Clinical Utility of Pediatric Whole Exome Sequencing
NCT03525431
Document Date: 02/09/2022

Study Application (Version 1.34)

1.0 General Information

***Enter the full title of your study:**

Program in Prenatal and Pediatric Genome Sequencing (P3EGS)

***Enter the study alias:**

P3EGS
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
○	**UCSF** - *707812* - CHO - Peds Neurology
◆	**UCSF** - *136225* - M_PEDS-MEDICAL GENETICS
○	**UCSF** - *707440* - SOM NEUROLOGY PEDIATRIC

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Norton, Mary MD, MD

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

Curry, Cynthia
Study Clinician
Gallagher, Renata MD, PhD , MD, PhD
Study Clinician
Gangaram, Balram
Study Clinician
Gardner, Marisa A

Study Clinician
Klein, Ophir MD
Study Clinician
Koenig, Barbara, PhD
Other Investigator
Sherr, Elliott MD, PhD
Study Clinician
Shieh, Joseph, MD, PhD
Study Clinician
Strober, Jonathan
Study Clinician
Tam, Allison C
Study Clinician
Tenney, Jessica L
Study Clinician
Weiss, William MD, PhD
Study Clinician

B) Research Support Staff

Ackerman, Sara, PhD, MPH
Clinical Research Associate
Anguiano, Beatriz
Study Coordinator
Chang, Jiyoo
Research Assistant
Chen, Flavia H
Data Manager
Chin, Garrett
Data Manager
Fairley, Cecilia F
Clinical Research Associate
Faubel, Amanda J
Research Assistant
Hoban, Hannah G
Study Coordinator
Lianoglou, Billie R
Study Recruiter
Outram, Simon M
Clinical Research Associate
Patel, Sachi
Study Coordinator
Prasad, Hannah L
Study Coordinator
Rego, Shannon M
Study Recruiter
Sahin Hodoglugil, Nuriye N
Study Coordinator
Yip, Tiffany A
Study Recruiter

3.3 *Please add a Study Contact

Koenig, Barbara, PhD

Norton, Mary MD, MD
Rego, Shannon M
Sahin Hodoglugil, Nuriye N
Slavotinek, Anne PhD, PhD
Yip, Tiffany A

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

3.5 If applicable, please select the Designated Department Approval(s)

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Initial Screening Questions

Updated April 2020 - Revised Common Rule (January 2018) Compliant / COVID-19 - v94

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here (Click on the orange question mark to the right for more detailed instructions):

Exome sequencing, which allows physicians to look at many genes concurrently, has been rapidly integrated into the clinical setting but its usefulness remains uncertain. The UCSF Program in Prenatal and Pediatric Genome Sequencing (P3EGS) will study the effectiveness of sequencing as a tool for 1) diagnosing infants and children with serious suspected genetic conditions, including developmental disorders. We will also address ethical, social and economic issues in the delivery of genomic sequencing results to diverse populations, such as under represented minorities and the medically underserved.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

- (●) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (REQUIRED) Select the option that best fits your project (Click the orange question mark to the right for definitions and guidance):

- (●) Biomedical research (including medical records review, biospecimen collection and/or use, other healthcare or health outcomes related activities, research database, biospecimen bank, or recruitment registry)
- ( ) Social, behavioral, educational, and/or public policy research
- ( ) Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- (●) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities:

- (●) Minimal risk
- ( ) Greater than minimal risk

4.6 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

- ( ) Full Committee
- (●) Expedited
- ( ) Exempt

4.7 * EXPEDITED REVIEW CATEGORIES: (REQUIRED) If you think this study qualifies for expedited review, select the regulatory categories that the research falls under: (check all that apply)

- [ ] Category 1: Research using approved drugs or devices being used for their approved indications
- [x] Category 2: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture in certain populations and within certain amounts
- [x] Category 3: Prospective collection of biological specimens for research purposes by noninvasive means (e.g. buccal swabs, urine, hair and nail clippings, etc.)
- [x] Category 4: Collection of data through noninvasive, routine clinical procedures (e.g. physical sensors such as pulse oximeters, MRI, EKG, EEG, ultrasound, moderate exercise testing, etc. - no sedation, general anesthesia, x-rays or microwaves)
- [x] Category 5: Research involving materials (data, documents, records, or specimens) that have been or will be collected solely for nonresearch purposes
- [x] Category 6: Collection of data from voice, video, digital, or image recordings made for research purposes
- [x] Category 7: Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factorsevaluation, or quality assurance methodologies

* Does the collection of blood samples meet requirements outlined by HHS Office for Human Research Protections for **Expedited Review Research Category 2**: **(REQUIRED)**

- For healthy, nonpregnant adults who weigh at least 110 pounds the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week;
- From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week

(●) Yes ( ) No

4.9 * DATA/SPECIMEN ANALYSIS ONLY: (REQUIRED) Does this study ONLY involve records review and /or biospecimen analysis (do not check 'Yes' if this is a registry, research or recruitment database, or biospecimen repository):

○ Yes ◉ No

4.10 * CLINICAL TRIAL: (REQUIRED)
Is this a clinical trial:

According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals.
Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called **ClinicalTrials.gov**.

The FDA requires registration for 'applicable clinical trials,' defined as follows:

- For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.
- For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.

For additional information on the **ClinicalTrials.gov** registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the **ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB**.

◉ Yes ○ No

Clinical Trial Registration - 'NCT' number for this trial:

NCT03525431

4.11 * CLINICAL TRIAL PHASE: (REQUIRED) Check the applicable phase(s):

- ☐ Phase 0
- ☐ Phase 1
- ☐ Phase 1/2
- ☐ Phase 2
- ☐ Phase 2/3
- ☐ Phase 3
- ☐ Phase 4
- ☑ Not Applicable

4.12 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

(•) Yes ( ) No

The UCSF IRB recommends use of the Virtual Regulatory Binder to manage your study.

4.13 * CORONAVIRUS RESEARCH: (REQUIRED) Does this study involve research on coronaviruses (COVID-19, SARS, MERS or other):

( ) Yes (•) No

4.15 * CANCER: (REQUIRED) Does this study involve cancer (e.g., the study involves patients with cancer or at risk for cancer, including behavioral research, epidemiological research, public policy research, specimen analysis, and chart reviews):

( ) Yes (•) No

4.16 * RADIATION EXPOSURE: (REQUIRED) Does your protocol involve any radiation exposure to patients /subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans):

( ) Yes (•) No

4.17 SCIENTIFIC REVIEW: If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final IRB approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Services (CRS) Advisory Committee
- [ ] CTSI Consultation Services
- [ ] Departmental scientific review
- [x] Other:

* Specify **Other: (REQUIRED)**

NHGRI, NIH

4.18 * STEM CELLS: (REQUIRED) Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

(•) No
( ) Yes, and requires IRB and GESCR review
( ) Yes, and requires GESCR review, but NOT IRB review

4.19 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

( ) Yes (•) No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

(•) Yes ( ) No

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

( ) Yes (•) No

5.3 SPONSORS: Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	NIH Natl Human Genome Research Inst.	01	UCSF	Grant		

Sponsor Name:	NIH Natl Human Genome Research Inst.
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	CSER2
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	
PI Name: (If PI is not the same as identified on the study.)	
Explain Any Significant Discrepancy:	

Other Funding Sources and Unfunded Research - Gift, Program, Departmental or other Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below)

- [ ] Unfunded (miscellaneous departmental funding)
- [ ] Unfunded student project

6.0 Sites, Programs, Resources, and External IRB Review

6.1 * UCSF AND AFFILIATED SITES (check all that apply): (REQUIRED)

- [x] UCSF Benioff Children's Hospital Oakland (BCHO)
- [ ] UCSF Cancer Center Berkeley
- [ ] UCSF Cancer Center San Mateo
- [ ] UCSF China Basin clinics and facilities
- [ ] UCSF Helen Diller Family Comprehensive Cancer Center
- [ ] UCSF Langley Porter Psychiatric Institute (LPPI)
- [x] UCSF Medical Center at Mission Bay (Benioff Children's Hospital, the Betty Irene Moore Women's Hospital, Bakar Cancer Hospital, or outpatient clinics)
- [ ] UCSF Mount Zion
- [ ] UCSF Parnassus (Moffitt-Long hospital, dental clinics or other outpatient clinics)
- [x] UCSF Other Sites (including Laurel Heights and all the other sites outside the main hospitals and clinics)
- [x] Fresno - UCSF Fresno OR Community Medical Center (CMC)
- [ ] Gladstone Institutes
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Vitalant (formerly Blood Centers of the Pacific and Blood Systems Research Institute)
- [x] Zuckerberg San Francisco General (ZSFG)

Research involving ZSFG: You are required to obtain additional approvals from the ZSFG Dean's Office. Download the ZSFG Protocol Application Form and submit the completed form to the ZSFG Dean's Office.

We rely on the Community Medical Center IRB for all research at the UCSF Fresno campus and Community Medical Center. Check 'Yes' to relying on an external IRB in 6.10 below.

6.2 LOCATIONS: At what locations will study visits and activities occur:

Recruitment, consent and results provision will take place at clinic outpatient appointments as part of standard healthcare and also as part of inpatient services. We will offer this study at Benioff Children's Hospital Mission bay, Benioff Children's Hospital Oakland and Zuckerberg San Francisco General Hospital, and UCSF Fresno/Community Medical Center.

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

- ( ) Yes
- (•) No

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)

- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program

6.5 * CTSI CRS SERVICES: (REQUIRED) Will this study be carried out at one of the UCSF Clinical Research Services (CRS) units or utilize CRS services:

(•) Yes ( ) No

The CRS budget request form can be found at: https://crs.ucsf.edu/sites/g/files/tkssra726/f/CRS%20Budget%20Request%20Form_Final_8.14.20%20Restricted%20Version.docx . Follow the instructions on the form to submit.

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multi-center or multi-site research trial:

By '**multi-center trial**' we mean a study where the protocol is developed by an lead investigator, an industry sponsor, consortium, a disease-group, etc.,and multiple sites across the nation or in different countries participate in the trial. The local sites do not have any control over the design of the protocol.

( ) Yes (•) No

6.8 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project:

Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor one of its faculty-linked affiliates (SF VAMC, Gladstone, ZSFG) are the coordinating center.

- [ ] Other UC Campus
- [ ] Other institution
- [ ] Other community-based site
- [ ] Foreign Country
- [ ] Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.14 * RELYING ON AN EXTERNAL IRB: (REQUIRED) Does this application include a request to rely on an external IRB (a central IRB (other than the NCI CIRB) or an external IRB (other UC campus, commercial, or institutional):

( ) Yes (•) No

Check 'Yes' since we rely on the Community Medical Center IRB for reseach that takes place in Fresno.

7.0 Research Plan and Procedures

7.1 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove:

We hypothesize that next-generation sequencing studies, such as whole exome sequencing, will have clinical utility in patients with medical conditions that have a genetic etiology.

7.2 AIMS: List the specific aims:

(1) To determine the clinical utility of whole exome sequencing in the minority and underserved population at 6 months after whole exome sequencing. We will recruit and consent up to 800 Pediatric patients and biological parents with a variety of indications, including intellectual disability, seizures, encephalopathy, metabolic disease, birth defects, neurodegerneative conditions and multiple congenital anomaly syndromes. We will perform whole exome seuqencng and provide a result(s) to the family. Results will be defined as:

1. Results of diagnostic or medical importance in relation to the probands presenting condition or the reason for the test;
and, 2. Secondary or additional findings that are deemed relevant to the health of the patient or parents and that will be reported out to the participants and/or their primary physician. These secondary results can include any other result that the study team determines that is of medical importance and must be reported to the participant and/or their primary physician.

We will use the American College of Medical Genetics and Genomics published list of 59 genes that are considered medically actionable: http://www.nature.com/gim/journal/v19/n2/full/gim2016190a.html
For genes that are not on this list and that may be considered actionable, the sign-out team will need to be in consensus that: 1) the sequence variant to be reported is ether pathogenic or likely pathogenic; and 2) the gene is medically actionable. If there is any controversy, a specialist in the relevant clinical area will be consulted regarding actionability of the gene.

After 6 months, we will see the families in follow up and assess clinical utility.

We will recruit patients from UCSF Mission Bay, UCSF Oakland and Zuckerberg San Francisco General Hospital and UCSF Fresno/Community Medical Center.

7.3 DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.):

This study aims to recruit and consent patients and biological family members who have at least one individual with a medical condition that is likely to have a genetic etiology. We will study the clinical utility of exome sequencing in underserved and underrepresented minority populations. To do this, we will perform whole exome sequencing as a test to generate sequence data in order to determine the genetic etiology of the medical condition. Families will undergo questionnaires and interviews to determine the clinical utility of exome sequencing for their healthcare. The medical providers involved in the study will also undergo questionnaires to determine if the exome sequencing has had clinical utility for their patient. The sequence variant data from the exome sequencing will be studied as part of reserach be sent to the National Institutes of Health for sharing in databases such as dbGAP and ClinVar, in accordance with current NIH policy. We will share sequence variants in the form of .vcf files and phenotype data in pedigree form that enables relationships between proband and other relatives to be determined. Data will be available for broad use that is not limited to specific diseases.

7.4 BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.g. why is this study needed) (space limit: one half page):

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

Congenital abnormalities and developmental disorders affect 3-5% of live born infants and children. Despite advances in both pre- and post-natal treatment, the utility of genetic testing in diagnosing the etiology underlying such conditions in order to guide management has been frustratingly limited. Traditional genetic testing with specific gene tests, or even gene panels, is diagnostic in only a small percentage of cases. Recent technological advances in next generation sequencing (NGS) have led to the ability to sequence and interpret the entire exome relatively quickly, allowing a diagnosis in 25-30% or more of cases of developmental disorders when other genetic tests have not yielded a result.

Although whole exome sequencing (WES) holds great promise for improved diagnosis leading to better clinical outcomes, challenges remain in determining how best to apply and utilize sequence data. Fulfilling the promise of WES also requires investigation of ELSI (ethical, legal, social) concerns, given skepticism in some communities that research will benefit them; economic considerations that ultimately determine access to and equitable use of WES; and a need to share clinical genetic results with families and across health care systems to enable better prognostication and management of rare conditions in community settings.

We propose a Program in Prenatal and Pediatric Genomic Sequencing (P^3EGS) at UCSF to examine the diagnostic and clinical utility of WES. P^3EGS will recruit and study affected individuals and their parents, including pregnancies in which the fetus has a confirmed structural anomaly and children with previously undiagnosed developmental disorders that are likely of genetic etiology. Following consent and collection of standardized phenotypic data, the families will undergo WES. To achieve diversity, patient ascertainment and recruitment will occur at four UCSF sites that serve a broad range of under-represented minorities (target of 75%) and span the full socio-economic spectrum, including the underserved.

7.5 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

UCSF has recently established a whole exome sequencing test and it is CLIA-approved. The researchers on this protocol have had experience consenting patients and families for whole exome sequencing and with results provision.

7.6 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

○ Yes ◉ No

7.7 * BILLABLE PROCEDURES: Does this study involve any procedures, lab tests or imaging studies that have a CPT code and could be billable to patients, their insurance, Medi-Cal, Medicare, or any other entity (answer 'Yes' even if the study is going to pay for all the procedures): (REQUIRED)

◉ Yes ○ No

7.8 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

☑ Interviews, questionnaires, surveys
☐ Educational or cognitive tests
☐ Focus groups

- [ ] Social media-based research activities
- [ ] Observation
- [ ] Fitness tests or other exertion activities
- [ ] Use of mobile health apps or other apps
- [ ] Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- [ ] Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- [ ] Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- [ ] Administration of contrast agent
- [ ] Randomization to one intervention versus another
- [ ] Use of placebo
- [ ] Biopsy conducted solely for research purposes
- [ ] Sham surgical procedure
- [ ] None of the above

7.9 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, **clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.**

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring
- additional biopsies to collect tissue for research
- extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

Recruitment and Phenotyping. We will enroll and obtain detailed phenotypic information on 800 pediatrics subjects with a variety of conditions suggestive of a genetic etiology, including intellectual disability, multiple congenital anomalies, seizures and other neurological findings such as a movement disorder, metabolic condition, or a neurodegenerative condition. As part of this group, 80 patients with encephalopathy and/or multiple congenital anomalies will be enrolled from Pediatric Intensive Care Unit (PICUs) or Neonatal Intensive Care Units (NICUs).
A minimum of 60% of enrolled individuals will be ascertained from URMs for all of the 800 study subjects.

Whole exome sequencing (WES) and sequence variant interpretation. We will perform WES on the patient and analyze variants with our existing and well established UCSF pipeline, first incorporating primary gene lists in the annotation analysis and then subsequently analyzing the entire exome, if necessary. We will also investigate the utility of a rapid exome, with a turnaround time of 1 to 2 weeks, in patients with encephalopathy and/or multiple congenital anomalies ascertained from the PICU and NICU. Samples will also be collected from the patient's parents and genetic testing may be done on those samples to help interpret genetic variants identified in their child. The genetic testing of parental samples may be exome sequencing or may be more targeted testing of individual genetic variants first identified in the child. The genetic testing patients receive is clinical testing done through a CLIA certified labratory.

Results delivery and follow up. We will deliver variant results to the family as part of clinical care. We will follow all 800 families, including those with a diagnostic, positive exome result

(pathogenic variant(s) or likely pathogenic variant(s)) and those without a positive result (negative result or VUS), between 6 and 12 months after results provision to assess clinical status and medical care post exome sequencing.

Assessment of clinical utility. We will assess clinical utility by examining health status and management changes of study subjects before and after exome testing, and perform a blinded comparison and then statistical analysis of those with a positive sequencing result versus those with no result or a variant of unknown significance (VUS) from the exome sequencing. Managing providers will be asked to complete a survey regarding the clinical utility of exome for their patient. This survey will be administered in person on paper or via email. These surveys are part of research.

Procedures

1) A consent form will be given, mailed or emailed to study subjects. Subjects will also be provided with the UCSF Experimental Subject's Bill of Rights. During the consent process, study subjects will have the chance to ask questions about the study and to decide if they would like to join the study. Subjects that take part in this study will need to sign written consent.

2) Participants will provide a sample for genetic testing. Subjects will have a blood test at UCSF or go to their physician to provide us with a blood sample. A saliva sample that can be obtained with a kit is an alternative procedure if a subject does not wish to have venepuncture. A buccal swab obtained with a kit is also an alternative to venepuncture. The blood, saliva, or buccal swab samples will be used to obtain the genetic material (DNA) for laboratory testing. Repeat studies may be needed in some cases and subjects may be asked to give another blood sample in the future, but may choose not to donate the second sample. About two ounces of blood will be drawn from adults (5-7 teaspoons; around 5 ml) and one ounce (3-4 teaspoons; around 2-3 ml) from children depending on weight. The maximum collected for each study subject will be less than 3 ml/kg in neonates and children and less than 20 ml in adults. The blood will be taken by needle in a similar manner to other blood samples. The blood or saliva samples will be sent to the testing laboratory with patient identifiers, such as name, date of birth and medical record number, and will be stored in a locked laboratory for the entire study.

3) The DNA sample from the patient will undergo whole exome sequencing (WES). WES entails searching for genetic changes that can lead to or predispose to intellectual disability, multiple congenital anomalies, seizures and other neurological findings such as a movement disorder, metabolic condition, or a neurodegenerative condition. After the patient's sample has been tested, we may also test parental samples to better understand the child's genetic information. Parental testing may be exome sequencing or more targeted testing of individual genetic variants identified in the child. Patient and family history and examination data (for example, pedigrees) will be collected as per standard clinical practice. These data may include information on family members who are not enrolled in the study as per standard clinical practice. We may also obtain photographs of some affected individuals as per standard clinical practice. These photographs will be obtained with the permission of the individuals concerned. Use of recognizable photographs (eyes showing) will require written permission from the participant(s) or guardian concerned using a separate consent form that is not part of the study.

4) The UCSF Clinical Exome sequencing test is a test that can provide various types of results. For example:

We can find gene variants that are known to cause or contribute to disease.

We can find gene variants that are known *not to* cause or contribute to disease, meaning they are normal variations of the exome.

We can find gene variants that are novel and of uncertain clinical importance, meaning that we do not know if they cause/contribute to disease or if they are normal variations of the exome.

As the majority of the gene variants that we find in the course of our research will fall into the third category, of uncertain clinical importance, we will not routinely return results to patients or other patients. However, if we find a gene variant that is known to cause or contribute to disease or to the patient's presentation, we will return this result. We will only give subjects results about specific abnormal gene variants that we think are important to their health, and that will be able to be confirmed by Sanger sequencing in a CLIA-certifed clinical laboratory.

In this case, we will contact the study subjects by phone or email to arrange a follow up appointment in clinic to provide results to families interested in learning about the results. The family may "opt out" of learning any of the results, and still be in the study.

If the patient and family choose to learn the results of their exome sequencing, they will be asked to return to Genetics clinic or to another clinic at UCSF, where they will meet with a genetic counselor or Clinical Geneticist who will explain the findings and what they mean for their health. She or he may also make recommendations for follow-up with a physician or with a specialist. For example, if a patient is found to have a gene variant that causes high cholesterol, it may be recommended to discuss this with a doctor so that he/she can monitor cholesterol closely. This is part of clincial care.

We will also discuss results that the study doctors think may have significant effects on patient or family health, but that are unrelated to the clinical indication for performing the test (secondary or additional findings). If the family has specified that they do not wish to learn such results, these will not be reported. This is part of clincial care.

Gene variants that are known not to cause disease or are of uncertain relevance (that may be normal variation) will not be reported to participants.
We will contact subjects about gene variants that are important to their health and health decisions; however, we expect to find very few of this type of gene variant. Subjects that are not contacted could still have gene variants that could cause disease or birth anomalies; not all gene variants that could cause disease are known and not all gene variants that could cause birth anomalies will be detected.

4) Material (DNA) taken from participants samples may be given to other researchers for studies on similar or other conditions. However, names or identifying details will not be given to the other researchers. On completion of the study, the DNA samples will continue to be stored at UCSF or at the institution where the work was carried out. The samples will not be given to other researchers outside UCSF for studies on different medical conditions.

We may publish a chart that shows family trees and who is affected with the condition, but we will not use subject identifying details. We may also publish photographs that do not show faces, but if we want to use photographs showing faces that are recognizable, we must first discuss this with participants and obtain written permission for this with a separate consent form.

The stored DNA samples will remain linked by code to patient and study identifiers. This is in order that the patient and family can be identified and informed if results are obtained that have direct implications for their health or medical care.
Participation in the study will take a total of about 2-3 hours over a period of 2 or more days.

We will place the resulting phenotypic and genotypic data in a controlled-access database at the National Institutes of Health. Use of the data will not be restricted to any one condition or the condition for which the sample was obtained.

Although the genetic testing will be performed as a clinical test in the study, we will use the results in the context of research, with sharing of phenotypic and genotypic information within the CSER2 consortium and with other researchers.

The UCSF Fresno/Community Medical Center, one of our study sites, will be enrolling patients starting in January 2020 (their own IRB was recently approved). Three of their team members will be adding data into our Redcap database directly and will therefore have access to our study identifiers. We were unable to add them to the personnel section of the study application because they are not UCSF employees, so we are adding them here as per Megan's instructions. They team members are

Claudia Cuan, a study coordinator, **CCuan2@communitymedical.org**; Leigh Ann Higa, a genetic counselor, **LHiga@communitymedical.org**; and Emily Massiello, a genetic counselor, **EMassiello@communitymedical.org**; Cory Airheart, a genetic counselor, cairheart@communitymedical.org

7.11 INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used for this study:

We will also analyze and describe clinical interactions and experiences across prenatal and pediatric clinic settings in order to understand context and document patient-provider

interactions. These activities are part of research and are not part of clinical care. Points 1-3 below (the video recordings of clinical interactions, ethnograhic observations and interviews are covered under a separate IRB protocol, 17-23118). Specifically, we wil do the following:

1. Conduct detailed, ethnographic observations in each clinical setting to elucidate the full contextual experience of families offered sequencing for a potential genetic disorder identified during pregnancy (the prenatal context) or during the care of their affected infant or child (the pediatric context).
2. Follow 60 families (1/3 prenatal) who accept sequencing and conduct in-depth interviews at two time points, targeting a sample constructed to include ancestral diversity (ascertained by self-reported race/ethnicity) and social/economic status (ascertained by insurance coverage). Physicians and genetic counselors will also video record key clinical interactions. Using the constant comparative method, we will compare and contrast the experience of families. Interviews and analysis of videos will elucidate strengths and limitations of communication, revealing how families—including those from diverse, underserved backgrounds—understand genomic sequencing, its potential outcomes, and its consequences.
3. Using semi-structured interviews, assess the reasoning and experience of 60 families who are offered but refuse sequencing, including the potential impact of economic and access issues.
4. Based on data gathered via the ethnography and the initial interviews, develop (in collaboration with the full P^3EGS team and with colleagues across the CSER2 "outcomes and measures" committee) and administer a utility assessment survey tool to the full sample of 800 families sequenced. Here we define utility to include both the parents' understanding of clinical usefulness as well as their personal views about the value and burden of sequencing.
5. In addition to the utility assessment tool, we will also administer surveys at baseline, return of results, and follow-up meant to provide data about patient demographics, information seeking habits, secondary finding preferences, quality of life, understanding of test results, satisfaction, etc. (see attached surveys). These surveys have been recommended for harmonization by the larger CSER2 consortium. These surveys will be administered in person, over the phone, or via mail or email.
6. We will also contact the providers who referred patients to the study via email and ask if they are willing to complete a provider survey meant to provide information about their experience and comfort level with genetics (this will be done once) as well as assessing their perception of the clinical utility of exome sequencing for the patient(s) they referred (this will be done twice for each patient, once after the patient's return of results appointment and once after their 5-7 month follow-up visit).
7. We will contact executives, administrators, managers or clinicans at UCSF via email to ask if they are willing to complete a survey about organizational readiness to change (ORCA). This survey will be administered once via Redcap or on paper and will not involve any personal identifiers. The goal of the survey is to learn more about their views on the potential for implementation of clinical sequencing in healthcare systems and communities. The de-identified data will be pooled by the University of Washington to include data from the rest of the CSER2 consortium.

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

7.12 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.) for analysis under this protocol and/or storage for future research: (REQUIRED)

(•) Yes ( ) No

* Could this study generate genetic data that may be broadly shared (e.g., submitted to NIH in compliance with **Genomic Data Sharing (GDS)/Genome-Wide Association Studies (GWAS)** requirements): **(REQUIRED)**

(•) Yes ( ) No

Please make sure your consent form includes the recommended genomic data sharing language.

7.13 STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed:

This study will involve DNA collection from patients with intellectual disability, metabolic disease, encephalopathy, seizures, birth defects and multiple congenital anomaly syndromes and we do not anticipate the enrollment of sufficient patients to justify statistical methods of data analysis. However, statistical analyses relating to genetic investigations will be performed according to standard methods.

7.14 REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with):

See attached bibliography.

8.0 Biospecimen Collection and/or Bank Administration

8.1 * TYPE OF SPECIMENS (check all that apply): (REQUIRED)

- [x] Blood (provide amount below)
- [ ] Tissue (describe below)
- [x] Other type of biospecimen, such as sputum, cerebrospinal fluid, buccal swabs, etc. (describe below)
- [ ] Existing/archival materials (name source below)

Briefly describe the types of biospecimens that will be collected. Provide the amount of blood, if applicable. For leftover/existing/archival material, identify the source:

We will collect venous blood from subjects who consent. In subjects who refuse venipuncture but who agree to a saliva sample, we will obtain a saliva sample or buccal swab using a commercial kit.

8.3 * SPECIMENS ARE: (check all that apply): (REQUIRED)

- [x] Leftover specimens from a clinical diagnostic or therapeutic procedure
- [ ] Specimens collected for research purposes only (including extra samples taken during a clinical procedure)
- [ ] Other

8.4 * FUTURE SPECIMEN USE: Will any specimens or portions of specimens be retained after the study is over for possible use in future research studies: (REQUIRED)

- (•) Yes
- ( ) No

8.5 * SPECIMEN BANKING - CONSENT METHOD: Consent for retaining specimens for future research studies will be obtained via (check all that apply): (REQUIRED)

- [x] Specimen section within a main research study consent form
- [ ] Separate specimen consent form
- [ ] UCSF surgical consent form with tissue donation brochure

8.6 * SPECIMEN DESTINATION: Indicate where specimens will ultimately be stored: (REQUIRED)

Outside Entities: Indicate where specimens will be sent if they will not remain at UCSF (choose at least one; check all that apply):

- [ ] Cooperative group bank
- [ ] NIH
- [ ] Other university or collaborator
- [ ] Industry sponsor
- [ ] Other
- [x] N/A - all specimens will remain at UCSF

Internal Storage: If specimens will remain at UCSF, in what kind of facility will they reside (choose at least one; check all that apply):

- [ ] UCSF repository/bank being established under this protocol
- [ ] Existing UCSF specimen repository/bank with IRB approval
- [ ] National cooperative group bank housed at UCSF
- [x] Other location at UCSF (please describe)
- [ ] N/A - no specimens will be retained at UCSF facilities

Please provide the name of the department, the program, and the physical location where the specimens will be housed. If the specimens will be stored in an already established bank, provide the name of the bank and its iRIS approval number.:

Genomic Medicine Laboratory (GML) at UCSF

8.8 * CLINICAL FOLLOW-UP DATA: Will clinical follow-up data be linked to specimens (i.e., will medical record information continue to be abstracted after the specimen is collected): (REQUIRED)

- (•) Yes
- ( ) No

Provide duration of follow-up or 'indefinitely':

the duration of the study

8.9 * UCSF-BANKED SPECIMENS - LINKING AND SHARING OF IDENTIFIERS: (REQUIRED)

- [ ] Samples are completely de-identified before being added to the bank/repository. There is no way to link the specimens back to the subjects.
- [x] Samples are coded and researchers are able to link the specimens to specific subjects.
- [ ] Samples are stored with direct identifiers in the repository.

Explain under what circumstances identifiers may be released with specimens or say 'None' if identifiers will **NEVER** be released with specimens:

Samples will not be sent with identifiers for future research.

8.10 UCSF-BANKED SPECIMENS – IDENTIFIERS: List the identifiers that will be collected, stored, or linked with the specimens:

- [x] Name

- [x] Date of birth
- [ ] Social Security number
- [x] Medical record number
- [ ] Address
- [ ] Phone number
- [ ] Email address
- [ ] Other dates (dates of surgery, visit dates)

8.11 DISTRIBUTION: Specimens banked at UCSF may be made available to (check all that apply):

- [x] UCSF researchers
- [ ] Non-UCSF researchers
- [ ] Industry
- [ ] None of the above - specimens will be retained and used within our own research program

8.12 UTILIZATION REVIEW: Is there a formal utilization review process for distribution of specimens:

○ Yes ◉ No

9.0 Drugs and Devices

9.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

○ Yes ◉ No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

Note: This question is frequently answered incorrectly. If any drugs or biologics, approved or unapproved, are being administered under this protocol, you should check 'Yes' unless you are *absolutely* sure that NONE of the drugs are part of the research protocol. Tip: Ask the PI or the sponsor if you are not sure how to answer this question.

9.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

◉ Yes ○ No

If you have questions about FDA requirements for drug or device research, you can send an email to request a consult.

9.4 * NSR: Are you requesting a Non-Significant Risk (NSR) determination for an investigational device: (REQUIRED) Note: an NSR determination is different from an Investigational Device Exemption (IDE). Check the Help link for more guidance on what types of devices can qualify for an NSR determination.

◉ Yes ○ No

* Explain why the use of the device in this study poses a non-significant risk: **(REQUIRED)**

-The device is not intended as an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject;

-The device (Illumina sequencer) is not purported or represented to be for a use in supporting or sustaining human life and does not present a potential for serious risk to the health, safety, or welfare of a subject;

-The device is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject; and

-The device otherwise does not present a potential for serious risk to the health, safety, or welfare of a subject.

Whole exome sequencing (WES) has been increasingly incorporated into laboratory genetic testing at academic and commercial laboratories. WES is aimed at detecting pathogenic sequence variants in patients with suspected genetic conditions and has become part of routine practice by Medical Geneticists, as well as an increasing number of clinicians from other medical specialties. Large case series from clinical laboratories (>2,800 patients) have confirmed the clinical validity of WES in the diagnosis of rare genetic diseases [1, 2]. Among subpopulations of patients, e.g. children with nervous system dysfunction, such as developmental delay, the diagnostic yield has been found to be as high as 41% [2]. In the Deciphering Developmental Disorders Study, which recruited >1,000 children with severe undiagnosed developmental disorders, WES combined with copy number analysis identified likely pathogenic variants in 28% of children [3]. These diagnostic yields are unprecedented and are not achievable with other testing strategies.

The purpose of WES is to identify an underlying etiology in patients with features suggestive of a genetic disorder, but without features diagnostic of a particular condition. Sequencing enables comprehensive screening that is not feasible with sequential single gene testing or gene panel testing. For individuals with rare genetic diseases, WES has proven invaluable in establishing a diagnosis, determining recurrence risk for patients and other family members, understanding prognosis, guiding therapies and health surveillance.

WES sequences the entire protein-coding region of the human genome in order to identify disease-causing variants. In the UCSF clinical exome test, blood or tissue is collected from a patient and his/her biologic parents. DNA libraries are prepared from each individual by capturing the exome (approximately 1-2% of an individual's entire genetic content). Libraries are then sequenced using Next Generation Sequencing (NGS) technologies. The aim of WES is to sequence the exome of each individual to a sufficient depth to detect variants; this requires tens of millions of 100 base pair sequences. The sequencing data is aligned to a reference genome and variants that differ from the reference are identified. Among the ~30,000-60,000 variants identified for each individual, filtering is performed to identify candidate variants that might be disease-causing and to filter out variants that are common in the healthy population and that are not predicted to alter protein function in the cell, or that occur in highly variable regions of DNA. Comparisons made between sequence variants in the proband and his/her parents are used to investigate different models of inheritance based on fundamental principles of Mendelian genetics. Ultimately, a focused list of variants is then reviewed for possible pathogenicity by experts in genetics, molecular pathology, and clinical medicine.

The UCSF Exome is designed to detect single nucleotide variants (SNVs). It may also detect small insertions or deletions (INDELs, typically <10bp). It is not designed to detect large insertions, large deletions, or structural rearrangements. Although on average, the vast majority of the exome will be covered by this test (99.6% at >10x during the validation), portions of the exome will be poorly covered in each test (which may include whole genes, select exons of genes or small regions of exons). Poor coverage may result from poor/absent capture during library preparation, difficulty in sequencing, or regions that are difficult to align to the reference sequence. Identification and interpretation of sequence variants is also limited by available databases and publications that provide the information for filtering, manual curation and interpretation of variants. Although the assay performed with high sensitivity and specificity during the validation process (see below), false positive or false negative results are possible, as for any test. False positive calls will be identified and eliminated by confirmatory Sanger sequencing. False negative results will also be investigated by Sanger sequencing in cases where there is a strong clinical suspicion for a gene of interest, such as an inherited condition with autosomal recessive inheritance, where the patient's phenotype matches the molecular genetic diagnosis, but a variant in just one allele was detected. Sanger sequencing uses custom-

designed primers, PCR amplification, and resolution using the Life Technologies 3500 capillary electrophoresis instrument.

Points to consider for IDE exempt device status for studies #17-22504 and 17-22420 based on Option C, Category 2 considerations:
The UCSF Genomic Medicine Initiative is currently undertaking two parallel studies to explore the clinical utility of whole exome sequencing in diverse patient populations including those in the pediatric and prenatal milieus. Specifically, IRB study #17-22504 *Program in Prenatal and Pediatric Genomic Sequencing (P3EGS*) and study #17-*22420 The Clinical Utility of Prenatal Whole Exome Sequencing*. These are investigator initiated studies and all study participants will be identified, counseled and consented by clinical geneticists or genetic counselors associated with the study.

Genetic counseling will be part of the informed consent process for all potential participants, in order to mitigate risk. Counseling will be offered by either a Certified Genetic Counselor, a Board-Certified or Board Eligible Clinical Geneticist, or in some cases both. This counseling will include a detailed discussion of the benefits, limits and risks to the primary study participant and their families from undergoing whole exome sequencing, as outlined in the respective patient consent forms. Additionally, for those that elect to pursue WES, a clinical geneticist or genetic counselor will review the WES results and discuss appropriate follow-up and management with the family.

To assure that our genetic counseling practices are understood by the diverse population that will participate in this study, we have developed a formal community engagement process that is described in the application. Following the initial engagement, several community members will be appointed to our Ethics Advisory Board for the P3EGS study. The board will meet regularly to address issues that might arise. The board will also review all materials developed for recruitment and will offer advice on the informed consent process. All of our materials will be translated into Spanish. Certified interpreters will be used for other, less common language groups. Finally, one of our project Co-Investigators, Galen Joseph, is nationally known for her pioneering work on genetic counseling in diverse populations and across language barriers. Her work has paved the way for counseling innovations that improve the understanding of low literacy groups. She will be part of the Ethics Advisory Board.

These studies should both be considered IDE exempt device studies under Category 2 considerations for the reasons articulated below.

We are using WES to identify a unifying genetic cause for developmental delays/intellectual disability, congenital anomalies, seizures, encephalopathy or neuromuscular conditions. The WES is therefore being used as a diagnostic test.
Samples obtained for WES will be collected by either blood draw or saliva sample for the pediatric patients (study #17-22504) and all parent participants. We may also use DNA derived from a specimen that was previously obtained for other diagnostic purposes, including microarray analysis. For participants undergoing WES in the prenatal study (study #17-22420), DNA samples submitted for WES will be derived from a previously obtained specimen -- an entry criterion for the prenatal study is that all participants will have previously undergone prenatal genetic diagnosis by established methods of karyotyping and/or chromosomal microarray analysis.
No invasive procedures other than a simple blood draw are connected with the use of the WES test in either study.
The testing does not introduce energy into study participants. All imaging performed for inclusion criteria in the prenatal arm is clinically indicated and will have been completed prior to enrollment by the patient's clinical provider(s). Magnetic resonance imaging (MRI) or computerized tomography (CT) scan will not be used for diagnosis of a fetal anomaly as part of this study.
To mitigate the risk for a false positive result from the WES pipeline, all sequence variants with clinical relevance that will be reported will be confirmed by Sanger sequencing, a test that is the current laboratory "gold standard" for variant detection. We anticipate that WES in both the pediatric and prenatal studies will yield an underlying genetic cause in approximately 30-40% of patients tested. The majority of study participants will therefore have non-informative test results. When appropriate, Sanger sequencing may be applied to investigate genes in which there is high clinical suspicion for sequence variants that may have been missed by WES.

Any necessary language for labeling will be applied.

Attach any documentation you have from the manufacturer and/or FDA to support this determination.

9.5 LIST THE DEVICES: List the medical devices or in vitro diagnostics to be studied or used. In the device details screen you will be asked questions such as:

- **Whether the device is FDA approved or investigational**
- **Medicare device category**
- **If the device will be provided at no cost**
- **If an IDE is necessary, the IDE number, and who holds the IDE**
- **Risk category of the device**
- **FDA status of the device**

Please see the UCSF IRB website for more details about the use of devices in research, including the Investigator Checklist for Significant Risk, Non-Significant Risk, and/or IDE Exempt Device Studies
Verification of IDE numbers: If the sponsor's protocol does not list the IDE number, you must submit documentation from the sponsor or FDA identifying the IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet. If you have any correspondence from the FDA or sponsor regarding this device, please attach it to the application.

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	Illumina Sequencer	No	Yes	

Manufacturer/Supplier of Device	Illumina
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	Parnassus
Will Devices be supplied at no Cost	Yes
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	No
Is this a new device or a new use of an already approved device	Yes
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE details	These studies should both be considered IDE exempt device studies under Category 2 considerations.
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

9.6 * EXPANDED ACCESS: Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (REQUIRED)

○ Yes ◉ No

10.0 Sample Size and Eligibility Criteria

10.1 ENROLLMENT TARGET: How many people will you enroll:

up to 800 families

If there are multiple participant groups, indicate how many people will be in each group:

Our enrollment goals for patients include up to 800 probands and up to 1700 biological parents or other family members.

There are no power calculations associated with this study. We chose 800 patients to maximize enrollment of pediatric patients with likely genetic diagnoses within the cost restraints of the grant. Patients will be enrolled with one or two biological parents, and in some cases with affected siblings as well.

We also estimate enrolling approximately 25 physicians who have referred patients to the study. These referring physicians, most of whom are study investigators, will be asked to complete surveys primarily meant to assess the clinical utility of exome sequencing for the patients they referred and to provide limited information about their own background.

We estimate enrolling approximately 10 administrators or clinicians at UCSF to complete the ORCA questionnaire.

10.3 SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites:

Our enrollment goals for patients include up to 800 probands and up to 1700 biological parents or other family members.

There are no power calculations associated with this study. We chose 800 patients to maximize enrollment of pediatric patients with likely genetic diagnoses within the cost restraints of the grant. Patients will be enrolled with one or two biological parents, and in some cases with affected siblings as well.

We also estimate enrolling approximately 25 physicians who have referred patients to the study. These referring physicians, most of whom are study investigators, will be asked to complete surveys primarily meant to assess the clinical utility of exome sequencing for the patients they referred and to provide limited information about their own background.

We estimate enrolling approximately 10 administrators or clinicians at UCSF to complete the ORCA questionnaire.

10.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- [x] 0-6 years
- [x] 7-12 years
- [x] 13-17 years
- [x] 18-64 years
- [ ] 65+

10.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- [x] Inpatients
- [x] Outpatients
- [ ] Family members or caregivers
- [ ] Providers
- [ ] People who have a condition but who are not being seen as patients
- [x] Healthy volunteers
- [ ] Students
- [x] Staff of UCSF or affiliated institutions

☐ None of the above

10.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

☑ Children / Minors
☑ Adult subjects unable to consent for themselves
☐ Adult subjects unable to consent for themselves (emergency setting)
☑ Subjects with diminished capacity to consent
☑ Subjects unable to read, speak or understand English
☑ Pregnant women
☐ Fetuses
☑ Neonates
☐ Prisoners
☑ Economically or educationally disadvantaged persons
☐ None of the above

If not already addressed in the Background and Significance questions in the Research Plan section or elsewhere, explain why it is appropriate to include the types of subjects checked above in this particular study:

We would plan to include minors or adults who are mentally impaired and persons who are unable to give consent for themselves in this study. We will use impartial observers (a physician who is not a study investigator) to determine the ability of a study subject to give consent. We will use the assent process for persons who are judged to have mental competence above that of an average seven-year old as judged by an impartial observer. For the consent for minors, an assent form and a guardian consent form have been prepared. If the study subject has cognitive impairment, we will use a surrogate for the consent process according to the guidelines of the University of California for consent in a non-emergency setting. Prior to consent, we will explain the nature of the research and the risks and benefits of surrogate participation to both the subject and the surrogate. The alternatives to participation will also be explained. For the surrogate, we will try to ensure that the surrogate has adequate knowledge of the study, that they are familiar with the subject's degree of mental impairment and that they are willing to serve as the substitute decision maker. We will ask the surrogate to make the decision about research participation based on the subject's known preferences or based upon a judgement of what the subject's preferences would be. The surrogate must also complete a self-certification form.
We would plan to include pregnant women in this study. The pregnant women will be involved in the study in the same way that non-pregnant women will be involved in the study, but we would not study the unborn children of the pregnant women.
We will offer the study and participation in the study to every ethnic population group. We will provide consent forms that are translated for families who speak Spanish, but for other languages, we will use certified translators for those who speak other languages rather than English, as a first language.

The providers who refer patients to our study will be asked if they are willing to participate in provider surveys to assess the clinical utility of exome sequencing for the patient(s) they referred and characterize their experience with and comfort level with genetics. As most of our referring providers are study investigators, the majority of those participating will also be study investigators. There may also be other non-investigator UCSF/SFGH/BCHO physicians who refer patients and whom we ask to participate.

Administrators and clinical staff who are involved with the research study may be asked to fill out a survey. The survey is regarding organizational readiness to change (ORCA). The ORCA is designed to evaluate the potential for healthcare systems, hospitals, and clinics to adapt when new healthcare practices and clinical services are introduced. We will ask six to ten executives, administrators, managers, or clinicians at each site participating in your project. Respondents of interest include hospital or healthcare system executives, administrators, and managers in roles such as chief executive officer, chief operating officer, chief of staff, vice president of patient care, chief financial officer, service chief, director, manager, supervisor, or clinician. Our principal investigators will identify respondants who are qualified to answer these questions.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Here are some examples:

- evaluating capacity to consent for individuals who may be decisionally impaired (specify how)
- calibrating payment amounts to be non-coercive for the financially disadvantaged
- conducting more in-depth evaluations of subjects' understanding of the study and the voluntary nature of participation
- involving advocates in the consent process

More information and other safeguards are described here: **Vulnerable Subject Populations** and **Recruiting Staff and Students**.

Patients will have study alternatives explained to them and have the right to refuse to participate. They also have the right to withdraw and have their samples destroyed at any time.

Providers also have the right to decline to participate in the surveys.

Administrators and other study staff and clinicians also have the right to decline to participate in the surveys.

10.7 INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.):

For patients:

1. Presenting clinical features suggestive of a genetic etiology, including ID, seizures, multiple congenital anomalies, metabolic conditions, and neurodegenerative conditions or idiopathic CP; 80 of these patients will have encephalopathy or multiple congenital anomalies so that they may benefit from rapid exome sequencing in the PICU or NICU. A total of 800 will be recruited, of which a minimum of 60% will be from URMs.
2. A minimum of one biological parent is available and willing to provide a biospecimen for WES, with a preference for two available parents. At least one parent consenting to WES of the child.
3. Pediatric patients must have had at least one prior genetics appointment or evaluation
4. Patients must have had a single nucleotide polymorphism (SNP) array or oligonucleotide array that did not provide a diagnosis, unless the principal investigator exempts the patient from this requirement due to having a condition for which array has a low diagnostic yield.
5. Proband must be under 26yo at time of enrollment.

For physicians:
1. We will enroll physicians in the study and ask them to complete surveys if they have referred at least one patient to the P3EGS study.

10.8 EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study):

For patients:

1. Prior WES performed for a clinical or research indication
2. Lack of phenotypic indication of a likely underlying genetic etiology
3. Both biological parents are unavailable.

For physicians:
1. They have not referred a patient to P3EGS.

10.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on any patient care units including inpatient wards, peri- or post-operative care units, operating rooms, or in the Emergency Department at UCSF Health medical facilities: (REQUIRED)

○ Yes ◉ No

10.10 * INTENSIVE CARE NURSERY (ICN): Will you be enrolling any babies who are admitted to the Intensive Care Nursery (ICN) (this includes critically ill babies as well as lower acuity patients who need overnight monitoring and support): (REQUIRED)

◉ Yes ○ No

Research projects recruiting in the ICN involve Screening Services provided by the CTSI CRS. This service is provided at no cost but they still need you to complete the **CRS Budget Request Form.** In the form, under 'Requested CRS Resources,' NCRC Coordinator, please check the box for 'Screening.' If you are requesting any other CRS services, complete the remainder of the form to receive a budget estimate. **Please contact the Nurse Manager, Kim Johnston via email or phone at 415-353-9672 to review your needs for this study.**

10.11 * EMERGENCY DEPARTMENT: Does your protocol or study involve any of the following patient related activities in the emergency department (e.g. subject identification, recruitment, consent, blood draws, specimen retrieval, involvement of ED staff (nursing, tech, and/or physician), or any other ED based procedures): (REQUIRED)

○ Yes ◉ No

11.0 Inclusion of Minors in Research

11.1 REGULATORY CATEGORIES OF RESEARCH: Select all the regulatory categories that apply:

- ☑ No greater than minimal risk (45 CFR 46.404, 21 CFR 50.51)
- ☐ Greater than minimal risk but presenting prospect of direct benefit (45 CFR 46.405, 21 CFR 50.52)
- ☐ Greater than minimal risk (though only a minor increase over minimal risk) and no prospect of direct benefit but likely to yield generalizable knowledge about the subjects disorder or condition (45 CFR 46.406, 21 CFR 50.53)
- ☐ Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407, 21 CFR 50.54)

Explain why the research in this study falls under the above category or categories:

The risks from venepucture and from data deposition in a shared scientific database are relatively small, and yet future patients may potentially benefit if a genetic cause is found for their medical condition.

11.2 MINORS CONSENTING: Will this study enroll minors who can legally consent for themselves (as in the case of emancipated minors or minors being treated for pregnancy or drug use without their parents knowing). This is different from agreeing to be in the study even when their parents are the ones providing 'official' consent, which we refer to as 'providing assent':

Note: This is very rare and the answer is usually 'No.'

○ Yes ◉ No

11.3 PARENTAL PERMISSION VS. WAIVER: Please review the guidance to see under what circumstances the IRB can waive parental permission.

- ☑ Parental permission will be obtained
- ☐ Waiver of parental permission is requested: The waiver meets the provisions for a waiver of consent (i.e., the research poses minimal risk, it could not practicably be carried out without the waiver of parental permission, AND the waiver will not adversely affect the rights and welfare of the minor participants (45 CFR 46.116(d))
- ☐ Waiver of parental permission is requested: Parental permission is not a reasonable requirement to protect the minor (e.g. neglected or abused children) or parental knowledge of the study may endanger the health or welfare of the minor (45 CRF 46.408(c))

Provide details on the other protections that will be in place:

11.4 ASSENT OF MINORS OR WAIVER: Please review the guidance to see under what circumstances the IRB can waive assent.

- ☑ Assent of children developmentally and psychologically able to provide assent will be obtained
- ☐ Waiver of assent is requested: The capability of some or all of the children is so limited that they cannot reasonably be consulted
- ☐ Waiver of assent is requested: The research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research
- ☐ Waiver of assent is requested: The activities involving the minor are limited to chart review or the something equally innocuous
- ☐ Waiver of assent is requested: It is not culturally appropriate to involve the minor in the decision to participate (e.g. some foreign research)

11.5 DOCUMENTATION OF PERMISSION AND ASSENT: (select all that will be used):

- ☐ Permission form addressed to the parents
- ☑ Simplified assent form addressed to the child, 7-12 years old (parents get separate form)
- ☑ Assent form addressed to the child, 13 years and older (for subjects and parents)
- ☐ Assent form addressed to the child, 13 years and older (parents get separate form)

Check one:

- ◉ One parent's signature will be obtained
- ○ Two parents' signatures will be obtained

If this study is approvable under regulatory category .405 and you plan to get permission from only one parent, explain why you think one parent's permission is sufficient:

The only invasive procedure in this study is venepuncture, and clinical decisions regarding this procedure are frequently made by one parent.

11.6 WARDS OF THE STATE: Might this study enroll wards of the state:

◉ Yes ○ No

11.7 WARDS JUSTIFICATION: It is appropriate to enroll wards in this study because:

We do not anticipate that it will be common that we will enroll wards of state. However, we will offer study participation to all potentially affected individuals, including wards of state as appropriate.

12.0 Recruitment and Consent

12.1 * COMPETITIVE ENROLLMENT: Is this a competitive enrollment clinical trial? By competitive enrollment, we mean that sites who do not enroll participants early may not get to participate at all: (REQUIRED)

- ○ Yes
- ◉ No

12.2 * SUBJECT IDENTIFICATION METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- ☑ Review of patients' conditions, history, test results, etc. (includes patients seen in clinic, scheduled for surgery, a procedure, imaging, or tests, or seen in the Emergency Department as well as searching through medical record data for possible cohort identification)
- ☐ Already approved recruitment registry
- ☐ Re-contact of participants from the investigators' previous studies
- ☑ Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- ☐ Referrals from the community / word of mouth
- ☐ Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- ☐ Online recruiting tool (describe below)
- ☑ CTSI Recruitment Services unit
- ☑ Posting on UCSF Clinical Trials, ClinicalTrials.gov or other publicly available clinical trial website
- ☑ Other method (describe below)

* Provide details about the subject identification methods: **(REQUIRED)**

We have created a brochure to hand out in clinic to explain the the study to potential participants. We may also mail the brochure to potential study participants who have been identified as candidates by study clinicians, but only after someone from the study team has discussed the study with the family at an in person clinic visit or over the phone.

12.3 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

- ☑ Investigators' own patients or patients seen within the same practice
- ☑ Patients not under the care of the investigators

How and by whom will records be accessed and searched (check all that apply):

- ☑ Self-search in APeX or other medical records source
- ☐ Self-search using UCSF's Research Cohort Selection Tool
- ☑ CTSI Consultation Service Recruitment Services
- ☐ UCSF Academic Research Services (ARS)
- ☐ University of California Research Exchange (UC ReX)
- ☐ Other method (describe below)

12.4 DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined:

All study activities will take place at outpatient clinic visits or inpatient consults, so that families will not be required to schedule additional medical visits. We anticipate that ascertainment of infants and children will occur most frequently in outpatient General Genetics, Neurology or Neurometabolic clinics or in the NICU or PICU. All patients will have had at least one previous outpatient or inpatient encounter with a study clinician (Geneticist or Child Neurologist) to establish care. These encounters prior to study entry will enable clinicians to determine if whole exome sequencing is an appropriate next step for patient care and tabulate the underrepresented minority status and socioeconomic status of the patient and family, in addition to establishing a therapeutic relationship with the family. All patients entering the study will also have had clinical genetic testing as appropriate to their presenting complaint that was achievable with their insurance (for example, fragile X testing for patients with ID), including CMA or a single nucleotide polymorphism (SNP) array to exclude clinically significant copy number variants prior to study entry.

Outpatients will be referred to the study by a clinician. Inpatients may be referred by clinicians or may be identified by the study team through chart review. In the latter situation, the study team (genetic counselor, study coordinator, principal investigator), will do periodic chart review of the patient lists in the ICN and PICU to identify eligible patients. Once identified, the study team will contact the patient's care team to ask for permission to approach the family.

12.5 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [x] Investigators/study team
- [ ] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [x] Potential participant
- [ ] Other (explain below)

12.6 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [x] In person
- [x] Phone
- [ ] Letter / email
- [ ] Website or app
- [x] Other (explain below)

Attach the telephone recruitment script in the Other Study Documents section of the Initial Review Submission Packet Form. If potential participants will initiate contact, attach the telephone screening script that will be used to provide more information about the study and determine if callers are eligible to participate.

12.7 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

The key clinicians from each of our study sites will ascertain and recruit patients together with dedicated genetic counselors and research assistants who will be located on-site.

We are also utilizing phone and telehealth to recruit.

The providers who refer patients to the study will also be asked to participate in provider surveys. They will be asked via email after they have reffered a patient who has been enrolled. The majority of the referring providers are study investigators.

12.8 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [x] Sign a paper consent form at the end of the consent discussion (signed consent)
- [ ] Sign an electronic consent form using DocuSign (signed consent)
- [ ] Provide online consent through an app, a website, or a survey tool such as Qualtrics or REDCap (waiver of signed consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent - waiver of signed consent)
- [x] Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent - waiver of signed consent)
- [ ] Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)
- [ ] Not be able to provide consent (emergency waiver of consent - allowed for minimal risk research or greater than minimal risk research with an approved community consultation plan)
- [ ] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

12.9 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**
- **For studies using online recruitment and consent or consent via mail, provide details here.**

Consent from patients will be obtained by study investigators. An explanation of the study and consent procedure together with the consent forms and the UCSF Experimental Subject's Bill of Rights will be provided by the study investigators to the patient and family when they are first approached. If the patient and family need more time to consider the research, another meeting for consent will be scheduled if the family agrees to this. The consent forms will then be signed at the second meeting. If the family is comfortable with the study, they may sign the consent forms and return them to the study investigator after the initial or second approach. It is anticipated that some families may not choose to retain the forms after the first approach, and that new consent forms may be needed for a second approach if they agree. If siblings under the age of 18 are also asked to participate in the study, parents will be asked to sign a separate consent form fpr each child.

Verbal consent for the ethnographical observations will take place in advance of the results session, either in person at the time of the family consent or by telephone. Before results are discussed, the study investigator in contact with the family will ask them if someone from the study team can observe and/or videorecord the results visit or phone call. They will also ask if the family would be willing to be interviewed about their experience of having WES testing. Choosing yes or no will not affect the family's medical care, or participation in the rest of this study.

Consent from the referring providers will be implicit if they agree to return the surveys that are emailed to them. We have requested a waiver of documentation of consent and have attached the email we plan to send to the providers.

Consent from the administrators, managers, etc. who will answer the ORCA questionnaire will be implicit if they agree to return the surveys that are emailed to them. We have requested a waiver of documentation of consent and have attached the email we plan to send to the providers.

* It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: **(REQUIRED)**

Patient informed consent will be obtained by trained, licenced genetic counselors and/or medical geneticists with extensive exerpience obtaining informed consent for exome sequencing and research participation.

12.10 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

- [x] The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation
- [ ] Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or through a mobile health app)
- [x] Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

We will provide study participants with the opportunity to ask questions and check their comprehension of a few key facts by asking them about their understanding of the study.

12.12 * NON-ENGLISH CONSENT METHOD: Indicate which method(s) you will use to consent non-English speaking subjects: (REQUIRED)

- [x] Preferred Method—Consent form and other study documents will be available in the subject's primary language Personnel able to discuss participation in the patient's language will be present for the consent process.
- [x] Short-Form—A qualified interpreter will translate the consent form verbally, and subjects will be given the Experimental Subject's Bill of Rights in their primary language, following instructions in Those Who do not Read, Speak or Understand English for required witnessing and signatures

* Explain how you will maintain the ability to communicate with non-English speakers throughout their participation in the study: **(REQUIRED)**

We will use qualified interpreters from Language Line Solutions and/or in-person interpreters based at the various recruitment sites.

12.13 * WAIVER OF DOCUMENTATION OF SIGNED CONSENT: Select the regulatory category under which the IRB may waive the requirement to obtain *signed* consent for this study:

- ○ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject

will be asked whether they want documentation linking them with the research. 46.117(c)(1)

- (•) The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. 46.117(c) (2)

12.14 TIME: What is the estimated time commitment for participants (per visit and in total):

The time required for participation in this study for patients includes reading of the consent form, a discussion to obtain consent and for questions (up to 1-2 hours) and sample collection (up to 30 minutes). The study will also include follow up visits at 3 and 6-12 months after whole exome sequencing to assess clinical utility.

For referring providers who agree to participate in our provider survey it will take approximately 10-15 min per patient referred.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

13.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when medical records may be reviewed to determine eligibility for recruitment.

13.1 * PRACTICABILITY OF OBTAINING CONSENT PRIOR TO ACCESS: Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified: (REQUIRED)

- (•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

13.2 * RISK TO PRIVACY: A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

13.3 * RIGHTS/WELFARE: Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

13.4 * IDENTIFIERS: Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [x] Email addresses

- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

13.5 * HEALTH INFORMATION: Describe any health information that will be collected prior to obtaining informed consent:

Physicians referring patients to the study submit screening forms to the study team that include names, DOBs, MRNs, address and phone number of the patient. This information is stored securely in Redcap.

Note: HIPAA requires that you collect the minimum necessary.

13.6 * DATA RETENTION/DESTRUCTION PLAN: Describe your plan to destroy any identifiable data collected to determine eligibility for recruitment. This should be done at the earliest opportunity. If you plan to retain identifiable recruitment data, provide the justification for doing so:

Information from those who did not qualify for the study or were not enrolled in the study will be deleted after the conclusion of the study; if subjects consent, our consent will include HIPAA language that enables us to link their medical information with a study number.

14.0 Risks and Benefits

14.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- [ ] For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- [ ] Risks associated with radiation exposure for imaging studies specifically for research purposes
- [ ] Risks associated with the administration of contrast agent for imaging studies
- [ ] Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- [ ] For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- [ ] For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- [ ] Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- [x] Risk of pain or physical discomfort caused by the research intervention
- [x] Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

14.2 * RISKS: Describe any anticipated risks and discomforts not listed above: (REQUIRED)

The physical risks from blood drawing or obtaining saliva are very small. There is usually a short-lived pain with a needle stick for a blood draw and there may be bruises at the place of the needle stick. There is also a very small chance of infection, excess bleeding or fainting (feeling lightheaded) from blood drawing. The risk involved will not be any different from that experienced during any clinical blood test. The amount of blood taken will not be enough to cause anemia. Saliva sample collection and buccal swab collection are non-invasive and don't pose any significant risks.

In some genetic studies, emotional and psychological risks are also possible. Some people are concerned that research about genetic causes of illness may give information that is not only about themselves, but also about their relatives and other groups of people who are like them. We will not provide information about the health of participants to other family members or other people, apart from family members who sign consent and participate in this study, such as parents. Issues of adoption and paternity (biological fatherhood) may be discovered from this study. We will not discuss such information with study subjects unless it has direct medical implications for them or their families, which is unlikely.

To do more powerful research, it is helpful for researchers to share information that they get from studying human samples by putting it into one or more scientific databases. Some of the genetic and health information from participants will be placed into a scientific database called "dbGaP" that is maintained by the National Institutes of Health. Some of the genetic and health information from participants may also be placed in another database called “ClinVar” that is maintained by the National Institutes of Health. For both databases, a researcher who wants to study the information must apply and be approved to use the database. Researchers with an approved study may be able to see and use participant information (along with that of many other people), but names and other identifiers (such as address or social security number) will not be placed into the scientific database. As genetic information is unique to study participants, however, there is a small chance that someone could trace it back to an individual subject. The risk of this happening is very small, but may grow in the future.

Subjects may be concerned that someone could get access to their genetic information and that it could be misused; for example, if genetic information suggested something serious about a participant's health, it could be used to make it harder for that person to get or keep a job or insurance. These problems may also occur if subjects disclose information themselves or agree to have research records released. There are laws in place that make it illegal for an employer or health insurance company to discriminate against an individual based on their genetic information.

Participation in research will involve a loss of privacy, but information about subjects will be handled as confidentially as possible. Participant names will not be used in any published reports about this study.

14.3

MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study**
- **having a plan for evaluation and possible referral of subjects who report suicidal ideation**

The risks of participation in this protocol for subjects and their families are small. They include the risks and discomfort from venipuncture such as bruising and bleeding, light-headedness and syncope. The psychological risks include the disclosure of affected status and family relationships from the publication of clinical details at conferences or in medical journals. Attempts will be made to minimize these risks by publishing the minimum amount of clinical material and by preserving anonymity. The benefits from this protocol include the identification of genetic loci and causative genes for medical conditions and the sharing of variant data with other reserachers. We will also gain valuable insights into the clinical utility of whole exome sequencing. However, there may be no direct benefits to the subjects of this study.

14.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained

and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

- **the proximity of an emergency facility for care of participant injury**
- **availability of psychological support after participation**
- **resources for participant communication, such as language translation services**

We will minimize the effects of venipuncture by offering saliva collection to those who do not want a blood draw. Adverse effects of venipuncture and adverse psychological effects due to research participation will be reported as required to the CHR if they occur. If injury occurs from a procedure performed in this study, treatment will be made available. The costs of this treatment may be provided by the University, depending on a number of factors. UCSF does not normally provide any alternative form of compensation for injury. For further information about this, the subjects may call the office of the Committee on Human Research at (415) 476-1814 or write to that office at Box 0616, University of California San Francisco, San Francisco, CA 94143-0616.

To minimize the risk of loss of privacy to providers who particpate in the study by answering survey questions we will pool the responses from all four study sites (UCSF, UCSF Fresno, BCHO, ZSFGH). The survey does not ask for the place of employment of the provider, so this will increase the total number of responses and should reduce the chances that any one provider could be identified. We have also added a sentence into our email template about the risk of loss of privacy.

To minimize the risk of loss of privacy associated with the ORCA survey given to administrators and clinicians at UCSF we have made the survey anonymous--it does not ask for personal information from the respondent. The only information we will know about the respondent is which institution they are employed and answers to questions on the survey. Since the survey is anonymous we believe the risk is minimal.

14.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [x] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [ ] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [x] Health and lifestyle changes may occur as a result of participation
- [x] Knowledge may be gained about their health and health conditions
- [x] Feeling of contribution to knowledge in the health or social sciences field
- [x] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [ ] Other benefit (describe below)
- [ ] None

14.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

The risks of participation in this protocol for subjects and their relatives if they consent include:
(1) the risks and discomfort from venipuncture such as bruising and bleeding, light-headedness and syncope
(2) the psychological risks from the disclosure of affected status and family relationships from the publication of clinical details at conferences or in medical journals.
(3) The risks of subject identification following data despoition in a shared scientific database.
However, the benefits, if new genes are identified, could be substantial in terms of improved patient care. In addition, assessing clinical utility is also likely to be helpful for patient care.

15.0 Confidentiality, Privacy, and Data Security

15.1 PROTECTING PRIVACY: Indicate how subject privacy will be protected:

- [x] Conduct conversations about the research in a private room
- [x] Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- [ ] Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission
- [ ] Other methods (describe below)

15.2 SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior:

- ( ) Yes
- (•) No

15.3 SIGNIFICANT CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation:

- (•) Yes
- ( ) No

Check all that apply:

- [x] Embarrassment
- [ ] Criminal or civil liability
- [ ] Loss of state or federal benefits
- [x] Damaging to the participant's financial standing, employability, or reputation
- [x] Potential risks to insurability (health, disability, or life insurance)

Describe the potential consequences:

Loss of privacy may result in recognition of an individual or a family, or that an individual or family are from a particular ethnicity or cultural group. Loss of privacy may occur from publication of a family pedigree or a photograph or through identification of a participant from genetic data deposited into a shared scientific database. This may conceivably lead to stigmatization or to discrimination regarding healthcare or insurance, although the chances of this happening are very small. We are almost always able to share papers that are being written with the family prior to submission to a journal so that they are comfortable with the submitted material.

15.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

We are almost always able to share papers that are being written with the family prior to submission to a journal so that they are comfortable with the submitted material. We would discuss modifying papers prior to submission if the family indicated that they felt uncomfortable.

15.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others: (REQUIRED)

- ( ) Yes
- (•) No

15.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obtain a Certificate of Confidentiality:

- (•) Yes
- ( ) No

Please include the recommended Certificate of Confidentiality language in the consent form.

15.7 SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers:

(•) Yes ( ) No

Note: This is unusual and not recommended, particularly in cases where the tests are carried out in a non-CLIA certified laboratory, the results are of unproven clinical significance, or where there are not known preventative strategies and/or treatments. If these are the most likely scenarios for your study, you should check 'No.'

If you have an incidental finding of clear clinical significance, call the HRPP QIU at 415-476-1814 for a consult.

Explain under what circumstances research results may be shared:

We will be providing exome sequencing results to the participants and their health care providers from this study. Families will decide if they wish to receive secondary findings unrelated to the indication for exome sequencing at the time of the consent process.
Both parents, when present as part of the biological trio, must agree to hear about secondary findings, or these will not be returned. These results will not be included in the medical records of the parents. We will not be releasing results such as APOE4 and Huntington's, as there are no definitive treatments available. For secondary findings that relate to adult onset disorders, we will report them and include them even if the child is not 18 years of age. Children may leave the area and not be traceable if the results are not released, and they cannot be stored without confidentiality risks.

15.9 * HIPAA APPLICABILITY: Study data will be: (REQUIRED)

- [x] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [x] Added to the hospital or clinical medical record
- [x] Created or collected as part of health care
- [x] Used to make health care decisions
- [x] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained ONLY from a foreign country or countries
- [ ] Obtained ONLY from records open to the public
- [ ] Obtained from existing research records
- [ ] None of the above
- [ ] Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH

In addition to signing a consent form, each subject will have to sign the UCSF Research Subject Authorization Form (HIPAA Form). Upload the HIPAA Authorization Form in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to have patients sign the HIPAA Authorization is one of the most common findings from QIU Routine Site Visits. Please call the IRB office at 415-476-1814 if you have questions about HIPAA research requirements.

If derived from a medical record, identify source:

UCSF medical record or other patient medical record

15.10 * IDENTIFIERS: Check all identifiers that will be collected and included in the research records, even temporarily: (REQUIRED)

- [x] Names
- [x] Dates
- [x] Postal addresses (if only requesting/receiving zip codes check Yes to the Zip Code question below instead of checking this box)
- [x] Phone numbers
- [ ] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [x] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

(•) Yes ( ) No

15.11 * ZIP CODES: Some research data sets include zip codes. Will you be receiving data with zip codes as the only portion of an address: (REQUIRED)

Checking 'Yes' here means that you will not be requesting access to any other data element of a patient's address. If you are requesting other parts of an address such as street names and address numbers, check 'No' here and check the box for 'Postal addresses' in the list of 18 PHI Identifiers in the previous question.

( ) Yes (•) No

15.12 * PATIENT RECORDS: Will health information or other clinical data be accessed from UCSF Health, Benioff Children's Hospital Oakland, or Zuckerberg San Francisco General (ZSFG): (REQUIRED)

(•) Yes ( ) No

15.13 * CLINICAL DATA - GENERAL DESCRIPTION: Provide a general description of the types of clinical data that you are requesting access to: (REQUIRED)

We have requested access to patients' medical entire medical records because data regarding the patient's medical history and phenotype is required by the laboratory in order to inform the

analysis of exome data, allows us to learn about the natural history and phenotypes of very rare conditions as part of this research study, and is also needed to assess the clinical utility of exome sequencing, which is a major focus of this study.

15.14 * CHART/CLINIC NOTES AND OTHER FREE TEXT FIELDS: Will the medical record data include any information extracted from free text fields: (REQUIRED)

(•) Yes ( ) No

Data sets that include free text from fields such as chart notes, clinic notes, and other text fields are considered identifiable, even without direct identifiers.

15.15 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)

- [ ] Drug or alcohol abuse, diagnosis or treatment
- [ ] HIV/AIDS testing information
- [x] Genetic testing information
- [ ] Mental health diagnosis or treatment
- [ ] None of the above

Important note: Ensure that participants initial the corresponding line(s) in Section C of the HIPAA authorization form during the consent process.

15.16 * ACCESS TO OTHER SENSITIVE OR PROTECTED DATA: Are you requesting access to any sensitive health data not protected under HIPAA (any other health history that patients would expect to be kept private such as records relating to treatment for obesity, STDs, compulsive behaviors, embarrassing health conditions, sexual orientation and practices, etc.): (REQUIRED)

(•) Yes ( ) No

* List the types of sensitive data and provide a scientific justification to support the request. The IRB may require additional safeguards to protect the confidentiality of participants: **(REQUIRED)**

Some types of sensitive infomation may be utilized to help identify a diagnosis through exome sequencing. For example, we summarize the patient's phenotype for the laboratory so that it can inform their analysis of the exome data and so if they identify a genetic variant that may be diagnostic, they will be able to ascertain whether the associated phenotype fits with our patient's phenotype and the expected inheritence pattern. Such sensitive information could include descriptions of psychiatric symptoms that may be suggestive of a specific genetic condition, or consanguinity (which suggests that the lab should be looking for variants in genes associated with autosomal recessive conditions).

15.18 * IDENTIFIABILITY OF FINAL DATA SET: (REQUIRED)

Which type of data set are you requesting IRB approval for:

A de-identified data set does not include ANY of the 18 HIPAA identifiers in the list above or any free text fields.

A limited data set (LDS) is described as health information that excludes direct identifiers but that may include:

- City
- State

- ZIP Code
- Elements of date (including dates such as admission, discharge, service, month and year)
- Other numbers, characteristics, or codes not listed as direct identifiers, including ages in years, months or days or hours

Identifiable data sets include direct identifiers and/or information from free text fields.
Review the **HIPAA FAQs on the IRB website** for more details about identifiability of data sets.

- ○ De-identified data set
- ○ Limited data set
- ○ Identifiable data set without direct identifiers (includes free text fields)
- ◉ Identifiable data set with direct identifiers (may or may not also include free text fields)

15.19 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- ☐ Electronic case report form systems (eCRFs), such as OnCore or sponsor-provided clinical trial management portal
- ☑ UCSF ITS approved Web-based online survey tools: Qualtrics or RedCap
- ☐ Other web-based online surveys or computer-assisted interview tool
- ☐ Mobile applications (mobile or tablet-based)
- ☐ Text Messaging
- ☐ Wearable devices
- ☐ Audio/video recordings
- ☐ Photographs
- ☑ Paper-based (surveys, logs, diaries, etc.)
- ☐ Other:

* What online survey or computer assisted interview tool will you use: **(REQUIRED)**

- ☐ Qualtrics (Recommended)
- ☑ RedCAP (Recommended)
- ☐ Survey Monkey (NOT recommended and may require UCSF ITS Security review)
- ☐ Other

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

- ☐ Study sponsor
- ☑ UCSF data center (including OnCore, RedCap, Qualtrics, and MyResearch)
- ☑ UCSF encrypted server, workstation, or laptop residing outside of UCSF data center
- ☐ Personal devices, such as laptops or tablets that are not owned or managed by UCSF
- ☐ SF VAMC
- ☐ Zuckerberg San Francisco General Hospital
- ☐ Benioff Children's Hospital Oakland
- ☐ Langley Porter Psychiatric Institution
- ☐ Other UCSF affiliate clinic or location (specify below)
- ☐ Cloud vendor such as Amazon Web Services (AWS), Salesforce, etc. (specify below)
- ☐ Other academic institution
- ☐ 3rd party vendor (business entity)
- ☑ Other (explain below)

* Provide more details about where study data will be stored: **(REQUIRED)**

Secure UCSF Box folders, which are HIPAA compliant.

15.20 * ADDITION OF RECORDS TO A REGISTRY: Will patient records reviewed under this approval be added to a research database, repository, or registry (either already existing or established under this protocol): (REQUIRED)

(•) Yes ( ) No

This activity generally requires patient consent and HIPAA Authorization. A Waiver of Consent/Authorization may be granted for patients who are deceased or lost to follow up, but ongoing patients should be consented at their next clinic visit prior to accessing their health records or they may provide consent and HIPAA authorization for research use of their health information by mail or through a certified E-Signature system such as DocuSign. You may be asked to revise your consent plans.

15.21 * DATA SHARING: During the lifecycle of data collection, transmission, and storage, will identifiable information be shared with or be accessible to anyone outside of UCSF: (REQUIRED)

( ) Yes (•) No

16.0 Financial Considerations

16.1 * PAYMENT: Will subjects be paid for participation, reimbursed for time or expenses, or receive any other kind of compensation: (REQUIRED)

(•) Yes ( ) No

16.2 PAYMENT METHODS: Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [ ] Cash
- [ ] Check
- [x] Gift card
- [ ] Debit card
- [ ] UCSF Research Subject Payment Card
- [ ] Reimbursement for parking and other expenses
- [ ] Other:

16.3 PAYMENT SCHEDULE: Describe the schedule and amounts of payments, including the total subjects can receive for completing the study:

- **If there are multiple visits over time, explain how payments will be prorated for partial completion**
- **If deviating from recommendations in Subject Payment Guidelines, include specific justification below**

Subjects who complete the return of results survey will receive a $20 gift card to Safeway or Target as a thank you gift for their time. Subjects who complete the survey for the 5-7 month follow-up visit will receive a $30 gift card to Safeway or Target. The gift cards are per family, so

one parent will be asked to complete the surveys on behalf of the family. Most families will have the opportunity to complete surveys and receive the gift cards, however some families (approximately 70) who agreed to be interviewed by our ethics (ELSI) team will not be asked to do surveys and will receive gift cards as part of the separate ELSI study IRB protocol for participating in interviews.

16.4 COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

(•) Yes ( ) No

Describe the costs that may be incurred by subjects or 3rd party payers as a result of participation:

- Explain why it is appropriate to charge those costs to the subjects
- If this is a therapeutic study, compare subjects' costs to the charges that would typically be associated with receiving care off-study (e.g. is it more expensive to participate in this study than to receive care off-study?)

Insurance will be billed for patient visits, as the visits are part of standard care. Consent and follow-up will be conducted when patients are seen during routine clinical visits.

17.0 Other Approvals and Registrations

17.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects (Help Link added Aug '15): (REQUIRED)

( ) Yes (•) No

17.2 * HUMAN GENE THERAPY: Does this study involve human gene therapy: (REQUIRED)

( ) Yes (•) No

17.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

18.0 Qualifications of Key Study Personnel and Affiliated Personnel

NEW: January 2019 - Affiliated personnel who do not need access to iRIS no longer need to get a UCSF ID. Instead, add them below in the Affiliated Personnel table below.

18.1 Qualifications of Key Study Personnel:

Instructions:

For UCSF Key Study Personnel (KSP)* listed in **Section 3.0,** select the KSP from the drop down list and add a description of their study responsibilities, qualifications and training. In study responsibilities, identify every individual who will be involved in the consent process. Under qualifications, please include:

- Academic Title
- Institutional Affiliation (UCSF, SFGH, VAMC, etc.)
- Department
- Certifications

NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Click the orange question mark for more information and examples.

Training Requirements:
The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through **CITI** prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our **website.**

* **Definition of Key Study Personnel and CITI Training Requirements (Nov, 2015):** UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors /advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application.

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
	Dr Anne Slavotinek is a Board-certified Clinical Geneticist who has Attending privileges at	

Dr. Slavotinek, Anne PhD, PhD	UCSF. She will recruit patients for this study from those seen as inpatients or outpatients at UCSF and BCHO, and from her colleagues who see patients in and outside UCSF. She will be responsible for the conduct of this study, for obtaining consent and for ensuring adequate data sharing if next-generation studies are performed.	Dr Slavotinek has many years of experience in tissue banking protocols and molecular genetics research.
Dr. Gallagher, Renata MD, PhD , MD, PhD	Dr Renata Gallagher is a Board-certified Clinical Geneticist who has Attending privileges at UCSF. She will recruit patients for this study from those seen as inpatients or outpatients at UCSF and BCHO.	Board-certified Clinical Geneticist who has experience with consent for exome sequencing.
Tenney, Jessica L	Dr Jessica Tenney is a Board-certified Clinical Geneticist who has Attending privileges at UCSF. She will recruit patients for this study from those seen as inpatients or outpatients at UCSF and BCHO.	Board-certified Clinical Geneticist who has experience with consent for exome sequencing.
Dr. Shieh, Joseph, MD, PhD	Dr Joseph Shieh is a Board-certified Clinical Geneticist who has Attending privileges at UCSF. She will recruit patients for this study from those seen as inpatients or outpatients at UCSF and BCHO.	Board-certified Clinical Geneticist who has experience with consent for exome sequencing.
Gardner, Marisa A	Dr Marisa Gardner is a Board-certified Clinical Geneticist who has Attending privileges at UCSF. She will recruit patients for this study from those seen as inpatients or outpatients at BCHO.	Board-certified Pediatric Neurologist who has experience with consent for exome sequencing.
Dr. Sherr, Elliott MD, PhD	Dr Elliott Sherr is a Board-certified neurologist who has Attending privileges at UCSF. He will recruit patients for this study	Board-certified Pediatric Neurologist who has experience with consent for exome sequencing.

	from those seen as inpatients or outpatients at UCSF.	
Strober, Jonathan	Dr Jonathan Strober is a Board-certified neurologist who has Attending privileges at UCSF. He will recruit patients for this study from those seen as inpatients or outpatients at UCSF.	Board-certified Pediatric Neurologist who has experience with consent for exome sequencing.
Dr. Weiss, William MD, PhD	Dr William Weiss is a Board-certified neurologist who has Attending privileges at UCSF. He will recruit patients for this study from those seen as inpatients or outpatients at ZSFGH	Board-certified Pediatric Neurologist who has experience with consent for exome sequencing.
Dr. Koenig, Barbara, PhD	Dr Barbara Koenig is an anthropologist who is involved in ethnographical research at UCSF.	Anthropologist involved in ethnographical aspects of this research.
Anguiano, Beatriz	Study Coordinator	Ms. Anguiano is certified in human subjects research
Sahin Hodoglugil, Nuriye N	Program Manager	Dr. Nuriye Nalan Sahin Hodoglugil, MD, MA, DrPH is the Program Manager for the P3EGS Project. Previously she worked in global health, and collaborated with partners in academia, Ministries of Health and international health organizations to generate evidence to guide programs and policy for improving women's health. She worked in reproductive health programs and research in several countries in sub-saharan Africa and Asia, as well as monitoring and evaluation of large scale maternal health interventions. She has also worked as a researher at UC San Francisco and UC Berkeley, and as a Senior Reproductive Health Technical Advisor at Johns Hopkins University.

		She holds an MD from Hacettepe University Faculty of Medicine, Turkey; an MA in cultural anthropology from Hacettepe University Institute of Social Sciences, and a DrPH from University of California, Berkeley.
Rego, Shannon M	Genetic Counselor. Responsibilities include recruiting and consenting subjects, returning results, entering data, and administering surveys.	Ms. Rego is a Licensed Clinical Genetic Counselor. She received her MS from Stanford University in 2014, and has worked with whole genome and whole exome sequencing since 2014, joining our team in late 2017.
Hoban, Hannah G	Assistant Clinical Research Coordinator. Responsibilities include recruiting and consenting subjects, entering data, and administering surveys.	Ms. Hoban holds a BS in Human Physiology, is a licensed phlebotomist, and has research experience. She is CITI certified in human subjects research.
Outram, Simon M	Research Associate: Dr. Outram will conduct ethnographic observations and interviews.	Dr. Outram, PhD, MSC, MA, is certified in human subjects research. He has done research in Cultural Anthropology, Qualitative Social Research, Science and Technology Studies, and Bioethics. He has experience with multiple social science research methodologies, including in-depth interviewing and ethnographic observation.
Fairley, Cecilia F	Genetic Counselor. Responsibilities include recruiting and consenting subjects, entering data, and administering surveys.	Ms. Fairley is a Licensed Clinical Genetic Counselor who has worked with genetics outpatients at BCHO for the past several years.
Lianoglou, Billie R	Genetic Counselor. Responsibilities include recruiting and consenting subjects, returning results entering data, and administering surveys.	Ms. Lianoglou is a Licensed Clinical Genetic Counselor with ten years of experience.
	Research Associate: Dr. Ackerman is leading the	Dr. Ackerman, PhD, MPH is an assistant professor of social and behavioral

Ackerman, Sara, PhD, MPH	ethnographic portion of the study and will be conducting observations and interviews.	sciences and has many years of experience in ethnography and qualitative genomic research.
Dr. Klein, Ophir MD	Dr. Ophir Klein is a Board-certified Clinical Geneticist who has Attending privileges at UCSF. He will recruit patients for this study from those seen as inpatients or outpatients at UCSF and BCHO.	Board-certified Clinical Geneticist who has experience with consent for exome sequencing.
Yip, Tiffany A	Genetic Counselor. Responsibilities include recruiting and consenting subjects, entering data, and administering surveys.	Ms. Yip is a licensed genetic counselor with experience consenting patients for exome sequencing.
Tam, Allison C	Dr. Allison Tam is a Board-certified Clinical Geneticist who has Attending privileges at UCSF. She will recruit patients for this study from those seen as inpatients or outpatients at UCSF and BCHO.	Board-certified Clinical Geneticist who has experience with consent for exome sequencing.
Curry, Cynthia	Dr. Cynthia Curry is a Board-certified Clinical Geneticist at UCSF Fresno. She will recruit patients for this study from those seen as inpatients or outpatients at Community Regional Medical Center.	Board-certified Clinical Geneticist who has experience with consent for exome sequencing.
Patel, Sachi	Clinical Research Coordinator. Responsibilities include recruiting and consenting subjects, entering data, and administering surveys.	Ms. Patel holds a degree from UC Irvine in Public Health Sciences and has over a year of experience as a research coordinator.
Faubel, Amanda J	Clinical research coordinator: Responsibilities include recruiting and consenting subjects, entering data, and administering surveys.	Ms. Faubel holds a degree from Cal Poly in social sciences and has a year of experience as a research coordinator.
	Dr. Gangaram is a medical geneticist and	

Gangaram, Balram	assistant professor who will assist with recruiting patients for this study at UCSF and UCSF Benioff Children's Hospital Oakland.	Medical geneticist with experience consenting for exome sequencing.
Chang, Jiyoo	Software developer /research assistant: responsibilities include assisting with the development of the application being developed as part of this project (covered under a separate protocol) and assisting with utilizing the app to return results to families who have undergone exome sequencing	Ms. Chang holds a degree from Dartmouth and has over two years of experience with software development at UCSF.
Chin, Garrett	Data Manager	Mr. Chin holds a Bachelors of Science degree in Psychobiology (UC Davis), and Masters in Biological Sciences from Drexel University, College of Medicine. He is certified in human subjects research.
Prasad, Hannah L	Study coordinator. Responsibilities include administering surveys and entering data.	Ms. Prasad holds a Bachelors of Science degree in Biological Sciences (UC Davis) and Doctor of Medicine Degree from Universidad Autónoma de Guadalajara, Mexico. She is certified in human subjects research.

18.2 Affiliated Personnel:

Instructions:

This section is for personnel who are not listed in **Section 3.0: Grant Key Personnel Access to the Study** because their names were not found in the User Directory when both the iRIS Database and MyAccess directories were searched. Add any study personnel who fit ALL of the following criteria in the table below:

- They meet the definition of Key Study Personnel (see above), **and**
- They are associated with a UCSF-affiliated institution (e.g., VAMC, Gladstone, Institute on Aging, Vitalant, NCIRE, SFDPH, or ZSFG), **and**
- They do not have a UCSF ID, **and**
- They do not need access to the study application and other study materials in iRIS.

Note: Attach a **CITI Certificate** for all persons listed below in the **Other Study Documents** section of the **Initial Review Submission Packet Form** after completing the **Study Application**.

Click the orange question mark icon to the right for more information on who to include and who not to include in this section.

Do not list personnel from outside sites/non-UCSF-affiliated institutions. Contacts for those sites (i.e. other institution, community-based site, foreign country, or Sovereign Native American nation) should be listed in the **Outside Sites** section of the application.

If there are no personnel on your study that meet the above criteria, leave this section blank.

Name	Institution	Telephone	E-mail	Role
No External Personnel has been added to this IRB Study				

Please describe the study responsibilities and qualifications of each affiliated person listed above:

19.0 End of Study Application

End of Study Application Form

To continue working on the Study Application:
Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes.

If you are done working on the Study Application:
Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and **Save and Continue** through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections.

Once you are sure the form is complete, click **Save and Continue**. If this is a new study, you will automatically enter the **Initial Review Submission Packet Form**, where you can attach **consent forms** or other **study documents**. Review the **Initial Review Submission Checklist** for a list of required attachments.

Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB welcomes feedback about the IRB Study Application Form. Please click the link to answer a **survey** about the application form.

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution A):
University of California, San Francisco

IRB Registration #: 00000229, 00000230, 00003471, and 00005096
Federalwide Assurance (FWA) #: 00000068

Name of Institution Relying on the Designated IRB (Institution B):
Children's Hospital & Research Center Oakland, dba UCSF Benioff Children's Hospital Oakland (BCHO)

OHRP Federalwide Assurance (FWA) #: 00000094

The Officials signing below agree that *(institution B)* BCHO may rely on the designated IRB for review and continuing oversight of its human subject research described below: (*check one*)

☐ This agreement applies to all human subject research covered by Institution B's FWA.

☒ This agreement is limited to the following specific UCSF IRB Approved protocol(s):
Name of UCSF Research Project: Program in Prenatal and Pediatric Genome Sequencing (P3EGS)
Name of UCSF Principal Investigator: Anne Slavotinek MD
Name of BCHO Principal Investigator: Rachel Kuperman, MD
UCSF CHR Number: 17-22504
BCHO IRB Number: 2017-102
Sponsor or Funding Agency: NIH 1U01HG009599-01

☐ Other (*describe*) : _____

The review and continuing oversight performed by the designated IRB will meet the human subjects protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the terms of its OHRP-approved Assurance. This document must be kept on file at both institutions and provided to OHRP upon request.

Signature of Signatory Official (Institution A): _____ Date: 2-21-18
Name: Laurie Herraiz, RD, CIP
Institutional Title: Director of Operations and Quality Improvement, Human Research Protections Program
Address: 3333 California Street San Francisco, CA 94118 Phone #: 415-514-9246

Signature of Signatory Official (Institution B): _____ Date: 1/8/18
Name: Jeanette Asselin, MS, RRT-NPS
Institutional Title: Chair, Institutional Review Board
Address: 747 52nd Street, Oakland CA 94609 Phone #: (510) 428-3763