Clinical Utility of Prenatal Whole Exome Sequencing: Study Protocol
NCT03482141
Document Approval Date: 9/30/2022

Study Application (Version 1.22)

1.0 General Information

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

Clinical Utility of Prenatal Whole Exome Sequencing

***Enter the study alias:**

Prenatal WES
* 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** - *118044* - M_Human Genetics

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

Ackerman, Sara, PhD, MPH
Other Investigator
Beleford, Daniah A MD, PhD
Other Investigator
Curry, Cynthia
Study Clinician
Keller, Roberta, MD
Other Investigator
Koenig, Barbara, PhD

Co-Principal Investigator
Kwok, Pui-Yan Dr., MD, PhD
Co-Principal Investigator
Lianoglou, Billie R
Other Investigator
Michie, Marsha, PhD
Other Investigator
Sanders, Stephan MDPhD
Other Investigator
Sherr, Elliott MD, PhD
Other Investigator
Shieh, Joseph, MD, PhD
Other Investigator
Slavotinek, Anne PhD, PhD
Co-Principal Investigator
Sparks, Teresa N
Study Clinician

B) Research Support Staff

Amezcua, Jessica M
Study Coordinator
Anguiano, Beatriz
Research Assistant
Chang, Jiyoo
Research Assistant
Chen, Flavia H
Research Assistant
Cullen, Caitlin
Clinical Research Associate
Dong, Shan
Technician
Downum, Sarah L
Study Coordinator
Farrell, Rachel L
Study Recruiter
Faubel, Amanda J
Study Coordinator
Gosnell, Kristen A
Study Nurse
Hoban, Hannah G
Study Coordinator
Hutchinson, Romobia
Study Coordinator
Michelson, Jeremy
Research Assistant
Norstad, Matthew
Research Assistant
O'Leary, Allison S
Study Coordinator
Oman, Natalie
Study Coordinator
Outram, Simon M
Clinical Research Associate

Patel, Sachi
Study Coordinator
Perry, Rachel L
Study Nurse
Rangwala, Naseem A
Research Assistant
Rego, Shannon M
Study Recruiter
Rigler, Nicole A
Study Coordinator
Ryan, Tamara L
Study Nurse
Sahin Hodoglugil, Nuriye N
Study Coordinator
Schwartz, Grace B
Technician
Scudmore, Janice C
Study Nurse
Shear, Matthew
Research Assistant
Silver, Julia M
Study Recruiter
Silver, Julia M
Study Recruiter
Thao, Kao N
Study Coordinator
Tick, Katherine
Clinical Research Associate
Tobias, Sarah E
Study Recruiter
Valdez Lopez, Priscila A
Study Coordinator
Yamane, Taylor A
Research Assistant
Yip, Tiffany A
Study Recruiter

3.3 *Please add a Study Contact

Koenig, Barbara, PhD
Lianoglou, Billie R
Norton, Mary MD, MD
Sahin Hodoglugil, Nuriye N

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 January 2019 - Revised Common Rule (January 2018) Compliant - v92

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):

Genome 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 developmental disorders, and, 2) providing genetic information to parents when a prenatal study reveals a fetus with a structural anomaly. 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. This protocol is specifically focusing on the prenatal aspect of the broader P3EGS project. A separate protocol will be submitted simultaeously for the pediatric patients. Other studies, such as those using interviews to follow families offered sequencing, will be submitted to the IRB as separate protocols.

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: A very limited number of studies of approved drugs and devices
- ☑ Category 2: Blood sampling
- ☑ Category 3: Noninvasive specimen collection (e.g. buccal swabs, urine, hair and nail clippings, etc.)
- ☐ Category 4: Noninvasive clinical procedures (e.g. physical sensors such as pulse oximeters, MRI, EKG, EEG, ultrasound, moderate exercise testing, etc.)
- ☑ Category 5: Research involving materials (data, documents, records, or specimens) that were previously collected for either nonresearch or research purposes
- ☐ Category 6: Use of recordings (voice, video, digital or image)
- ☑ Category 7: Low risk behavioral research or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, 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:

NCT03482141

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
- [x] 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 * 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

4.14 * 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

4.15 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
☑ Other:

* Specify **Other: (REQUIRED)**

NIH

4.16 * 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

4.17 * 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			Awardee	Contract	Project	UCSF RAS System Award

Details	Sponsor Name	Sponsor Type	Institution:	Type:	Number	Number ("A" + 6 digits)
	NIH Natl Human Genome Research Inst.	01	UCSF	Grant	P0518017	

Sponsor Name:	NIH Natl Human Genome Research Inst.
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	
Awardee Institution::	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
Project Number:	P0518017
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	Genomic sequencing to aid diagnosis in pediatric and prenatal practice: Examining clinical utility, ethical implications, payer coverage, and data integration in a diverse population.
PI Name: (If PI is not the same as identified on the study.)	Pui-Yan Kwok
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

* Identify the gift, program, departmental, or other internal funding source: **(REQUIRED)**

UCSF Women's Reproductive Health Research (WRHR) Career Development Program

6.0 Sites, Programs, Resources, and External IRB Review

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

- ☑ UCSF Benioff Children's Hospital Oakland (BCHO)
- ☑ UCSF China Basin clinics and facilities
- ☐ UCSF Helen Diller Family Comprehensive Cancer Center
- ☐ UCSF Langley Porter Psychiatric Institute (LPPI)
- ☑ UCSF Medical Center at Mission Bay (Benioff Children's Hospital, the Betty Irene Moore

Women's Hospital, Bakar Cancer Hospital, or outpatient clinics)

- [x] UCSF Mount Zion
- [x] 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)
- [x] Zuckerberg San Francisco General (ZSFG)
- [ ] SF VA Medical Center (SF VAMC)
- [x] Fresno - UCSF Fresno OR Community Medical Center (CMC)
- [ ] Gladstone
- [ ] Institute on Aging (IOA)
- [ ] Jewish Home
- [ ] SF Dept of Public Health (DPH)
- [ ] Vitalant (formerly Blood Centers of the Pacific and Blood Systems Research Institute)

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:

Study participants will be seen, recruited and followed up with primarily at UCSF Betty Irene Moore Women's Hospital (BIMWH), UCSF Benioff Children's Hospital Mission Bay (BCHMB), UCSF Benioff Children's Hospital Mission Bay (BCHO), Zuckerberg San Francisco General Hospital (ZSFGH) 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

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.)

6.11 * OUTSIDE RELIANCES: (REQUIRED) Are any of the collaborating sites requesting to rely on UCSF's IRB:

○ Yes ◉ No

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 Outside Site Information

7.1 Outside Site Information

If you have more than 10 sites to add, list the outside sites in the Outside Sites List document and upload it in the Other Study Documents section of the Initial Review Submission Packet form. Any sites requesting to rely on UCSF's IRB must be listed below.

Click "Add a new row" to enter information for a site. Click it again to add a second site again to add a third site, a fourth site, etc.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

UCSF Fresno/Community Medical Center

Contact name:

Cynthia Curry

Email:

cynthia.curry@gmail.com

Phone:

559-459-2269

For Federally-funded studies only, corresponding FWA#:

*** The research at this site will be reviewed by:**

- (•) The non-affiliated site's IRB or a private IRB
- ( ) The non-affiliated site is requesting UCSF to be the IRB of record for this study
- ( ) The non-affiliated site is not engaged in the human subjects research and has provided a letter of support

If the other site's IRB approval letter is available now, attach it to the application. If the IRB approval letter is not yet available, submit it once you receive it.

Or, if the other site is **not engaged** in human subjects research, attach the letter of support to your application.

8.0 Research Plan and Procedures

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

In the pediatric population whole exome sequencing is estimated to identify a diagnosis in approximately one-third of all cases. Considering the extreme phenotype of cases with congenital anomalies and experience from labs that are currently offering prenatal whole exome sequencing, we expect the yield to be higher than the pediatric experience. Whole exome sequencing is an ideal approach to the prenatal population given its comprehensive nature and ability to detect involved genes that may not have initially been suspected. Additionally, initiating genetic studies with whole exome sequencing, as opposed to targeted sequential genetic testing, would reduce turn around time to facilitate earlier parental understanding of a fetal diagnosis and maximize family planning options.

This research will contribute novel information about the frequency of genetic disorders in fetuse with congenital anomalies, enabling providers to more accurately counsel about prognosis, individualize antenatal care, allow more informed decision-making, and anticipate specific neonatal needs. By examining genotype-phenotype correlations, it will facilitate a precision-based approach for future targeted neonatal (and ultimately antenatal) therapies such as enzyme replacement or stem cell transplantation. The NIH has recognized the importance of such a

precision-based approach to medical care.[21] Further, this research will contribute substantially to our understanding of women's preferences surrounding crucial decision points during an affected pregnancy and after delivery.

8.2 AIMS: List the specific aims:

Our specific aims will:

1) examine the clinical utility of exome sequencing, including assessment of a variety of health-related and reproductive outcomes, in 400 undiagnosed prenatal cases.

2) address ethical, social and economic issues in the delivery of genomic sequencing results to ancestrally and economically diverse populations through (2.1) a mixed methods, longitudinal empirical study of clinical interactions and experiences, (2.2) an economic analysis of insurance coverage, price and reimbursement of multigene tests, and (2.3) creation of an Ethics Advisory Board to respond to emerging issues and establishment of authentic stakeholder engagement; and

3) pilot a user-friendly web-based patient/provider application integrating genomic and clinical data as a shared evidence base to support result communication, interpretation and clinical decision making; the application will be based on the "Bioscreen" model created and successfully implemented at UCSF.

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

Any patient with a fetus identified by ultrasound to have a severe congenital anomaly and have had or will have prenatal diagnosis for chromosome analysis or microarray analysis will be offered the option for additional testing by whole exome sequencing. The patient will be educated regarding the anomalies identified on ultrasound and meet with a genetic counselor associated with the study to review the risks, benefits and limitations of whole exome sequencing (WES). After a comprehensive conversation related to WES the patient will be offered to pursue this testing with the cost of testing covered through the study. Because exome sequencing is a new approach, a small number of parents and families will be invited to participate in an additional study, this would include both patient that pursued WES and those that declined. That study will involve being interviewed by a member of our team, by telephone or in person.

To achieve diversity, patient ascertainment and recruitment will occur at three sites where prenatal imaging and counseling take place, these sites that serve a broad range of under-represented minority (URM) populations and span the full socio-economic spectrum, including the underserved. The sites include UCSF Betty Irene Moore Women's Hospital (BIMWH), UCSF Benioff Children's Hospital Mission Bay (BCHMB), Zuckerberg San Francisco General Hospital (ZSFGH) and UCSF Fresno Community Medical Center; these sites have patient populations representing up to 80% URM and 60% from underserved backgrounds.

Following consent and collection of standardized phenotypic and demographic data, the families will undergo WES as part of clinical care. If prenatal testing had been performed at an outside laboratory specimen will be coordinated, for WES at UCSF. After counseling, sequencing and variant analysis and interpretation by our expert group, study subjects will meet with their clinicians to receive results. For pregnancies resulting in a live birth, infants will continue to be

followed for 6-12 months after birth to assess medical decision-making for the child and provision of genetic information for other family members.

We will examine the following outcomes in order to assess clinical utility in prenatal patients: (i) pregnancy termination, (ii) in-utero medical or surgical intervention, (iii) perinatal decision-making, e.g. antepartum surveillance, location and mode of delivery, non-intervention or perinatal hospice care, (iv) immediate neonatal management, and (v) reproductive decision-making subsequent to the index pregnancy.

Our team of clinicians, molecular genetics specialists and bioinformaticians are highly qualified to perform these analyses; we will examine and contrast clinical and personal utility across the social spectrum and among under-represented minority groups. In parallel, our bioethics and health economics groups will follow and study patient/provider interactions and insurance coverage/reimbursement. And to enhance clinical decision making, our clinical and informatics groups will design and implement a pilot approach to user-friendly sharing of clinical and genetic information to families and health care providers.

A series of surveys will be administered to the patient at various time points including the time of consent, return of results and 6-12 month follow-up. These surveys are designed to further the study goals of understanding the personal and clinical utility of exome sequencing. These surveys may be done in person, by phone, emailed, or mailed to you after the clinic visit. A $50 total in gift cards will be provided to subjects that complete the surveys. $20 will be provided after the first survey and $30 for the second.

8.4 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.

Next-generation sequencing (NGS) is changing the paradigm of clinical genetic testing. Unlike highly focused single-gene tests, NGS allows one to examine gene panels, the exome, and the whole genome. With the broad array of molecular tests now available, ordering physicians face the conundrum of selecting the best diagnostic tool for patients with suspected genetic conditions. Single-gene testing is often most appropriate for conditions with distinctive clinical features and minimal locus heterogeneity. NGS-based gene panel testing, which can be complemented with chromosomal microarray analysis (CMA) and other ancillary methods, provides a comprehensive and feasible approach for well documented but genetically heterogeneous disorders. Whole exome sequencing (WES) and whole genome sequencing (WGS) have the advantage of enabling parallel interrogation of most of the genes in the human genome. To some, WES is preferable to previously used methods due to higher diagnostic yield, shorter time to diagnosis, and improved cost-efficiency.

The ability to survey the exome opens up both new opportunities and new challenges. For example, all coding regions of known genes must be analyzed when applying WES to undiagnosed cases with unclear inheritance patterns. Current limitations on variant interpretation capabilities and clinical validity raise questions about the clinical utility of WES as either a stand-alone or a first-choice diagnostic test. Additional challenges include pre- and post-test counseling with appropriate and robust informed consent, bioinformatics analysis setup and validation, variant interpretation and classification, the need for policies and protocols concerning the discovery and reporting of secondary findings unrelated to the presenting indication, a requirement for validation of WES results, assurance of conformation to quality control standards, data storage and accessibility, and reimbursement issues.

Current clinical standards recommend offering chromosomal microarray (CMA) in the prenatal setting when fetal structural anomalies are detected via prenatal ultrasound. In these cases, clinically relevant copy number variants have been reported in 6.0-9.1% of fetuses with a normal karyotype. However, informed consent processes for prenatal CMA are challenging—particularly in cases with ultrasound anomalies, as parents are absorbing challenging news and under considerable stress. Women have reported being "blindsided" by positive CMA results, or feeling that these results were "toxic information"—information they wished they did not have, particularly in cases of uncertain genetic information or uninterpretable variants. Nonetheless, in that same study women who were referred for CMA because of ultrasound anomalies reported less frequent negative reactions, since they already anticipated abnormal results.

Introducing WES into prenatal clinical care of underrepresented populations raises additional issues and considerations of payment coverage, access, and standards of care. Beyond the sheer complexity of the test and its results, clinicians and health systems must address numerous considerations, including: private and public insurance coverage; language and culture differences and their implications for genetic counseling and clinician-patient relationships; ability to access follow-up testing and clinical care; ability to access appropriate treatment and services; and particularly in the prenatal setting, local, state, and national abortion laws and decision-making about pregnancy termination. These issues and others will affect not only patients' decision-making regarding WES, but also their post-test needs for patient follow up, counseling and support. The importance of systematically assessing the clinical utility of NGS is critical for determining in which clinical and health care contexts WES will be useful and for commencing research on these considerations.

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

The UCSF group has gained significant experience over the past 3 years in providing NGS to patients through its Personalized Genomics Clinic and the Genomic Medicine Initiative. UCSF BCHMB has a specialized clinic that unifies the consent process, results session and follow up for patients undergoing WES. The clinic is currently held twice a month and staffed by Drs. Slavotinek and Shieh, together with a dedicated genetic counselor, Marta Sabbadini. To date, more than 150 patients ranging in age from newborn to adult, referred from numerous providers, have been seen in this clinic. Referring indications have included ID, multiple congenital anomalies, seizures/encephalopathy, and other neurological presentations, including stroke /hemorrhage, chronic pain, ataxia, muscle weakness, central hypoventilation, dysautonomia, pontocerebellar hypoplasia, and movement disorders. Over 90% of patients have been sequenced as trios (proband and both biological parents). In the first 57 patients taken from the group of greater than 150 patients, a possible causative sequence variant was identified, and a definitive diagnosis was made in 25/57 (44%). In an assessment of clinical utility for the first 49 positive results (excluding fetuses), 24/49 had a result-directed improvement in clinical care, one had withdrawal of care, three had the introduction of a targeted treatment or diagnosis related therapy, 43/49 received critical reproductive information and 13/49 received reproductive information that was directly relevant for testing of other family members or for other family members planning children (data not shown).We therefore have experience in the assessment of clinical utility from patients undergoing WES.

IHG Genomics Core Facility and the Genomic Medicine Initiative. Under the auspices of the UCSF Genomic Medicine Initiative, we have achieved CLIA certification for next-generation sequencing for over one year. The first clinical sequencing test launched was a cancer gene panel that compares the tumor and germline DNA of a patient. Over the last year, we have sequenced 2,844 samples successfully, resulting in many cases where target specific therapies are chosen for the patients. We have also obtained WES data for 152 clinical and control samples in the process of obtaining CLIA certification for clinical WES at UCSF. The data obtained so far compared favorably against sequencing data for the same samples from outside CLIA certified laboratories (including that at UCLA and GeneDx). In addition, we have performed WES on 10,768 samples for research purposes. With a highly experienced sequencing staff and bioinformatics group, we have established a strong team to perform both clinical and research sequencing.

8.6 * 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

8.7 * 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

If you are not sure if your study involves billable procedures, send an email to the UCSF Office of Clinical Research (OCR) for help answering this question.

8.8 * 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

8.9 * PROCEDURES / METHODS: (REQUIRED)

Describe the research methods and study activities taking place at each site (e.g. what will participants be asked to do and what will members of the study team do?). If there will be multiple participant groups or study sites, explain what will happen with each group or study sites.

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.**

Please call our office at 415-476-1814 and ask to speak to someone on the Expedited Review team if you need help differentiating between what parts are research and what parts aren't.

We anticipate enrolling up to 75-85 participants per year.

1. Recruitment:

Personnel within the UCSF Fetal Treatment Center, UCSF Prenatal Diagnosis Center, Benioff Children's Hospital Oakland Fetal Treatment Center, Zuckerberg San Francisco General Hospital or UCSF Fresno Community Medical Center will identify and recruit

participants. Additionally, we will offer enrollment to patients consented to exome sequencing through a second study our team is offering (IRB 17-21662 (Fetal birth defects prospective database: Toward a precision-based approach)).

2. Consent:

Personnel at each site will consent to Exome Sequencing. Anticipated enrollment will be around 75-85 cases per year from all sites.

Trio Exome Sequencing obtained for each enrolled participant

Affected fetus and biological parents are both important for estimating clinical implications of variants. The following fetal samples will also be collected: chorionic villli, amniotic fluid, cord blood, fetal tissue (stillbirth or Intrauterine Fetal Demise), neonatal blood, or extracted fetal/neonatal DNA from the above detailed specimens. Parents saliva or blood will suffice for biological parents samples.

Sample Processing and Reporting

Consent, sample collection, whole exome sequencing and banking. Findings will be reported to clinical staff including physicians and genetic counselors associated with this study. These clinicians will review results with the the patient and their family.

Results from exome sequencing that will be provided to the participants and their families, and that could contribute to clinical decision-making include (1) variants known to cause or contribute to the birth defect found in the fetus and, (2) in cases where the participant has indicated in the consent form that they wish to learn about additional findings with medical significance, variants in genes of medical significance outside of the primary indication for testing (additional or secondary findings).

In cases in which a variant is identified that could be either inherited or de novo, if the father has declined participation, the potential that this variant could be inherited from the father will not be shared with him, given his active declination.

If the father has declined participation, and a variant is found in the fetus that is likely to have been inherited from the father (e.g. an autosomal recessive disorder is diagnosed in the fetus), the basic genetic inheritance will be explained to the mother. If the father has declined participation, we will not contact him again to share results.

As part of the consenting process, when talking with the fathers, we will explain these potential outcomes to assure they understand the full implications of consenting, or declining to consent.

We may use exome sequencing to sequence a large proportion of the currently known and unknown genes in some affected individuals. Sequencing unknown genes, such as many of the tests that will be performed for this study, are considered experimental in nature. As such, the accuracy and usefulness of these experimental tests has yet to be determined, and the conclusions of these test results may be uncertain.

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. The patient will have the option to opt out of inclusion of their data in this database in the consent process.

After informed consent has been obtained a series of surveys will be administered to the patient at various time points including the time of consent, return of results and 6-12 month follow-up. These surveys are designed to further the study goals of understanding the personal and clinical utility of exome sequencing.These surveys may be done in person, by phone, emailed, or mailed to you after the clinic visit. A $50 total in gift cards will be provided to subjects that complete the surveys. $20 will be provided after the first survey and $30 for the second.

Participation in the study will take a total of about 2-3 hours over a period of 3 or more days.

In addition: We will contact executives, administrators, managers or clinicians 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. The ORCA will be administered to 6-10 administrators, managers, or clinicians at each site participating on our project.

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.

ORCA survey data will be collected anonymously and will be pooled with data from other sites in our NIH-funded consortium in order to minimize risk of re-identification.

The completion of this survey should take approximately 10-15 minutes.

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

If the instruments are not complete or not available because they will be developed as part of this study, describe the basic content or include an outline and submit the final versions to the IRB with a modification for approval prior to use.

A series of surveys will be administered to the patient at various time points including the time of consent, return of results and 6-12 month follow-up. These surveys are designed to further the study goals of understanding the personal and clinical utility of exome sequencing.

Specifically, after initial consent is obtained the patients will be administered a demographic survey to characterize the patient population undergoing exome sequencing through our study. Subsequent surveys will be specific to the patient's circumstance and have been tailored to be appropriate for patients that have an on-going pregnancy, a pregnancy that has resulted in a live birth, or a pregnancy loss due to either elective termination or natural causes.

After the return of results the patient will be administered a survey that can be conducted in patient or through email, or can be return to us by mail. Finally there will be surveys obtained after the 6-12 month point of having received results from the exome sequencing. All of these surveys are designed to obtain information regaring the patient's experience of having undergone genetic sequencing in their pregnancy, what information they understood about the results of their testing, where they sought information outside of our clinical service to understand these results and how the sewuencing results were incorporated into their understanding of their child's health or adverse pregnancy outcome.

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.

8.12 * 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.

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

Our study design will allow several statistical comparisons that will generate useful data regarding exome sequencing implementation. Clinical outcomes will be scored across multiple domains; for example, assigning one point for changes in care or interventions that are deemed to have minor clinical utility, two points for those with moderate utility and three points for those with high clinical utility. The scoring will be independently performed by two clinicians who did not see the patient or family, and who are not familiar with the case. The clinical information will derive from a compilation of material derived from direct examinations that occurred prior to study initiation and all clinical information available in the EHRs. Results for parents and/or family will be based on interviews. The study coordinator or a research assistant will prepare this information for review by the clinicians and will remove, when possible, all statements that could reveal whether the subject had a positive or negative exome result (i.e. unblind the raters). The two raters will reconcile any differences in their scores, or simply average them if agreement does not occur. Our group will work with the CSER consortium to develop the specific clinical utility outcomes that will be scored.

After all scores are made for each patient, scores will be totaled within and across domains. The analyst will also have the results of the exome sequencing, and separate the patients into two groups – one with a positive (i.e. diagnostic) test result, and the other without such a result (negative test result). We will compare the scores of those with a positive test result versus those with a negative test result. By comparing these two groups, we are not evaluating the overall clinical utility that may derive from having any exome sequencing test performed (i.e. we have no comparison group of those without exome sequencing). We have chosen to focus instead on only those benefits that may derive from having a diagnostic exome sequencing result.

The size of the "positive" and "negative" groups will depend on the diagnostic success rate of exome sequencing in our cohort. Based on prior experience in the Personalized Genomics Clinic (see Preliminary Results), we anticipate a minimum of 17% of subjects will have a positive result – but that rate could be as high as 38%. In any event, assuming a low rate of 20%, we expect a minimum of 220 individuals/families with a positive test result, which should be adequate for the analyses we propose.

It is also important to determine how clinical utility may vary based on a number of factors, including setting (prenatal, neonatal, pediatric), by disease indication, by race/ethnicity, and by socioeconomic status. Such stratified analyses will depend on the actual observed sample sizes within each stratum.

8.14 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):

1. Yang Y, Muzny DM, Reid JG, Bainbridge MN, Willis A, Ward PA, Braxton A, Beuten J, Xia F, Niu Z, Hardison M, Person R, Bekheirnia MR, Leduc MS, Kirby A, Pham P, Scull J, Wang M, Ding Y, Plon SE, Lupski JR, Beaudet AL, Gibbs RA, Eng CM. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. N Engl J Med. 2013;369(16):1502-1511. PubMed PMID: 24088041; PubMed Central PMCID: PMC4211433.
2. Norton ME, Rink BD. Changing indications for invasive testing in an era of improved screening. Seminars in Perinatology. 2016;40(1):56-66. PubMed PMID: 26725145
3. Cowan RS. Aspects of the history of prenatal diagnosis. Fetal Diagnosis and Therapy. 1993; 8(Suppl. 1):10-17. PubMed PMID: 11653011.
4. Chervenak FA, McCullough LB. Ethical issues in perinatal genetics. Seminars in Fetal and Neonatal Medicine. 2011;16(2):70-73. PubMed PMID: 21051301.
5. Donley G, Hull SC, Berkman BE. Prenatal Whole Genome Sequencing: Just because we can, should we? Hastings Center Report. 2012;42(4):28-40. PubMed Central PMCID: PMC4113095.
6. American College of Obstetricians and Gynecologists Committee on Genetics, Society for Maternal- Fetal Medicine. Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. Obstet Gynecol. 2013;122(6):1374-1377. PubMed PMID: 24264715.
7. Wapner RJ, Martin CL, Levy B, Ballif BC, Eng CM, Zachary JM, Savage M, Platt LD, Saltzman D, Grobman WA, Klugman S, Scholl T, Simpson JL, McCall K, Aggarwal VS, Bunke B, Nahum O, Patel A, Lamb AN, Thom EA, Beaudet AL, Ledbetter DH, Shaffer LG, Jackson L. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J

Med. 2012;367(23):2175-2184. PubMed PMID: 23215555; PubMed Central PMCID: PMC3549418.
8. de Wit MC, Srebniak MI, Govaerts LC, Van Opstal D, Galjaard RJ, Go AT. Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound abnormalities and a normal karyotype: a systematic review of the literature. Ultrasound Obstet Gynecol. 2014;43(2):139-146. PubMed PMID: 23897843.
9. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010;86(5):749-764. PubMed PMID: 20466091; PubMed Central PMCID: PMC2869000.
10. Hussain-Gambles M, Atkin K, Leese B. Why ethnic minority groups are under-represented in clinical trials: a review of the literature. Health & Social Care in the Community. 2004;12 (5):382-388.
11. Robinson JO, Carroll TM, Feuerman LZ, Perry DL, Hoffman-Andrews L, Walsh RC, Christensen KD.
12. Green RC, McGuire AL. Participants and Study Decliners' Perspectives About the Risks of Participating in a Clinical Trial of Whole Genome Sequencing. J Empir Res Hum Res Ethics. 2016;11(1):21-30. PubMed PMID: 26928896; PubMed Central PMCID: PMC4842131.
13. Lupo PJ, Robinson JO, Diamond PM, Jamal L, Danysh HE, Blumenthal-Barby J, Lehmann LS, Vassy JL, Christensen KD, Green RC, McGuire AL. Patients' perceived utility of whole-genome sequencing for their healthcare: findings from the MedSeq project. Per Med. 2016; 13(1):13-20. PubMed PMID:27019659; PubMed Central PMCID: PMC4806392.
14. Kohane IS. Ten things we have to do to achieve precision medicine. Science. 2015;349 (6243):37-38.
15. Reiff M, Bernhardt BA, Mulchandani S, Soucier D, Cornell D, Pyeritz RE, Spinner NB. "What does it mean?": uncertainties in understanding results of chromosomal microarray testing. Genet Med. 2012;14(2):250-258. PubMed PMID: 22241091; PubMed Central PMCID: PMC3445036.

9.0 Biospecimen Collection and/or Bank Administration

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

- [x] Blood (provide amount below)
- [x] Tissue (describe below)
- [ ] Other type of biospecimen, such as sputum, cerebrospinal fluid, buccal swabs, etc. (describe below)
- [x] 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:

Exome sequencing of prenatal specimens will include either cultured cells or extracted DNA from chorionic villi, amniocytes of products of conception including fetal tissue, fetal cord blood or neonatal blood. These specimens would have been left over from previous testing, no additional procedure would be performed to obtain fetal specimen. Maternal and paternal samples will also be requested and can be blood, bucchal swab or saliva samples. For particpants of IRB 17-21662 (Fetal birth defects prospective database: Toward a precision-based approach) we will only be collecting a single sample to perform exome sequencing for participation in both studies. No additional sample will be obtained for the purposes of enrollment in this study if they elect to participate in both.

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

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

☐ Other

9.3 * 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

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

☑ Specimen section within a main research study consent form
☐ Separate specimen consent form
☐ UCSF surgical consent form with tissue donation brochure

9.5 * 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
☑ 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
☑ 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.:

UCSF Genomic Medicine Laboratories
University of California, San Francisco
Institute for Human Genetics
513 Parnassus Ave., HSW 901A
San Francisco, CA 94143

9.7 * 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':

12 months after delivery

9.8 * 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:

The samples will be stored with the UCSF Genomic Medicine Laboratories. Upon lab recipt specimens receive non-PHI lab identifiers and will be maintained in that way.

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

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

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

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

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

- ( ) Yes
- ( ) No

10.0 Drugs and Devices

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

- ( ) Yes
- (•) No

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.

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

◉ Yes ○ No

10.4 * 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)**

1) We plan to use exome sequencing to clarify a possible genetic cause of congenital anomalies identified clinically by fetal anatomic ultrasound. As an entry criterion for the study, all participants will have previously undergone prenatal genetic diagnosis by established methods of chromosome analysis and microarray. DNA samples submitted for WES in this study will be derived from a previously obtained specimen. No invasive procedures are connected with the use of the exome sequencing test in our study.

Thus, our use of exome sequencing meets the "non-significant risk" criteria:

1) Exome sequencing testing is non-invasive, and is done on previously obtained samples.
2) Exome sequencing presents no risk to the health or welfare of the subject; results provide information only.

3) and 4)

We first address "informational risks" associated with return of results relevant to the primary finding of a fetal anomaly.

We believe this use constitutes "non-significant risk" to study participants as they will only be asked to participate in research after the clinical diagnosis of a severe congenital anomaly has been made. Any genetic finding revealed by sequencing of the trio (fetus plus parents) will inform the clinician's understanding of the etiology of the anomalies identified, but will not modify the severity of the already-diagnosed physical anomaly.

All clinically significant findings identified through whole exome sequencing will be confirmed by a secondary sequencing method, specifically Sanger sequencing.

Although information will be returned to the family based on the exome sequencing testing, we believe this constitutes non-significant risk because results based on CLIA-approved tests for single genes and gene panels are routinely offered to pregnant women. Thus our use of exome sequencing— findings confirmed by an orthogonal method— to obtain genetic information does not convey additional risk to the fetus or pregnant women.

We next address "informational risks" associated with return of results not relevant to the primary finding of a fetal anomaly, referred to here as secondary or additional findings.

Results, including "additional findings," will be returned to the pregnant woman in order to assess their utility (one of the study aims). These results will be returned in accord with our established clinical pathway. That policy includes an allowance for return of secondary/additional findings in accord with the American College of Medical Genetics recommendations. We will follow that clinical policy, which is available on request. In all cases, all family members sequenced are given the option to "opt out" of receiving all secondary findings.

The purpose of this study is to determine if exome sequencing can help identify the etiology of structural fetal anomalies in pregnancy, to clarify additional benefits to the family and/or fetus from identifying risks to the fetus secondary to a pathogenic result from exome sequencing, and to clarify reproductive risks for future pregnancies, or cascade testing of other family members.

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

10.5

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	UCSF
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	
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	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

10.6 * 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

11.0 Sample Size and Eligibility Criteria

11.1 ENROLLMENT TARGET: How many people will you enroll:

400

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

1. 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 will recruit individuals with African American, Latino, Native American, Asian/Pacific Islander, and mixed ancestries, with a target of 75% underrepresented minorities (URM) overall, but at a minimum 60%. Our anticipated breakdown is approximately 40% Latino, 20% African American, 15% other URM; 25% non-Hispanic white and non-URM Asian patients based on current clinical composition (see Enrollment form). More than 500 cases of fetal anomalies identified by ultrasound are seen per year, indicating an easily achieved recruitment rate of 14% overall, 20% for URM and 8% for non-URM.

2. We anticipate recruiting 6-10 administrators, managers or clinicians at each participating site to complete the Organizational Readiness for Change (ORCA) survey.

11.3 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:

UCSF Fetal Treatment Center at UCSF Betty Irene Moore Women's Hospital. Pregnant women carrying fetuses with anomalous ultrasound findings will be recruited through the UCSF Fetal Treatment Center (FTC). The FTC was the first such program in the world, established nearly 30 years ago, and sees a diverse patient population with a broad spectrum of congenital anomalies and suspected genetic disorders. Approximately 500 patients per year are seen through the FTC, which has a long history of participation in clinical studies involving fetal abnormalities.63-65 Recently, the Center for Maternal-Fetal Precision Medicine (CMFPM) has been established to conduct clinical and translational research through the FTC; Dr. Norton is a co-Director of the CMFPM and an active member of the FTC clinical team. The FTC includes a genetic counselor that is actively involved in research efforts, and a team of research nurses who are supportive of, and experienced in, the recruitment of patients and the conduct of clinical research. A protocol is in place for recruitment of women with fetal anomalies for WES

ZSFGH will also be a site for recruitment of fetal cases. The obstetrical service at ZSFGH cares for approximately 1,200 pregnant women per year from a very diverse patient population, and these women all undergo obstetrical ultrasound on site. When fetal anomalies are detected, patients will be counseled by a genetic counselor and a perinatologist or obstetrical specialist with genetics training. Dr. Juan Vargas, the Director of Obstetrics at ZSFGH, is very supportive of this project. Our teams have collaborated on a large number of clinical studies and our research staff screen and recruit patients at ZSFGH for a number of clinical trials, having access to the electronic medical record (EMR) and the clinics for patient recruitment. We anticipate recruitment of approximately 50 antenatal patients from ZSFGH over the 4 years of the project; recruitment efforts will be supported by the genetic counselor and research assistants who are enrolling at the FTC.

UCSF Fresno Community Medical Center will also be a site for recruitment of fetal cases. UCSF Fresno Community Medical Center serves a diverse patient population, and these women all undergo obstetrical ultrasound on site. When fetal anomalies are detected, patients will be counseled by a genetic counselor and a perinatologist or obstetrical specialist with genetics training. We anticipate recruitment of approximately 30 antenatal patients from UCSF Fresno Community Medical Center over the remaining 2 years of the project; recruitment efforts will be supported by the genetic counselor and research assistants who are enrolling at the FTC.

We are electing to recruit patients participating in an analogous study (17-21662 (Fetal birth defects prospective database: Toward a precision-based approach)) as this study is also offering exome sequencing in pregnancies affected by a specific anomaly called non-immune hydrops fetalis. The additional participation in this protocol would involve these participants completing the surveys related to clinical utility of the test. There is no additional procedures other than these study surveys.

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

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

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

- [x] Inpatients
- [x] Outpatients
- [x] Family members or caregivers
- [x] Providers
- [ ] People who have a condition but who are not being seen as patients
- [ ] Healthy volunteers
- [ ] Students
- [x] Staff of UCSF or affiliated institutions
- [ ] None of the above

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

- [x] 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
- [x] Pregnant women
- [x] Fetuses
- [x] 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:

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**.

We will be offering whole exome sequencing to potential research subjects who have already completed a prenatal diagnostic procedure and would be performing this testing on the previously obtained specimen. Study subjects will be educated using non-directive counseling by a board certified and licensed genetic counselor who is trained in educating patients on complex genetic topics and providing information including the risks, benefits and limitations of genomic analysis.

11.7 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.):

Women carrying a pregnancy with an ultrasound diagnosis of a major structural anomaly (or multiple anomalies) in a major organ system (cardiac, central nervous system, thorax, genito-urinary, gastrointestinal/ventral wall, skeletal and or multiple anomalies)

Clnical concern for a potential underlying genetic condition

Completed or plan to complete CVS or amniocentesis with chromosome analysis or microarray (including VOUS) or this testing on products of conception

Available maternal sample

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

Prior exome sequencing performed for a clinical or research indication

Lack of phenotypic indication of a likely underlying genetic etiology

Mother unwilling or unable to provide a specimen

11.9 * 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

Attach a letter of acknowledgement for the study from the involved patient care manager. If you don't know who the patient care manager is, click here to send an email to the nursing group.

11.10 * 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

11.11 * 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

12.0 Inclusion of Minors in Research

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

- [x] 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:

12.2

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

12.3

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

- [x] 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:

12.4 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)

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

- [x] 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:

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

( ) Yes (•) No

13.0 Recruitment and Consent

13.1 * 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

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

- [x] 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
- [x] Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- [x] Referrals from the community / word of mouth
- [x] 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)

Attach your recruitment materials (e.g., flyers, ads, recruitment letter templates, email text, etc.) in the Other Study Documents section of the Initial Review Submission Packet Form.

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

Potentail referring providers have been sent the study brochure and heard about the study by word of mouth. We will use the attached exome sequencing recruitment script to reach out to patients that have been identified by their provider that is not directly involved in the study recruitment. We will also use this brochure to offer enrollment to this study for patients enrolled and consented under IRB 17-21662 (Fetal birth defects prospective database: Toward a precision-based approach).

Our principal investigators have identified a list of potential respondents who meet the criteria for completion of the Organization Readiness for Change (ORCA) survey.

13.3 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

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

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

- [x] 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)

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

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. This will occur at the time of a prenatal clinical visit and involve review of ultrasound findings and previously completed prenatal diagnosis procedures.

Our principal investigators have identified a list of potential respondents who meet the criteria for completion of the Organization Readiness for Change (ORCA) survey.

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

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

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

- [x] In person
- [x] Phone
- [x] Letter / email
- [ ] Website or app
- [ ] 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.

Attach the recruitment letter or email template in the Other Study Documents section of the Initial Review Submission Packet Form.

13.7 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)

For fetal cases, patients will be approached by a clinician, typically a maternal-fetal specialist, who has counseled the patient regarding the fetal anomaly that has been detected. At the time of recognizing a potential study participant they will be educated regsarding the option for research participation and provided an informational study specific brochure. Written informed consent will be obtained by the study prenatal genetic counselor. Many patients will have undergone prenatal diagnostic testing in an outside laboratory; in such cases, cells or extracted DNA from the original fetal sample will be used for the purpose of this study. The consent process for prenatal WES will include pre-test counseling and the option of choosing whether or not to receive uncertain results and secondary findings. A study brochure, informing prospective participants of the aims of the study and whole exome sequencing procedure has been created and will be provided for review.

This study is specific to UCSF/ZSFGH and UCSF Fresno Community Medical Center locations. We will educate providers in our MFM and genetic counseling program through the already established methods of information dissemination in these teams. We will educate the UCSF MFM community that services the prenatal diagnosis center in their quarterly PDC meeting. The genetic counselors in the UCSF prenatal diagnosis center also service the genetic counseling needs of ZSFGH. They will be educated and given updates regarding this study in their weekly meeting held Wednesdays. This meeting is devoted to discussing complex cases, testing strategies and/or research opportunities to offer to patients.

We will not be actively recruiting from sites outside of UCSF, however, patients sent to UCSF for a second opinion with concern for a fetal anomaly that is confirmed will be offered enrollment during their visit to UCSF.

Finally, study participants pursuing exome sequencing under IRB 17-21662 (Fetal birth defects prospective database: Toward a precision-based approach) will be offered enrollment in this study as well. These participants will be recruited for the purposed of enabling us to incude their health data and exome sequencing results in our database, there will not be any study procedures such as blood draw or exome duplicated by participating in both projects. Those that have consented to IRB 17-21662 and agree to also enroll in this study will also be asked to complete the surveys associated with this study protocol.

We will also be recruiting 6-10 administrators, managers or clinicians at each participating site to complete the Organizational Readiness for Change (ORCA) survey, which will be emailed to these potential participants. Completion of the survey reflects these participants consent since these surveys are anonymous and project activities do not involve the collection of personal information about the respondent.

13.8 * 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 consent form at the end of the consent discussion (signed consent)
- [x] Provide online 'eConsent' using an E-Signature system
- [x] Click through a link in a survey or email after reading about the study and then complete the study online (electronic consent)
- [x] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent)
- [ ] 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)
- [ ] 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.

13.9 * 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.

The patient will be educated regarding the anomalies identified on ultrasound in their pregnancy and meet with a genetic counselor associated with the study to review the testing completed so far in the pregnancy and how it contrasts from whole exome sequencing. A detailed explaination of the risks, benefits and limitations of whole exome sequencing (WES) will take place. After this discussion the patient will be offered to pursue this testing with the cost of testing covered through the study. Because exome sequencing is a new approach, a small number of parents and families will be invited to participate in an additional study, this would include both patient that pursued exome sequencing and those that declined. That study will involve being interviewed by a member of our team, by telephone or in person. For those patients being consented remotely we will be using Docusign as the e-consent platform.

Regarding the ORCA survey for administrators, managers or clinicians, these participants will be sent and email explaining the survey. Completion of the survey reflects these participants consent since these surveys are anonymous and project activities do not involve the collection of personal information about the respondent.

* 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)**

Informed consent will be obtained by genetic counselors supporting this study. Genetic counselors are uniquely trained to educate patients on complex genetic information to ensure informed decision making regarding the benefits, limits and risks for pursing this tesitng that may be related to the fetus, their parents and other family members,

13.10 * 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.

☑ 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)

☐ Other method (describe below):

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

13.11 * DECEPTION: Does this study rely on some deception or misinformation about what the researchers are observing to get valid data? (REQUIRED)

○ Yes ◉ No

13.13 * 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)

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

Initial participation in the study will take a total of 2-3 hours on 2 different days. One of these visits will be devoted to education around the benefits, limits and risks of whole exome sequencing, as well as patient consent. The second visit will be edvoted to review results. The follow up interviews and visits will take 5 minutes to one hour during several follow up visits. Participation in this study will take place over 12-18 months.

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

13.17 OTHER ALTERNATIVES: Describe other alternatives to study participation, if any, that are available to prospective subjects:

For study participants that declined whole exome sequencing a small number of parents and families will be invited to participate in an additional study. That study will involve being interviewed by a member of our team, by telephone or in person. This interview is expected to take about 20 minutes.

Potential study participants may also pursue clinical prenatal whole exome sequencing outside of this study.

14.0 Waiver of Consent/Authorization for Recruitment Purposes

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

14.1 * 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.

14.2 * 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.

14.3 * 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.

14.4 * 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.

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

Prior to obtaining informed consent the patients prenatal ultrsaound reports and results from prenatal diagnosis will be reviewed.

Note: HIPAA requires that you collect the minimum necessary.

14.6 * 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:

All study participants will be assigned a study number and clinical information for data analysis will be performed using that assigned study number. There will be a locked master list that will include a key to identify study subjects with their study number.

15.0 Risks and Benefits

15.1 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:

- [x] Physical discomforts or pain
- [x] Risks to employment, or social or legal standing
- [ ] Risk that the study team may observe possible evidence of child abuse, elder abuse, or a threat to self or others that they are required to report

* For any boxes checked above, describe how you will minimize these risks and discomforts, e.g., adding or increasing the frequency of monitoring, additional screening to identify and exclude people with diminished kidney or liver function, or modification of procedures such as changing imaging studies to avoid giving contrast agent to people who are more likely to suffer side effects from it, etc.: **(REQUIRED)**

Physical discomfort or pain from blood draws:

Risks to employment, or social or legal standing from genetic research:

Possible personal discomfort due to sensitive topics (genetic testing in pregnancy)

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

- Sometimes people feel anxiety about learning new or uncertain genetic information about their pregnancy or their family. Uncertain results in a pregnancy can be especially challenging to incorporate into prenatal decision making.***Information about biological relationships will not be shared by the researchers, unless this information is of medical importance to you or your family.***
- Information about family relationships can be learned during testing. Testing may reveal unexpected information about blood-relatedness. It may reveal situations where a father or another relative has no biological relationship with a child.
- Genetic testing can also cause stress to family relationships when different family members disagree about the need for testing.
- The Genetic Information Nondiscrimination Act (GINA) is a federal law that protects patients against employment and health insurance discrimination. That means that employers and health insurance companies cannot use genetic information when making hiring or coverage decisions. The law has limits, however. Life insurance, long-term care insurance, and disability insurance, are not included in the law's protections. GINA does not cover those serving in the military. Some state laws also include protection against genetic discrimination but safeguards are not completed
- We will take appropriate steps to ensure that personal health information is kept private, however, unforeseen events could result in a loss of privacy.

15.3

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

We will take extensive precautions to maintain participant confidentiality throughout the study. First, lists of individuals who will be participating will be kept in a locked drawer and in password protected computer files in the office of the study coordinator. Used consent forms will also be locked in a filing cabinet in the office of the study coordinator, and electronic forms of the transcripts will be maintained securely on her computer. Confidentiality of all study-related records will be maintained in accordance with State and Federal laws. Only the PI and a limited number of study personnel will have access to data which will be encrypted and stored on a

secure server. De-identified data will be stored in a secure HIPAA compliant database. Datasets used for analysis will be de-identified. Participant identities will not be revealed in any publication that may result from the proposed study.

While there is a risk of emotional distress should be acknowledged, women are only eligible for this study if they have already elected to undergo prenatal genetic diagnosis, where the potential pychological and personal/family health risks upfront for patient consideration and informed decision making regarindg research participation by a consultation with a licensed and certified genetic counselorwhere the potential risk for false negative and positive results are typically discussed with a genetic counselor. Every effort will be made to educate study subjects and provide information about the study in a way that mitigates this risk.

To mitigate risks for inaccurate information from the technology we will confirm all variants using a secondary Sanger sequencing.

15.5 * 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):

- ☐ 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
- ☐ Health and lifestyle changes may occur as a result of participation
- ☑ Knowledge may be gained about their health and health conditions
- ☑ Feeling of contribution to knowledge in the health or social sciences field
- ☐ 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

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

We may find a gene variant or variants that are important to the health of the patient's pregnancy and/or the health of their family.
If a variant is found to explain the birth defects identified in the pregnancy this information may be valuable to enable providers to more accurately counsel about long term outcomes, individualize antenatal care, allow more informed decision-making, and improve the ability of the care team to plan for specific neonatal needs.

15.7 * DATA AND SAFETY MONITORING: Do you have a Data and Safety Monitoring Plan (DSMP) for this study (A DSMP is required for Greater than Minimal Risk research): (Click the Help link for guidance on risk determination) (REQUIRED)

○ Yes ◉ No

This is not required for minimal risk research but the UCSF IRB strongly recommends one to ensure the data collected are adequate to meet the research aims:

16.0 Confidentiality, Privacy, and Data Security

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

- ☑ Conduct conversations about the research in a private room
- ☑ 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.

- [x] 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)

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

- ( ) Yes (•) No

16.3 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
- [ ] Damaging to the participant's financial standing, employability, or reputation
- [x] Potential risks to insurability (health, disability, or life insurance)

Describe the potential consequences:

The Genetic Information Nondiscrimination Act (GINA) is a federal law that protects patients against employment and health insurance discrimination. That means that employers and health insurance companies cannot use genetic information when making hiring or coverage decisions. The law has limits, however. Life insurance, long-term care insurance, and disability insurance, are not included in the law's protections. GINA does not cover those serving in the military. Some state laws also include protection against genetic discrimination but safeguards are not completed

16.4 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:

For our analysis all study subjects including their clinical information (ultrasound findings in the pregnancy, prenatal health records, pregnancy decision making and long term pregnancy outcome) and whole exome sequencing test results will be fully de-identified and assigned a study number. The master key that identifies study subject with their study number will be maintained in a locked folder with only a small amount of study staff including key researchers to have access to this key.

16.5 * 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

16.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obain a Certificate of Confidentiality:

- (•) Yes ( ) No

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

16.7 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:

This testing will be performed in a CLIA certified lab to perform prenatal clinical whole exome sequencing. These results will therefore be shared with both the patient and their care team per patient consent indications.

16.9 * 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
- [ ] 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
- [x] 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:

APeX, Epic systems

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

- [x] Names
- [x] Dates
- [x] Postal addresses
- [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

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

( ) Yes (•) No

16.11 * 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

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

We will be collecting data regarding fetal ultrasound findings, postnatal phenotype information, maternal prenatal labwork and any genetic testing results including microarray analysis, other specific genetic testing if pursued and the results of the exome sequencing that is coordinated as a part of the study participation.

16.13 * 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.

16.14 * 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.

16.15 * 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

16.17 * 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)

16.18 * 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
- [x] 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
- [x] 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)

16.19 * 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.

16.20 * 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

17.0 Financial Considerations

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

- (•) Yes
- ( ) No

17.2 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:

Specify **other** payment/compensation method:

Exome sequencing test will be covered for by the study.

17.3 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

Patient are asked to complete mutliple surveys in the study period. They will be compensated $50 total in gift cardsall surveys are completed. $20 after the first survey and $30 for the second.

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

○ Yes ◉ No

18.0 Other Approvals and Registrations

18.4 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

19.0 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.

19.1 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. Norton, Mary MD,MD	As Principal Investigator, Dr. Norton will be responsible for overseeing development and implementation of study guidelines and protocols, as well as the analysis and publication of data.	The Principal Investigator, Mary Norton MD, is a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences at UCSF. She has been the principal and co-investigator of numerous clinical studies, which have involved recruiting, consenting, enrolling, and following thousands of pregnant women from throughout the San Francisco Bay area.
		Kao Thao earned her

Thao, Kao N	Study Coordinator, Research Assistant	Bachelors of Art in Integrative Biology from University of California, Berkeley. She will be involved with coordinating patient recruitment at UCSF. She has experience as a research assistant in multiple studies in a women's health setting.
Lianoglou, Billie R	Study Recruiter: Recruitment and Consent patients	Billie Lianoglou is a board certified and licensed genetic counselor at the UCSF Fetal Treatment Center and is certified in human subject research.
Dr. Slavotinek, Anne PhD, PhD	Medical Geneticist	Dr. Slavotinek is certified in human subject research
Dr. Shieh, Joseph, MD, PhD	Medical Geneticist	Dr. Shieh is certified in human subject research
Dr. Kwok, Pui-Yan Ph.D., MD, PhD	Dermatologist	Dr. Kwok is certified in human subject research
Gosnell, Kristen A	Clinical Nurse Specialist	Ms. Gosnell is certified in human subject research
Dr. Koenig, Barbara, PhD	Medical Anthrologist	Dr. Koenig is certified in human subject research
Scudmore, Janice C	Nurse Practitioner	Mrs. Scudmore is certified in human subject research
Dr. Keller, Roberta, MD	Neonatologist	Dr. Keller is certified in human subject research
Dr. Michie, Marsha, PhD	Anthropologist	Dr. Michie is certified in human subject research
O'Leary, Allison S	Study Coordinator, Research Assistant	Ms. O'Leary is certified in human subject research
Dr. Sherr, Elliott MD, PhD	Pediatric Neurologist	Dr. Sherr is certified in human subject research
Michelson, Jeremy	Study Coordinator	Mr. Michelson is certified in human subject research

Anguiano, Beatriz	Study coorinator	Ms. Anguiano is certified in human subject 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.
Dong, Shan	bioinformatician	certified in human subject research
Rangwala, Naseem A	study coordinator	certified in human subject research
Outram, Simon M	Dr. Outram is also a study coordinator and will conduct ethnographic observations and interviews.	Dr. Outram is certified in human subject's 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.

Dr. Sanders, Stephan MDPhD	Bioinformatician	Dr. Sanders Dr Sanders trained as a pediatric physician at Nottingham and London in the UK before undertaking a PhD and postdoctoral research position at Yale. His research focuses on using genomics and bioinformatics to understand the etiology of human disease, especially autism spectrum disorder (ASD). He is certified in human subject research
Schwartz, Grace B	lab technician	certified in human subject research
Tobias, Sarah E	Study Recruiter: Recruitment and Consent patients	Sarah Tobias is a board certified and licensed genetic counselor at the UCSF Fetal Treatment Center and is certified in human subject research.
Farrell, Rachel L	Study Recruiter: Recruitment and Consent patients	Rachel Farrell is a board certified and licensed genetic counselor at the UCSF Prenatal Diagnosis Center and is certified in human subject research.
Hoban, Hannah G	study coordinator	certified in human subject research
Rego, Shannon M	Study Recruiter: Recruitment and Consent patients	Shannon Rego is a board certified and licensed genetic counselor working as the lead genetic counselor in the Program for Prenatal and Pediatric Genomic Sequencing study. She is certified in human subject research.
Ackerman, Sara, PhD, MPH	Medical Anthropologist	Dr. Ackerman is certified in human subject research
Norstad, Matthew	Study coordinator	Certified in human subject research
Chen, Flavia H	Study coordinator	Certified in human subjects research

Yip, Tiffany A	Study Recruiter: Recruitment and Consent patients	Tiffany Yip is a licensed genetic counselor, and the assistant genetic counselor in the Program for Prenatal and Pediatric Genomic Sequencing study. She is experienced in consenting for exome testing and certified in human subject research.
Silver, Julia M	Study Recruiter: Recruitment and Consent patients	Julia Silver is a board certified and licensed genetic counselor at the UCSF Prenatal Diagnosis Center and is certified in human subject research.
Patel, Sachi	Study coordinator	Certified in human subjects research
Curry, Cynthia	Medical Geneticist	Dr. Cynthia Curry is a Board-certified Clinical Geneticist at UCSF Fresno. She will recruit patients for this study from those seen at Community Regional Medical Center. Board-certified Clinical Geneticist who has experience with consent for exome sequencing.
Amezcua, Jessica M	Study coordinator	Certified in human subjects research
Faubel, Amanda J	Study coordinator	Certified in human subjects research
Rigler, Nicole A	Study coordinator	Certified in human subjects research
Oman, Natalie	Study coordinator	Certified in human subjects research
Downum, Sarah L	Study coordinator	Certified in human subjects research
Yamane, Taylor A	Study coordinator	Certified in human subjects research
Cullen, Caitlin	Study coordinator	Certified in human subjects research
Tick, Katherine	Study coordinator	Certified in human subjects research

19.2 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:

20.0 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.