use/share the resources of the cluster as a whole. MBNI's high performance cluster has 25 computing nodes. The computing nodes have a total of 304 cores and 2064GB RAM. Three nodes have 128GB RAM each for memory intensive analyses. The main storage uses a unified scale-out file system, and total size is 230TB. Storage can be accessed with multiple file access protocols, such as SCP, SFTP, HTTPS, Samba and NFS.

Data Coordination Facilities
As a Data Coordination and Analysis Center for a number of large epidemiological studies including the Rochester Family Heart Study (RFHS), Genetic Epidemiology Network of Arteriopathy (GENOA), Heart Failure study, Study of Women's Health Across the Nation (SWAN), and genotyping for the Health and Retirement Study (HRS), we have established computer programs that allow us to log in participant records received from field centers, perform double entry, and compare and verify the accuracy of the data entry. We have also created programs to generate reports to be sent to individual field centers to resolve any questions and/or inconsistencies discovered during the double entry process. In addition, we created a Medication Coding program that allows us to translate medications reported by participants to the standard numeric Medication Codes used across the country. All participant records are physically secured, double checked to make sure there are no personal identifiers (i.e. names, addresses) and maintained in a room which uses a keypad lock system.

Bioinformatics Support
In order to facilitate the data analyses for high-throughput data including SNP genotyping, gene expression microarray, methylation microarray, array CGH for DNA copy number variation, metabolomic data, and proteomic data, we have developed our database management system (DBMS) to be able to connect to other public databases. We also designed our databases to be compliant with information standards and ontology in the field such as MIAME and MIAPE, to make our data and results easily shared and distributed for the research community and the public. For the growing SNP and epigenetic marker database, we keep genomic information as well as the population genetic information from public resources and update our local database regularly. We have also implemented a reference database to host our in-house effort of marker annotation by mining the literature. To address the issue of the existence of many synonyms for a single marker or gene in publications, we assign unique identifiers (rs number, GENE ID) to such markers by comparing the flanking sequences on the reference genome and use these IDs to connect public databases such as dbSNP. The annotated literature data including population, sample size, study design, statistical method and results are incorporated with the genomic information for the cross-study comparison and finding the replication effects.

In addition to the basic statistical modeling tools for phenotypic and genotypic data analyses provided in R, we also obtained several advanced pattern recognition R packages for neural networks, classification and regression tree, support vector machine, random forests, boosting and RuleFit. These are the best pattern recognition algorithms available for complex systems. Using these methods with the high-dimensional genotypic and phenotypic data, we are able to find out how to accurately predict disease status and which are the most important genetic factors contributing to the target outcomes. Besides the in-house developments using R language, we have acquired commercially available software specific for gene expression analysis.

The Partek software program provides the capability to easily integrate gene expression, SNP, and exomic sequencing data, and to quickly and flexibly visualize results.

High Throughput Statistical Analysis System
In order to analyze large amounts of data quickly and consistently while still allowing researchers complete control over the methods and variables being used, our research group has developed a high throughput statistical analysis system. We perform traditional statistical analyses of genetic/epigenetic marker data and phenotype data in parallel using our high performance computing cluster. We have developed a number of highly efficient pipelines for genome-wide SNP data, including genotype cleaning and quality control, imputation to HapMap and the 1000 Genomes Project, single variant association testing, gene-based association testing (burden testing), and gene-gene as well as gene-environment interaction analysis.

Programs and software that comprise our pipeline include R, PLINK, GCTA, SNPTest, MACH, miniMACH, SHAPEIT, IMPUTE2, Haploview, MMAP, SKAT, GESAT, skatMeta, ProbABEL, SOLAR, MENDEL, and others. Python and shell scripts have been developed to connect various steps of the analysis and make the whole process automatic and highly efficient, yet flexible.

Custom Analysis Software
Our research group has also developed custom software packages in Java which are used in our analysis and data visualization areas of the high-throughput statistical analysis system. Using Java for these software packages allows the software to operate correctly on any computer platform that supports the Java Virtual Machine.

ChromoScan is our open-source implementation of the Scan Statistic algorithm. ChromoScan automatically finds entire regions of a chromosome that are highly associated with a specific outcome. When operating this software, the graphical interface allows the user to manipulate their data, and visualize the distribution of their marker data in order to get the most accurate results. This software can also perform optional permutation-testing of the input data to ensure confidence in the algorithmically selected regions.

KGraph is another open-source software package we have developed to assist in the visualization of large amounts of statistical data. The KGraph allows all aspects of genetic/epigenetic marker and phenotype associations/correlations with the outcome to be visualized on one graphic, including: Marker-Outcome association, Covariate-Outcome association, Marker-Covariate association, Marker-Covariate interaction, Covariate-Covariate correlation, Covariate-Covariate interaction, linkage disequilibrium, and Epistasis. In addition to displaying all this information on the graphic, KGraph also integrates cross-validation and dataset replication into the same graphic.

Data Protection System
The Kardia Lab has a number of automated systems to help protect the data stored on the network from multiple threats and possible failures. Beyond the network security policies and procedures outlined above, we use redundant backup procedures for both archival and recent history, and we also utilize Redundant Array of Inexpensive Disks (RAID) to mitigate the risk of hard disk failure wherever possible. There is a nightly backup of the Kardia lab data residing on the MBNI network to two Dell PowerVault NX3100 disk storage units, each with 30TB of useable space, and one build-to-order (BTO) backup server with 51TB of useable space. These Dell PowerVaults are housed at the Michigan Academic Computing Center (MACC) and the custom BTO backup server is in the School of Public Health server room to provide geographical separation for the backup data. The MACC is one of the University's data centers and provides redundant power and requires multiple forms of physical identification for access.

MBNI also has a daily remote synchronization backup solution that stores daily backups and keeps incremental changes to all files up to 14 days. This sophisticated backup system is in place to minimize the risk of file loss by deletion or hardware failure. Each of the primary data store uses RAID with hot-plug technology to automatically distribute data across a number of hard disks. If any one of the disks in the RAID disk array fails, it can be replaced without suffering data loss or downtime. Critical RAID arrays also have hot spare disks. Finally, all compute servers and backup infrastructure have a battery backup system to prevent electrical outages from crashing the computers and risking data corruption and loss.

Workstations
All workstations for researchers have at least 4GB RAM with multi-core processors. All workstations operate on Windows 7 with a standard set of software including or, Microsoft Office suite, and other office productivity software. Each research workstation is loaded with appropriate statistical analysis software including SAS, S-Plus and R. Some of these workstations have a complete library of statistical genetic analysis software installed including our custom R and Java programs specifically developed for advanced genetic analysis of high dimensional genetic data. Additionally, each of the research workstations can be loaded with a comprehensive suite of development software including PERL, C/C++, Java and FORTRAN for method development of cross-validation, combinatorial partitioning algorithms, and more.

Network Security

The security of the Kardia lab network is regularly monitored and improved to adapt to the changing threats and conditions of the outside world. The School of Public Health (SPH) employs an intrusion detection system that scans network traffic for signs of known malicious activity. The lab is also protected by the University's virtual firewall that has both ingress and egress rules to restrict traffic to only those ports that have been explicitly permitted. Finally network traffic itself is monitored for known deviations from derived baselines that may indicate anomalous or malicious attack activity.

The threats of viruses, spyware, malware, and other software computer maladies are all countered with a stringent virus control policy. First, all workstation computers have Forefront Enterprise antivirus software to detect files infected with known viruses. Virus/malware alerts are sent to the SPH-run SCCM 2012 server. Second, all email attachments are scanned for malicious software. Through SCCM 2012 all computer updates, both operating system and third party, are applied in a timely manner. Machines that have not received the required updates are investigated by SPH help desk staff.

All MBNI servers are in private networks localized in the MBNI server room and protected by a firewall with hundreds of iptables rules to fine-grain security policy. All external network traffic for file access and messaging is encrypted with SSL protocol to prevent man-in-the-middle attacks. User activities are audited and logged on all MBNI.org computers. Access to the MBNI server room goes through two levels of security; entry to the server room floor is secured by access control system with card reader, and entry to the server room is secured by a password protected door lock. Additionally, video surveillance system is installed on all MBNI hallways.

All MBNI resources use the same Kerberos service as authentication. The minimum password length is ten, and the minimum number of password character classes is two. All resources use the same OpenLDAP service as authorization. Users and data are divided into groups, and user can only access his own group's data.

Flux High Performance Computing Cluster
In addition to the computing resources described above, we also have access to the University of Michigan's High Performance Computing Cluster, Flux. The Kardia research group utilizes Flux for processes that require very long run times or large amounts of memory that exceed the capacity of the MBNI cluster. Flux consists of roughly 10,000 standard-memory cores (4GB RAM) and 360 larger-memory cores (25GB RAM) that can be accessed by all University of Michigan researchers. Standard compute nodes are composed of 12, 16, or 20 cores of at least 4 GB of RAM per core, while larger memory compute nodes comprise 40 CPU cores per node with 25GB of RAM per core. The compute nodes are connected to each other and to 640TB of high-speed scratch storage with 40Gbps InfiniBand networking. Flux is operated by the staff of Advanced Research Computing, who have over 15 years of operational experience supporting high performance computing environments and who have supported the delivery of over 16,000 CPU-years of computing time and over 7 million compute jobs.

Other:
Michigan Institute for Clinical and Health Research (MICHR)
The Michigan Institute for Clinical and Health Research (MICHR), approved by the Regents of the University of Michigan in November 2006, serves as the administrative home of the UM Clinical and Translational Science Award (CTSA). The institute follows the footsteps of UM's strong history of investment in centralized resources for clinical and translational research, and optimizing institutional support and success. MICHR, a trans-institutional academic unit, connects scientists across the University in order to accelerate and strengthen all research at the university related to human health. The schools of Business, Dentistry, Medicine, Nursing, Information and Public Health, the colleges of Engineering, Pharmacy and the College of Literature, Sciences and the Arts, the division of Kinesiology, the Institute for Social Research and the Life Sciences Institute are among 33 separate schools, departments and centers that have pledged resources to the new institute. The total dollar pledge from these units is $55 million.

An Operations Committee representing leadership from all of the participating schools provides day-to-day management of MICHR. An Executive Committee comprised of high-level institutional officials, and a Scientific Advisory Council comprised of many of our University's leading scientists, provides advice and oversight. A

Scientific Review Committee has the authority to distribute pilot monies and education offerings to worthy trainees, faculty, and research.

The institute secures an academic home for the full spectrum of activities needed to support such research, including informatics, statistics, ethical oversight, regulatory support, community engagement resources, education programs, health disparities and pediatric-focused research and more. MICHR has developed a web resource with clinical research information that applies to the community and to research staff, and continues to support study recruitment activities through the *UMClinicalStudies* database and subject registry. This Registry will be used for subject recruitment.

The Research Support Core (RSC) offers a variety of services on a contractual basis for investigator-initiated, federally sponsored, and pharmaceutical industry studies. RSC meets with faculty and trainees and assists them in developing their projects and writing grants.

The Clinical Research Informatics Core is the home of Michigan's Roadmap NECTAR grant and the ongoing development of IT platforms and tools necessary to perform translational research. This unit resides within the MICHR Biomedical Informatics Program where its functions, leadership, and institutional resources are integrated with those from Michigan's Roadmap National Center for Integrative Biomedical Informatics (NCIBI) grant, and the overlapping UM Center for Computational Medicine and Biology (CCMB). MICHR provides free pre-award and charge-back post-award data coordination center functions under the faculty leadership of the Biostatistics Program.

The goal of the Education Core is to offer faculty and staff within the University of Michigan educational opportunities and resources for good clinical practices and clinical research. Education Core is integrated with the K12, K30, T32, and IRB education programs, and also directly provides education aimed at research staff. The MICHR organizational structure and governance encourages co-investment and partnering of various components of the health research and care enterprise. The MICHR Programs build on tremendous faculty expertise in a wide variety of areas, and immeasurably increase the breadth and depth of services, mentoring, and research expertise available to investigators. MICHR provides a university-wide umbrella organization to serve as a partner, advocate, and coordinator of the infrastructure and support that are necessary for investigators to successfully carry out their missions.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

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

Prefix:
First Name*: Alexandra
Middle Name:
Last Name*: Stern
Suffix:

2. Human Subjects

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

3. Permission Statement*

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

● Yes ○ No

4. Program Income*

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

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

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

Funding Opportunity Number: PA-14-278. Received Date: 2015-02-12T10:38:04.000-05:00

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

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

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

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

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ○ Yes ● No

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

Previously Reported*: ○ Yes ○ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

BUDGET JUSTIFICATION

Personnel

University of Michigan

Alexandra Stern, PhD (Principal Investigator EFFORT calendar months)
Dr. Stern is a Professor in the Departments of Obstetrics and Gynecology, American Culture, History, Women's Studies and a core faculty member in the School of Public Health's Center for Social Epidemiology and Population Health and the Latina/o Studies Program. Dr. Stern has done extensive research on the history of eugenics and genetics in United States and the Latin America. Dr. Stern has published widely on the history and contemporary implications of involuntary sterilization with a focus on Latina/o communities and people with disabilities, and is recognized as the leading expert on sterilization in California. Recently, she served as co-PI of study supported by the Centers for Disease Control and Prevention to understand the responses of U.S. cities and communities to the 2009-2010 H1N1 influenza pandemic, a project that involved close attention to racial and ethnic health disparities. Dr. Stern will be responsible for project oversight and management, qualitative research design, and leading the collaborative team.

Sharon Kardia, PhD (Co-Investigator, EFFORT academic and EFFORT summer months)
Dr. Kardia is a Professor of Epidemiology, and Director of the Life Sciences and Society Program at the School of Public Health. Dr. Kardia's main research interests are in the genetic epidemiology of common chronic diseases and their risk factors. She is particularly interested in gene-environment and gene-gene interactions and in developing novel statistical strategies to understand the complex relationship between genetic variation, environmental variation, and risk of common chronic diseases. Her research utilizes genomic, epigenomic, transcriptomic, and proteomic measures on large epidemiological cohorts. As Director of the Life Science and Society Program, she also studied the public's views on informed consent, data sharing, and biobanks. Dr. Kardia will be responsible research design, and guidance of the quantitative methods used in this study. In addition, she will be instrumental in assessing the lessons of the eugenic past to contemporary ethical and social issues in the uses of genetic tests and technologies.

Siobán Harlow, PhD (Co-Investigator EFFORT academic and EFFORT summer months)
Dr. Harlow is a Professor of Epidemiology and Director of the Center for Midlife Science at the School of Public Health. As a reproductive epidemiologist, Dr. Harlow's research focuses on understanding patterns of menstrual function and gynecological morbidity across the lifespan, including most recently leadership in studies of the natural history of ovarian aging, development of a staging system for reproductive aging, and studies of the interface between ovarian aging and chronic disease. As Director of the Center for Midlife Science (formerly Center for Integrated Approaches to Complex Diseases), she provides stewardship for two 20-year cohort studies -- the Study of Women's Health Across the Nation (SWAN) and the Michigan Bone Health and Metabolism Study (MBHMS), and fosters research opportunities for junior faculty associated with this Center. Dr. Harlow will share with Dr. Kardia responsibility for the research design, and guidance of the quantitative methods used in this study. In addition, Dr. Harlow will ensure that methods from reproductive population health, where appropriate, are included in the analysis.

Graduate Student Research Assistant (6.0 calendar months year 1; 3.0 calendar months year 2)
A graduate student research assistant under the direction of Drs. Stern, Kardia, and Harlow will be responsible for management and organization of the dataset, and for conducting the bulk of the quantitative analysis using applications such as SPSS and SASS. This person will also assist in organization of data to allow for qualitative analysis of keywords and sterilization refusals. This person will devote 9 calendar months effort over 18 months of the project. The graduate student research assistant has a 6 calendar month appointment which is equal to a full-time University effort for the first year.

Research Assistant (12 calendar months year 2)
A PhD-level research assistant will work in year 2 on advanced data analysis and preparation of articles for peer-reviewed journals, and conference presentations, as well as on the charts and graphs that will be key to conveying the patterns we uncover in the data.

Data Analyst (1.2 calendar months)
A temporary student data analyst will work in years 1 and 2 at 1.2 calendar months with Dr. Stern on qualitative data analysis, including identifying relevant documents in the data set and conducting literature reviews on issues such as reproductive control, eugenics history, and bioethics history.

Justification for the Additional Module in Year 2

In year 2 of the grant, we have requested one additional module of $25,000. This additional module is necessary as year 2 will involve more data analysis and effort to produce articles ready for peer-reviewed publications and professional dissemination. Additional staffing is needed in year 2 to accommodate this.

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	Specific_Aims.pdf
3. Research Strategy*	Research_Strategy.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	Human_Subjects.pdf
6. Inclusion of Women and Minorities	Women_Minorities.pdf
7. Inclusion of Children	Children.pdf
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	LOS.pdf
13. Resource Sharing Plan(s)	Resource_Sharing.pdf
Appendix (if applicable)	
14. Appendix	Appendix.pdf

SPECIFIC AIMS

Our overall objective is to conduct epidemiologic and historical analysis with a large dataset to better understand relationships, patterns, and experiences of eugenic sterilization in California where 20,000 patients and inmates were sterilized in state institutions in the 20th century. Working with a dataset that contains 15,000 of these records from the period 1921 to 1952, and that comprises 25% of recorded eugenic sterilizations in the United States, we seek to show the relevance of our historical findings to contemporary ethical, legal, and social issues in human genomics. Thousands of those sterilized under eugenic laws were deemed "unfit" based on I.Q. scores and psychiatric classifications, or as delinquent due to their sexual behavior or petty criminal records. While today reproductive autonomy is a cherished bioethical precept and a largely protected legal right, we can learn a great deal from closely studying an era in which a particular variant of genetic determinism resulted in the state-mandated deprivation of reproductive capacity.

Our specific aims are:

1. To conduct extensive quantitative analysis using the eugenic sterilization dataset we have created during the pilot phase of this project. This de-identified HIPAA-compliant dataset was created using REDCap and includes 212 discrete variables for each of the 15,000 records. Using this wealth of coded data, we intend to describe patterns of sterilization according to gender, age, ethnicity, nationality, and diagnosis, as well as contextual factors such as patient's institution, medical superintendent, and family structure.
2. To link the eugenic sterilization dataset to individual-level census microdata and tract-level census reports to permit population-based estimates of sterilization rates. By linking the two datasets we will be able to test the associations of gender, age, ethnicity, nationality, diagnosis and other variables with the risk of sterilization. For example, we hypothesize that Spanish-surnamed patients and young teenagers were disproportionately sterilized. Preliminary data analysis confirms this hypothesis for one institution, and we wish to test this hypothesis and a larger set of hypotheses related to social bias in and across institutions.
3. To conduct qualitative analysis with the sterilization records, supplemental files, charts, and forms in the digitized microfilm reels. Once our eugenic sterilization dataset is completed in summer 2015, we will be able perform keyword searches to identify themes, such as familial resistance to sterilization or patient refusals, and to trace terminology trends over time. In addition, we will explore the meaning and limits of consent in a context where sterilization was the precondition for institutional release.
4. To incorporate our findings into a companion digital archive that features data visualization, historical interpretation, and patient stories; this is under parallel development with digital humanities colleagues.

We will devote 24 months to quantitative and qualitative analysis of the dataset of 15,000 sterilization recommendations (approximately 30,000 individual documents) that we have built with an internal pilot grant. We will link the sterilization data to census microdata (individual-level data) constructed from the 1920, 1930, and 1940 censuses and tract-level data from the 1950 census, which will enable us to understand discrete and longitudinal patterns of sterilization in and across state institutions. This rich data source provides a unique opportunity to conduct an empirical analysis of the practice of eugenics in the United States coupled with an informative textual analysis of state-institutional practices. The companion digital archive will create an important historical resource for future researchers.

During Year 1, we will create the census microdata set for all nine institutions under study; produce descriptive statistics according to gender, ethnicity, age, nationality, diagnosis, and other variables; and conduct population-based quantitative analyses. In addition, we will undertake coding of the documents for the qualitative analysis of keywords and trends. We will submit abstracts to present our findings at public health, history, ethics, and ELSI community conferences, and begin to draft and outline peer-review articles.

During Year 2 we will test hypotheses about increased risk of sterilization among particular subgroups by combining the eugenic sterilization data set and the census microdata set. We will conduct our qualitative analyses to analyze familial and patient objections to sterilization and to examine the limits of consent process in an institutional setting. We will prepare articles for peer review in scholarly journals and disseminate findings to history, public health, and ELSI communities. Relevant findings will inform a companion digital history archive under parallel development and for which we will apply for funding from humanities and history programs. We will prepare articles for peer review in scholarly journals and continue to disseminate findings to history, public health, and ELSI communities.

RESEARCH STRATEGY

Significance

During much of the twentieth century, eugenics was a popular “science” in much of the world (Bashford and Levine 2010). In its “positive” or softer form, eugenics manifested in activities such as better babies contests, infant welfare programs, or pronatalist programs directed at groups deemed superior (Schneider 1990; Stepan 1996; Kline 2001). In its more negative form, eugenics involved heavy-handed forms of reproductive control such as sterilization or mass euthanasia (Proctor 1988; Weindling 1989; Lombardo 2010; Black 2012; Hansen and King 2013). Genetic determinism undergirded both “positive” and “negative” eugenics although the former allowed greater latitude for environmental factors. From the 1900s through the 1960s, both variants of eugenics influenced policies and attitudes on local and national levels in the United States (Paul 1995; Kevles 1995; Largent 2008; Lombardo 2011).

Indeed, many people are surprised to learn that in 1907 the Midwestern state of Indiana passed the world’s first sterilization law, which authorized medical superintendents in homes and hospitals to sterilize people whose deleterious heredity appeared to threaten society (Stern 2007). From this first law in 1907 to 1937, 32 U.S. states passed eugenic sterilization laws, which were used to control the reproduction of vulnerable populations until the 1970s, when legislatures started to repeal these statutes. Over the period of about six decades, over 60,000 sterilizations were officially recorded, principally in state homes and hospitals for the feebleminded and mentally ill. Sterilization rates were fairly steady in the 1910s and 1920s as eugenics gained currency, and increased markedly after 1927 when the U.S. Supreme Court upheld the constitutionality of the procedure in *Buck v. Bell,* a case that tested Virginia’s 1924 law (Lombardo 2010). California passed the third law in the nation in 1909 and performed 1/3, or 20,000 of all documented sterilizations, the vast majority of these between the 1920s and 1950s (Braslow 1997; Kline 2001; Stern 2005; Wellerstein 2011).

The broad contours of eugenic sterilization and coercive eugenics in the United States are familiar to many historians, geneticists, and bioethicists (Kelves and Hood 1993; Paul 1998; Buchanan et al. 2001; Andrews 2002; Duster 2003; Mehlman 2009; McCabe and McCabe 2010; Comfort 2012) and it is not uncommon for eugenic sterilization to be held up as an egregious example of early “pseudoscientific” human genetics. However, few empirical historical analyses of this practice are available.

- Who was sterilized?
- Were some groups disproportionately sterilized?
- Did racial or ethnic bias affect sterilization decisions and patterns?
- Were age, gender, diagnosis, and nationality associated with a higher risk of sterilization?
- How did sterilization practices and patterns change over time?
- How did sterilization patterns and patient experiences vary from institution and institution?
- Was consent obtained and how might we evaluate such consent with bioethical hindsight?
- What happened to patients and inmates who protested sterilization?

Our project seeks to answer these questions using a unique set of historical resources. In 2007, while pursuing archival research in California, Dr. Stern located 19 microfilm reels in file cabinets housed at the Department of Mental Health (now Department of State Hospitals) in Sacramento, California. She soon discovered that these reels contained a treasure trove of data --- tens of thousands of sterilization recommendations from nine institutions along with supplemental letters, forms, and sterilization rosters (See Appendix A: Sample Sterilization Recommendation Form). After receiving approval from the State of California Committee on Human Subjects Protections and the University of Michigan Biomedical IRB (See Letters of Support), and pilot funding from the University of Michigan, she began to collaborate with Dr. Kardia and Dr. Harlow to create a de-identified HIPAA-compliant data set that incorporates 212 discrete variables contained in these forms. These variables include basic demographic information (Figure 1) as well as a long list of categories related to diagnosis, family situation, purported evidence of criminality or sexual delinquency, just to give a few examples (for the full-length REDCap Data Capture Instrument see Appendix B).

Over the past two years, the interdisciplinary team of Drs. Stern, Kardia, and Harlow has overseen the creation of this original dataset in Dr. Kardia’s data laboratory at the University of Michigan School of Public Health. This R21 would provide support for the multi-pronged data analysis phase of this project. For the first time, a large data set related to eugenic sterilization in the United States can be carefully and comprehensively

examined through epidemiologic and historical analysis to track patterns in eugenic sterilization and recover the stories of forgotten historical actors.

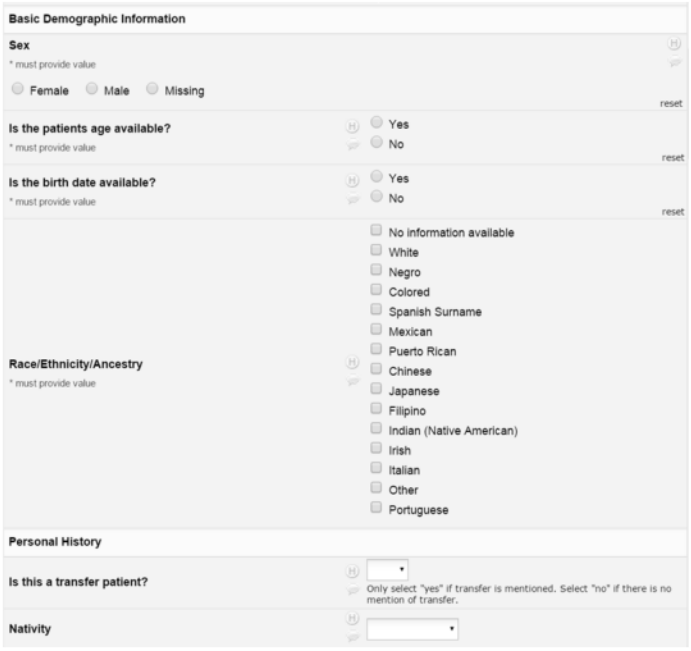

Figure 1. Screenshot of REDCap Data Capture Instrument

This project has the potential to reshape how several scholarly communities and the lay public understand the history of eugenics and reproductive control in the United States, by demonstrating social biases associated with demographic patterns of sterilization and by producing an interpretative mosaic of the experiences of the thousands of people sterilized in California state institutions from the 1920s to the 1950s. Along a similar vein, it can add a new dimension to understandings of consent in institutional settings in the pre-bioethics era. Although consent for sterilization was not legally required in California, and procedures for appeal not articulated until the late 1940s, superintendents at state homes and hospitals put a great deal of effort into obtaining signatures – from parents, spouses, or guardians – for sterilization recommendations. Undoubtedly, this practice reflected concerns about liability and about professional standards; the dynamic of consent provides a window through which to examine familial acceptance of and resistance to sterilization, patient refusal, and the extent to which sterilization became a mundane procedure subject to bureaucratic habituation.

Even though the majority of these sterilizations occurred over fifty years ago, their after-effects inform approaches to reproduction and genetics, usually by standing as a negative example. We surmise that there are discomfiting lessons to be learned from our historical and epidemiologic analysis with respect to attitudes about people with intellectual disabilities, the worthiness of certain groups to reproduce their kind, and the vulnerability of institutional populations. Thus, our findings, might offer useful historical keys for assessing the assumptions about ability and disability that insinuate themselves into routinized and often medically valuable prenatal and genetics tests. Moreover, the rationale of societal burden that bolstered eugenic sterilization in the 20th century did not disappear in the 21st century. In 2013, an investigative report revealed that approximately 150 women in California state prisons had received unauthorized sterilizations (Johnson 2013), many from a contracted physician who stated in an interview that money spent sterilizing inmates was minimal “compared to what you save in welfare paying for these unwanted children – as they procreated more.” (quoted in Johnson 2013). These revelations triggered an exhaustive state audit, which determined that unauthorized procedures had been performed on 144 women from 2006 to 2010, 39 of whom were sterilized “following deficiencies in the informed consent process.” (California State Auditor 2014). They also led to the passage of a bill in the California legislature prohibiting sterilizations in state prisons, which Governor Jerry Brown signed in September 2014. This project, then, might shed light on a longer history of the sterilization of vulnerable, institutionalized populations in California.

Innovation

The core resource for this project, the California eugenic sterilization database, is the result of an innovative interdisciplinary collaboration. This resource will permit us to elucidate patterns and track trends that hitherto have been demonstrated largely through descriptive statistics or anecdotal narratives. Two studies of sterilization programs, in North Carolina (Schoen 2005) and Alberta, Canada (Dyck 2013), effectively use descriptive statistics and basic cross-tabulation to capture overall patterns and to explore issues of consent. In the case of North Carolina scholars and journalists have demonstrated that sterilization rates of African American women rose in the 1950s and 1960s (Begos, Deaver, Railey, and Sexton 2012). For California, Chávez-García (2012) utilizes sterilization data to demonstrate that minority youth committed to juvenile reformatories were more likely than white youth to be sent to state hospitals for sterilization. However, to date no study of eugenic sterilization has employed statistical analysis to test associations between demographic

characteristics and risk of sterilization. We anticipate completing the data entry of all 15,000 files in summer 2015. Nevertheless, using data sub-sets we have been able to discern important historical patterns, particularly with regard to the comparatively high level of resistance to sterilization exhibited by Mexican-origin parents and families (Lira and Stern 2014). We have also been able to show that Spanish-surnamed patients were sterilized at high rates vis-à-vis their general population in the California in three institutions.

For all of its strengths, our eugenic sterilization database has a glaring limitation: the reels do not include comparable yearly data from un-sterilized human subjects in California state institutions or the population from the hospital catchment area. In order to address this lack of control data, a key component of this R21 exploratory grant is to create a complementary data set of microdata (individual-level data) from the 1920, 1930, and 1940 censuses and tract-level data from the 1950 census in order to produce a population profile of each institution over four decades. In each of these historic censuses, the nine state institutions under study were surveyed. By reconstructing the total resident populations of these institutions, we will be able to determine identical and/or commensurate demographic variables such as gender, ethnicity, nationality, age, and length of commitment. We will create comparable variables by reconstructing the population characteristics for each of the hospital catchment areas. More specifically, we will take advantage of new technologies to validate public records (census rolls) digitized through crowdsourcing methods for use in scientific enquiry.

Our approach incorporates methodological innovation into a project characterized by interdisciplinary collaboration. In addition, this project will directly inform a companion project to create a digital archive that Dr. Stern is developing with colleagues in the digital humanities. This archive will utilize the latest methods of data visualization including a wide range of interactive graphs and charts and tell the stories of those sterilized, in accordance with IRB and HIPAA requirements. Using OMEKA, an open source web-publishing platform for the display of archives and images, Dr. Stern has developed a prototype that she will expand, as a separate sister project, into a “proof of concept” for a digital humanities submission to the National Endowment for the Humanities and similar funding agencies. (Prototype viewable at: californiaeugenicsarchive.omeka.net).

Approach

Overall Approach

We will create a rich statistical portrait of eugenic sterilization in California using a dataset that includes information on the 15,000 individuals recommended for eugenic sterilization between 1921 and 1952. We will link this data to census records of over 100,000 residents of sterilizing institutions in the same time period in order to estimate population-based sterilization rates and compare risk of sterilization across institutions and demographic subgroups, and over time. In addition, we will conduct qualitative analysis on the sterilization dataset in order to find patterns, track changes over time, and understand nuances in the historical records that cannot be captured using quantitative variables.

Planned analytical approach

We will use Stata 13 statistical software (StataCorp 2013) to analyze the sterilization data and corresponding census data (see Table 1). We will tabulate the total number of sterilization recommendations, by year and by institution, to document longitudinal trends. We will also describe the individuals who were recommended for sterilization according to their gender, age, ethnicity, nationality, and diagnosis.

We will use microdata (individual-level data) from the 1920, 1930, and 1940 U.S. Censuses (available through the Institute for Social Research at the University of Michigan) to create a companion dataset that includes the gender, age, nativity, race, and ethnicity of all residents of sterilizing institutions during the same time period as the sterilization dataset. Individual-level data from the 1950 Census are not yet available, but we will use census-tract-level data from census reports to add information on the demographic composition of institutions in 1950. We will also consult institutional annual and bi-annual reports for population level data. We will link this data to the sterilization dataset to estimate population-based sterilization rates, with residents recommended for sterilization as the numerator and total institution residents as the denominator. We will use a case-cohort study design to compare risk of sterilization across institutions, between demographic subgroups, and over time. We will use Poisson regression to test whether particular demographic groups (Spanish surnamed, females, individuals under age 18, immigrants) were more likely to be sterilized than others. We will also evaluate this cross-tabulated data vis-à-vis aggregate state-wide and county-specific census data that

approximates each hospital's catchment area. We hypothesize that we will find that Spanish-surnamed and foreign-born individuals, as well as teenagers, were disproportionately institutionalized, and that certain counties had high numbers of residents committed to state institutions. We also hypothesize that associations between demographic variables and sterilization risk varied from institution to institution.

Table 1. Available data sources for Specific Aims 1 and 2.

Data Source	Resolution	Time periods		Key variables						
				Gender	Age	Nativity	Race	Ethnicity	Surname	Diagnosis
Sterilization recommendations	Individual level	1921-1952	1921-1934	X	X		X		X	
			1935-1952	X	X	X			X	X
Census microdata	Individual level	1920, 1930, 1940	1920	X	X	X	X	Mexican birthplace	X	
			1930	X	X	X	X	"Mexican" race	X	
			1940	X	X	X	X		X	
Census reports	Tract level	1950		X	X	X	White/ Nonwhite		Crosstabs by Spanish surname: selected tracts	
Institution reports	Institution level	Annual, 1922-1952		X	X	X				X

Identification of Spanish surnames in census and sterilization records

In order to rigorously document patterns of sterilization among individuals of Spanish surname and test hypotheses about over-sterilization of individuals of Spanish surname we have developed a systematic protocol for identifying Spanish surnames in the sterilization and census records. We will draw on standardized lists of Spanish surnames developed by the US Census Bureau (Word and Perkins 1996) and will also systematically review lists of surnames to identify Spanish surnames misspelled by census enumerators or institution staff (Gratton and Gutmann 2000). (See Appendix E: Protocol for identifying Spanish surnames).

Preliminary Results: Sterilization recommendations (1935-1944) and census data (1940) at Pacific Colony

To demonstrate our analytic approach, we have performed sample analyses on a subset of our data from one institution, Pacific Colony, for the years 1935-1944 (the decade when sterilization reached it numeric peak).

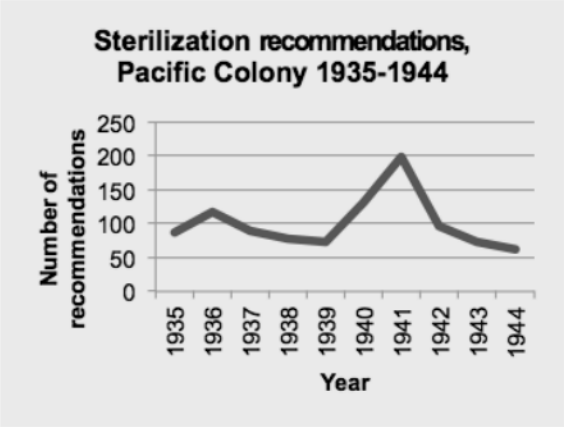

Figure 2. Number of sterilization recommendations, Pacific Colony 1935-1944.

Mental Grade	n	%
Normal	20	2.0
Borderline	42	4.2
Moron	571	56.9
Imbecile	288	28.7
Idiot	67	6.7
Other	15	1.5

Table 2. Assessed mental grade of Pacific Colony residents approved for sterilization, 1935-1944 (n=1003).

As a home for the feebleminded, Pacific Colony designated the "mental grade" of its inpatients according to their assessed IQ. As displayed in Table 2, the majority of individuals approved for sterilization (56.3%) were assessed as "Morons", a category assigned to individuals with an IQ between 51 and 70. Annual institution reports from Pacific Colony indicate that about 35% of all residents were classified as Morons during this time period, versus 30% Imbeciles and 20% Idiots. This suggests that Pacific Colony was more likely to recommend sterilization for patients classified to have mid-level IQ versus very low levels of IQ.

Table 3. Other signs of "bad heredity", by Spanish surname, among Pacific Colony residents recommended for sterilization 1935-1944 (n=1003)

	Spanish surname	Non-Spanish surname
"Sexual delinquency"	33.8%	22.0%
Petty crime	15.0%	7.5%
Violent crime	0%	0%

Table 3 displays the proportion of individuals recommended for sterilization who were judged to have other signs of "bad heredity" that could justify sterilization: sexual delinquency and criminality. Individuals with Spanish surnames were more likely to be termed "sexually delinquent" compared to individuals without Spanish surnames (34% vs. 22%), and twice as likely to have been flagged for petty crime such as theft (15% vs. 7.5%). No individuals recommended for sterilization at Pacific Colony were flagged for violent crime.

Comparison of individuals approved for sterilization to total institutionalized population

Table 4 compares general characteristics of the individuals recommended for sterilization at Pacific Colony between 1935-1944 to the total population of individuals living at the institution in 1940. The most striking differences are by age (67% of individuals recommended for sterilization were under 18 years of age, versus 38% of the general institution population) and by ethnicity (29% of individuals recommended for sterilization had Spanish surnames, vs. only 15% of the total institution population). Thus individuals under the age of 18 had 3.3 times the odds of sterilization compared to individuals age 18 or older. Individuals with Spanish surnames had 2.4 times the odds of sterilization compared to individuals without Spanish surnames. We also observed statistically significant differences in odds of sterilization by gender, with females having 20 percent higher odds of sterilization compared to males.

Table 4. Comparison of residents of Pacific Colony recommended for sterilization (1935-1944) to total institution population in 1940 census (n=2071).

		Recommended for sterilization 1935-1944 (n=1003)	**Census 1940 (n=1068)**		
		%	**%**	**Odds Ratio (95% CI)**	**p-value**
Sex	*Female*	51.9%	47.7%	1.20 (1.01, 1.43)	0.036
	Male	48.1%	52.3%	(reference)	
Age	*<18*	66.9%	37.8%	3.33 (2.78, 3.98)	<0.001
	18 or older	33.1%	62.2%	(reference)	
Ethnicity	*Spanish Surname*	29.2%	14.6%	2.41 (1.94, 3.00)	<0.001
	Non-Spanish Surname	70.8%	85.4%	(reference)	
Nativity	*Foreign Born*	3.5%	3.7%	0.96 (0.60, 1.53)	0.843
	US Born	96.5%	96.3%	(reference)	

In multiple logistic regression models gender, Spanish surname, and being younger than 18 each remained associated with higher risk of sterilization, such that the group at highest risk would be Spanish-surnamed women under age 18 (Table 5).

Table 5. Logistic Regression Results: Odds of sterilization according to sociodemographic characteristics in Pacific Colony, 1935-1944 (n=2071)

Variables	OR (95% CI)	p
Female	1.27 (1.05, 1.53)	0.012
Spanish surname	2.07 (1.65, 2.60)	<0.001
Age <18	3.21 (2.67, 3.86)	<0.001

Approaches for Qualitative Analysis

The qualitative analysis will be conducted using data collected from the sterilization forms, interdepartmental letters, patient communications, and other documents related to the patient files. Using data captured via REDCap, we will code for patient diagnosis over time tracking the different terminology used by the institutions and the changing description of the patients who fit these changing diagnosis criteria. Additionally, we will manually code the data from letters of protest or non-consent in order to identify trends. We will evaluate letters written by patients who opposed their own sterilization and analyze all cases in which the patient, parent, next of kin, or guardian refused consent. Preliminary analysis shows that non-consent often involved religious and familial objections as well as disagreement about diagnosis. We will situate these in broader historical context, connecting them to histories of eugenics, reproduction, and institutionalization. We seek to achieve a balance between the statistical analysis of trends and the personal experiences of patients; to ensure that this project does not forget that each of the 15,000 people sterilized during this period in these California hospitals were human beings deserving of dignity and justice. For example, the digitized reels contain 50 handwritten letters produced by inmates in Patton, a psychiatric hospital, who objected to their own sterilization and wrote impassioned pleas to agency directors in Sacramento (See APPENDIX C: Sample Handwritten Protest Letter). These documents beg for historical contextualization and analysis as small yet important acts of resistance against reproductive control.

We will carry out our multi-pronged analysis in two overlapping phases. During Year 1 we will create the census microdata set, begin to test our hypotheses, and launch coding on the qualitative data. In Year 2 we will test a large set of hypotheses, advance our qualitative analysis, and disseminate our findings via conferences, lectures, and poster presentations, and prepare articles for submission to high-impact peer-reviewed public health, history, and ELSI-oriented journals.

Timetable for Project Activities

Project Activities	Preliminary 6/2013-6/2015 Funding: MCUBED University of Michigan	Year 1 9/2015-8/2016	Year 2 9/2016-8/2017
Creation of Eugenic Sterilization Data Set (Entry Complete by Summer 2015)			
Data Analysis (Expand Data, Test Hypotheses, Conduct Qualitative Analyses, Produce Resulting Narratives, Create Census Microdata Set)			
Data Analysis (Continue Testing Hypotheses, Conduct Further Qualitative Analyses, Track Trends)			
Dissemination of Findings (Includes conference papers, lectures, and poster presentations, as well as preparation and submission of articles to high-impact peer-reviewed journals)			

In conclusion, our proposed project has the potential to advance knowledge about eugenic sterilization in the state that carried out the greatest number of procedures in the 20th century. It also proposes methodological innovation, as we link the eugenic sterilization database to census microdata to order to conduct a population-based analysis that to date has not been attempted. By joining historical and epidemiologic analysis, we hope to produce new empirical findings that will be of value to specialists and generalists interested in understanding past patterns and experiences of eugenic sterilization and reproductive control and contemplating their implications for contemporary ethical, social, and legal issues in genetics, genomics, and reproductive health.

PROTECTION OF HUMAN SUBJECTS
Risks to the subjects
Human subject involvement and characteristics:
This is a retrospective study using historical records without direct involvement of human subjects. The data set includes records of 15,000 people sterilized in California state institutions from 1921 to 1952. The data set was shared with us in its complete form and we digitized it for the facility of manual data entry.

The individuals in the documents are aged 7 to 58 and include men, women, children, and vulnerable populations, specifically those with limited mental capacity and diagnosed psychiatric disorders. The records include names, county of residence, and other identifying information. Because we are using a pre-existing dataset that contains identifiable data, we have trained the entire data team to comply with HIPAA and patient confidentiality protocols. Our data capture system REDCap ensures that the master files are de-identified during the coding process. Since this study will be conducted on data previously obtained for clinical purposes, there is no chance of physical harm or discomfort to the subjects.

Sources of materials: The data for this study comes pre-existing historical records that have been digitized and are stored on a password-protected server. The original records were housed for many years at the Department of State Hospitals, and recently (with the assistance of PI Stern) have been transferred to the California State Archives. The data from the records is entered into a database using the HIPAA-compliant program REDCap. Data is managed and analyzed only by study staff, all of whom are included on the project's IRB and must complete appropriate PEERRS (Program for Education and Evaluation in Responsible Research and Scholarship) modules.

Potential risks: Use of this dataset will pose very minimal risk to exposing personal or confidential information. The process of data extraction and input into REDCap does not involve the analysis of any identifying personal information. The data collected in this study is not of a sensitive nature. There would be no reason to believe that by using the subjects' retrospective data that the subjects would be caused any harm, insults, injury to relationships, loss of job or insurance, injury to their health or well-being.

Adequacy of protection against risks
Data access and security:
The study team can only access the digitized sterilization authorizations on a password-protected server to which they will be granted access after completion of REDCap training, PEERRS training, and IRB inclusion. They will extract and code the information from the digitized records on the server and transfer that data to the de-identified HIPAA-compliant REDCap instruments. There is only one identifier field in REDCap during the data entry process. Once data entry is complete, REDCap de-identifies the field so it will not be included in data exports or reports.

Digitized copies of the records are held on a password protected hard drive and locked in a safe box. All data collection will take place in a locked office and on password-protected computers. No notes will be shared with anyone outside of the study and no information that could be used to identify an individual patient will be disseminated or published. While REDCap is a web-based software, notes and data are not made available online. In the unlikely event that the records are transported we will use a secure carrier only.

Potential Benefit of the Proposed Research to the Human Subjects and Others
There is no potential benefit of the proposal research to human subjects and others.

Importance of Knowledge to be Gained
The analysis performed on the dataset has the potential to yield new understandings of state-mandated sterilization during the eugenics era in the United States. The knowledge to be gained is historical with potential implications for contemporary bioethical issues related to reproduction and genetics.

Inclusion of Women and Minorities

This is a retrospective study using historical records from 1921-1952 without direct involvement of human subjects. The digitized files and eugenic sterilization dataset contain records of women and minorities, the latter identified through ethnic and racial classification, nationality, and Spanish-surname. The research team has access to identifiable information in the master files and has been trained to adhere to HIPAA and patient confidentiality protocols. Once entered into REDCap, the coded data for quantitative analysis becomes de-identified.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Demographic Patterns of Eugenic Sterilization in California: Quantitative and Qualitative Analysis of Reproductive Control of the ?Unfit?

Domestic/Foreign: Domestic

Comments: The planned enrollment is estimated and projected based on the data entered thus far. We have approximately 15,000 sterilization recommendations in the pre-existing data set being used for this retrospective study. Racial and ethnic categories have changed since era of these sterilizations (1921-1952) and thus we have determined classifications using the most logical corresponding category.

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	30	20	4	1	**55**
Asian	101	126	0	0	**227**
Native Hawaiian or Other Pacific Islander	8	6	4	3	**21**
Black or African American	120	100	13	4	**237**
White	6500	5712	1217	1023	**14452**
More than One Race	2	2	2	2	**8**
Total	**6761**	**5966**	**1240**	**1033**	**15000**

Study 1 of 1

Funding Opportunity Number: PA-14-278. Received Date: 2015-02-12T10:38:04.000-05:00

INCLUSION OF CHILDREN

This is a retrospective study using historical records from 1921-1952 without direct involvement of human subjects. The digitized files and eugenic sterilization dataset contain records of minors aged 7 to 21. The research team has access to identifiable information in the master files and has been trained to adhere to HIPAA and patient confidentiality protocols. Once entered into REDCap, the coded data for quantitative analysis becomes de-identified.

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RESOURCE SHARING PLAN

The University of Michigan is aware of and committed to supporting the NIH Statements on Sharing Research Data as they apply to data and resources resulting from performance of research translation. The research team will make unique research resources readily available for research purposes to individuals within the scientific community after publication. The University has used a variety of appropriate and expeditious means to share data that results from sponsored projects with research colleagues, such as depositing data into secure web-accessible data warehouses or arranging distribution of data, reagents, protein targets, and protocols to other researchers using established mechanisms and repositories. The University of Michigan is a signatory to the Uniform Biological Materials Transfer Agreement and will use the simple letter agreement to distribute appropriate research materials to the research community. The availability of data sharing will be publicized by individual investigators in publications and presentations.

The University will assure the timely release and sharing of data no later than after acceptance for publication of the main findings from the final dataset. The University will protect the rights and privacy of human subjects who participate in NIH-sponsored research by redacting all identifiers and by adopting other strategies to minimize risks of unauthorized disclosure of personal identifiers in accordance with authorization and consent documents. The University of Michigan agrees that data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. To enable efficient data sharing, the Project Manager will coordinate requests for data and maintain documentation for requests and distributions. The University has an established Institutional Data Use Agreement that can easily be adapted and deployed.

If it is necessary to license a patented invention, the University expects to elect its title as appropriate under the Bayh-Dole Act to inventions made with federal funds in accordance with the NIH grants policy. The University understands that NIH encourages the filing of patent applications on unique research resources if doing so will aid in the prompt commercialization of diagnostic, prognostic, or therapeutic products. Since institutional ownership of such inventions may be of concern, especially those who are in the source of proprietary technologies, the University will develop agreements with third party collaborators that assures them both adequate patent coverage and opportunities to license such patent rights, as appropriate, in a manner that does not restrict research use by the scientific community, both nonprofit and for profit, but promotes and facilitates their active involvement in NIH supported projects.