Study Protocol for the PDAID trial

Neuroinflammatory Cohort

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Clinical metagenomic next-generation sequencing for diagnosis of meningitis and encephalitis – the PDAID trial

Short title – Precision Diagnosis of Acute Infectious Diseases – PDAID

Protocol Number NCT02910037

Version 1.2 (Initial IRB Approval for Study Protocol)	03/01/2016
Version 1.4 (Original Study Protocol at start of enrollment)	06/10/2016
Version 1.16 (Final Study Protocol at completion of study)	08/17/2017

STATEMENT OF COMPLIANCE
This document is a protocol for a clinical research study. The study was conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

1. PROTOCOL SYNOPSIS

Title	Clinical metagenomic next-generation sequencing for diagnosis of meningitis and encephalitis – the PDAID trial
Short Title	Precision Diagnosis of Acute Infectious Diseases – PDAID
Objectives	To compare the performance of a clinically validated metagenomic next-generation sequencing (mNGS) assay with conventional microbiological testing in diagnosis of infectious causes of meningitis and encephalitis in acutely ill hospitalized patients
Design	Single-group, multisite, prospective clinical diagnostic trial.
Outcomes	Primary 1. Clinical mNGS assay performance (sensitivity, specificity, positive predictive value, negative predictive value) 2. Number and proportion of infectious diagnoses made using the mNGS assay Secondary 1. Impact of mNGS results (positive and negative) on clinical reasoning 2. Impact of mNGS results (positive) on clinical management and outcomes 3. Potential clinical utility of communicating results from supplementary mNGS analyses to physicians 4. Feasibility of a clinical microbial sequencing board (CMSB) for discussing and interpreting mNGS results in clinical context
Interventions	1. Running an mNGS assay for pathogen detection from cerebrospinal fluid (CSF) in a CLIA (Clinical Laboratory Improvement Amendments)-certified laboratory. 2. Reporting mNGS results in the patient electronic medical record 3. Discussing mNGS results with primary care providers and associated consulting physicians during weekly CMSB meetings

Sample Size 300

Population Pediatric and adult patients with meningitis, encephalitis, and/or myelitis

Eligibility Criteria

Inclusion Criteria
Age: Any
Hospital admission or transfer with clinical syndrome of meningitis, encephalitis or myelitis
Symptom onset (or exacerbation) within 2 weeks of CSF sampling
Lack of an etiologic diagnosis at time of enrollment
Meningitis
Fever ≥ 38°C*
AND:
Abnormal neuroimaging or CSF WBC count ≥ 5/cubic mm*
With or Without:
stiff neck, headache or seizure
Encephalitis
Major Criterion:
Altered mental status lasting ≥ 24 h with no alternative cause identified
Minor Criteria (at least 2 required):
Fever ≥ 38°C*
Seizures not fully attributable to a preexisting seizure disorder
New onset of focal neurologic findings
CSF WBC count ≥ 5/cubic mm*
Abnormal brain imaging suggestive of encephalitis
Abnormal electroencephalography consistent with encephalitis
Myelitis
Abnormal spinal cord imaging suggestive of myelitis
AND
CSF WBC count ≥ 5/cubic mm*
Exclusion Criteria
Psychiatric hold
Hospital or university employees or students, or close associates of key study personnel

Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell.
*Fever and CSF pleocytosis were not required for patients with an immunosuppressed state if the treating physician was suspicious for a neurologic infection.

Study Duration 1 year: 06/01/2016 – 07/31/2017

Study Application (Version 1.4)

1.0 General Information

*Enter the full title of your study:		
Precision Diagnosis of Acute Infectious Diseases		
*Enter the study number or study alias		
DAID * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

2.0 Add Department(s)

2.1 List departments and/or research programs associated with this study:

Primary Dept?	Department Name
○	**UCSF** - *115001* - M_Biochemistry and Biophysics
○	**UCSF** - *135118* - M_CTSI-SOS
◉	**UCSF** - *144075* - M_Laboratory Medicine
○	**UCSF** - *138300* - M_MEDICINE
○	**UCSF** - *140020* - M_Neurology

3.0 Assign key study personnel(KSP) access to the study

3.1 *Please add a Principal Investigator for the study:

Chiu, Charles Y 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

Berger, Amy
Other Investigator
Chow, Eric D PhD, PhD
Other Investigator
Chow, Felicia
Other Investigator
Derisi, Joseph L. PhD
Co-Principal Investigator
Gelfand, Jeffrey M
Other Investigator
Geschwind, Michael D MD, MD, PhD
Other Investigator
Langelier, Charles R
Other Investigator
Miller, Steven A
Co-Principal Investigator
Naccache, Samia N
Other Investigator
Samayoa, Erik L
Other Investigator
Wilson, Michael R, MD
Co-Principal Investigator

B) Research Support Staff

Federman, Scot M
Biostatistician
Naccache, Samia N
Data Manager
Pham, Elizabeth
Technician
Samayoa, Erik L
Technician
Sample, Hannah
Study Coordinator
Stryke, Doug
Biostatistician
Yu, Guixia
Technician

3.3 *Please add a Study Contact:

Chiu, Charles Y MD
Derisi, Joseph L. PhD
Mccaleb, Kristen L
Miller, Steven A
Sample, Hannah
Wilson, Michael R, MD

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):

Hauser, Stephen L M.D., M.D,
Department Chair
Lowell, Clifford A MD
Department Chair

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 June 2017

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.

Currently, up to 50% of hospitalized patients with pneumonia, sepsis, and encephalitis / meningitis are treated without a laboratory-confirmed cause of their disease, resulting in delayed and ineffective therapy, increased mortality, and excess healthcare costs. Here ***we aim to use metagenomic next-generation sequencing (mNGS) to provide the first-ever demonstration of precision medicine for the diagnosis of acute infectious diseases in hospitalized patients, with immediate impact on clinical care and patient outcomes.*** We are currently clinically validating the mNGS assay in a licensed clinical diagnostic laboratory (the UCSF Clinical Microbiology Laboratory). Clinical validation of cerebrospinal fluid (CSF) for diagnosis of encephalitis / meningitis, plasma for sepsis, and bronchoalveolar lavage (BAL) fluid for pneumonia is estimated to be complete by Mar 2016, July 2016, and Dec 2016, respectively. In Mar 2016, we will launch a prospective clinical study enrolling patients from 3 UC hospitals (UCSF, UCLA, and UC Davis) to evaluate the performance of the clinically validated mNGS assay relative to routine microbiological testing. Patients will be consented for (1) review of their medical chart and eventual publication, (2) blood draw for orthogonal laboratory testing and/or research, and (3) collection and mNGS analysis of excess material from related sample types that have not been clinically validated (e.g. brain biopsy). We will specifically evaluate how the mNGS results obtained from the clinically validated test affect patient management and clinical outcomes. Ultimately, we aim to deliver a clinically reimbursable, self-sustaining genomic test for infectious diseases that will improve patient outcomes long past the 1-year study time frame.

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: (Click the Help link for definitions and guidance): (REQUIRED)

- ◉ Biomedical research
- ○ 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 * RADIATION EXPOSURE: 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): (REQUIRED)

- ○ Yes ◉ No

4.6 * RISK LEVEL: (REQUIRED)
What is your estimation of the risk level, including all screening procedures and study activities (Help Text updated 9/13):

- ◉ Minimal risk
- ○ Greater than minimal risk

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

- ○ Full Committee
- ◉ Expedited
- ○ Exempt

4.8 * 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

4.11 * 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:

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

◉ Yes ○ No

4.14 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 CHR approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Services (CRS) Advisory Committee
- [ ] CTSI Consultation Services
- [ ] Departmental scientific review
- [x] Other:

* Specify **Other: (REQUIRED)**

California Initiative to Advance Precision Medicine

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

embryos:

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

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

( ) Yes (•) No

5.0 Funding

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

( ) Yes (•) No

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

( ) Yes (•) No

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

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	CALIF Governors Ofc of Planning & Resrch	02	UCSF	Grant	P0509948	

Sponsor Name:	CALIF Governors Ofc of Planning & Resrch
Sponsor Type:	02
Sponsor Role:	Funding
Grant/Contract Number:	P0509948
Awardee Institution:	UCSF

Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
UCSF RAS "P number" or eProposal number:	P0509948
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	Clinical Implementation of Metagenomic Next-Generation Sequencing for Precision Diagnosis of Acute Infectious Diseases
PI Name: (If PI is not the same as identified on the study.)	Charles Y Chiu
Significant Discrepancy:	

If the funding is coming through UCSF and you don't know the A or P number, you can search the eProposal side for the contract or grant (this does NOT replace adding the sponsor by name above AND entering the A or P number):

Project Status	Proposal Number	Project Title	Principal Investigator
Submitted to Sponsor	P0509948	CIAPM Full Proposal Clinical implementation of metagenomic next-generation sequencing for precision diagnosis of acute infectious diseases	Charles Y Chiu MD
Submitted to Sponsor	P0522592	ChiuC New NSF BIGDATA 22Mar201 ... BIGDATA: IA: Collaborative Research: Patient Data-Driven Machine Learning for Diagnosis of Infectious Diseases	Charles Y Chiu MD
Submitted to Sponsor	P0526430	Dr. Gu_new K08_due 10/12/2017_ ... Noninvasive Risk Stratification of Prostate Cancer Using Cell-Free Nucleic Acids	Wei Gu, MD/PhD

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

- [x] Funded by gift (specify source below)
- [ ] Funded by UCSF or UC-wide program (specify source below)
- [x] Specific departmental funding (specify source below)
- [ ] Unfunded (miscellaneous departmental funding)
- [ ] Unfunded student project

* List the gift, program, or departmental funding source: **(REQUIRED)**

Sandler-Bowes Foundation Award, UCSF Clinical Laboratory

6.0 Sites, Programs, Resources, and External IRB Review

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

- [x] UCSF (including Laurel Heights and all the other sites outside the main hospitals)
- [x] Parnassus
- [x] Mission Bay
- [x] China Basin
- [ ] Mount Zion
- [ ] Helen Diller Family Comprehensive Cancer Center
- [ ] Langley Porter Psychiatric Institute
- [x] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Blood Centers of the Pacific (BCP)
- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno Community Medical Center
- [ ] Gallo
- [ ] Gladstone
- [ ] Jewish Home
- [ ] Institute on Aging (IOA)
- [ ] SF Dept of Public Health (DPH)

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

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

UCSF/Clinical Microbiology Laboratory
185 Berry Street, Suite #290
San Francisco, CA 94107
UCSF/Chiu Lab
185 Berry Street, China Basin 185
San Francisco, CA 94107
UCSF/DeRisi Lab
1700 4th Street
QB3 Room BH 401
San Francisco, CA 94158
UCSF/Pleasure Lab
Department of Neurology
675 Nelson Rising Lane, Room 260-270
San Francisco, CA 94158
UCSF/Oksenberg Lab
Department of Neurology
675 Nelson Rising Lane, Room 240-242
San Francisco, CA 94158

UCSF/ Center for Advanced Technology
Genentech Hall, Second floor, room S252
600 16th St.
San Francisco, CA 94158
UCLA Medical Center
UCD Medical Center

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

(•) Yes ( ) No

Please identify which procedures may be done off-site:

UC Davis and UCLA Medical Centers will serve as a major patient recruitment sites for the DAID study outside of UCSF. They will be identifying eligible patients and once consented, collecting patient clinical data and biospecimens relevant to the study. All biospecimens will be shipped to UCSF and relevant clinical data will be uploaded into a RedCap project maintained by the UCSF coordinating team and relying sites for their respective research candidates.

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 multicenter research trial? By multi-center trial, we mean a study where the protocol is developed by an industry sponsor, consortium, a disease-group, etc., who then selects sites across the nation or in different countries to participate in the trial. The local sites do not have any control over the design of the protocol.

(•) Yes ( ) No

Is UCSF the coordinating center:

(•) Yes ( ) No

6.7 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 its affiliates are the coordinating center.

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

6.8 OTHER UC COLLABORATORS: Check any other UC campuses with which you are collaborating on this research study:

- [ ] UC Berkeley
- [x] UC Davis
- [ ] Lawrence Berkeley National Laboratory (LBNL)
- [ ] UC Irvine
- [x] UC Los Angeles
- [ ] UC Merced
- [ ] UC Riverside
- [ ] UC San Diego
- [ ] UC Santa Barbara
- [ ] UC Santa Cruz

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

- ○ Yes
- ◉ No

6.11 UC RELIANCES: Are any of the above UC campuses requesting to rely on UCSF's IRB:

- [x] Yes
- [ ] No

7.0 Outside Site Information

7.1 Outside Site Information

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.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

University of California, Los Angeles

Contact name:

Dr. Jeffrey Klausner

Email:

JDKlausner@mednet.ucla.edu

Phone:

415 876 8901

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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

◉ Yes ○ No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

UC Reliance Registry Application #1595

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

◉ Yes ○ No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

◉ Yes ○ No

Note: your application cannot be processed without the training certificates.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

University of California, Davis

Contact name:

Dr. Christopher Polage

Email:

crpolage@ucdavis.edu

Phone:

(916) 734-3655

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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

◉ Yes ○ No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

UC Reliance Registry #1595

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

◉ Yes ○ No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

◉ Yes ○ No

Note: your application cannot be processed without the training certificates.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Syapse

Contact name:

Adam Jonas

Email:

adamj@syapse.com

Phone:

608.320.1042

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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

◉ Yes ○ No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

Andi Barsan
Andrew Fisher
Maylee Wu
Preeti Bhat
Taylor Horwood
Tom Lemberg
Adam Jonas
Sonny Van
Stephen Mitchell
Syapse team is responsible for 1) facilitating the reporting of metagenomic NGS data, 2) correlating clinical data extracted from the Electronic Medical Record, alongside mNGS data from research samples in a easily searchable database. In addition, Syapse provides the software platform to enable the Precision Medicine Consult service; where subject matter experts can offer clinical guidance to providers, in the context of mNGS and other clinical information.

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

(•) Yes ( ) No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

(•) Yes ( ) No

Note: your application cannot be processed without the training certificates.

8.0 Research Plan and Procedures

8.1 This new consolidated section requests information about:

- **Hypothesis**
- **Aims**
- **Study Design**
- **Background and Significance**
- **Preliminary Studies**
- **Procedures**
- **Statistical Methods**
- **References**

Later sections include:

- **Drugs and Devices**
- **Sample Size, Eligibility, and Subjects**
- **Recruitment and Consent**
- **Risks and Benefits**

- **Data and Safety Monitoring Plan**
- **Confidentiality, Privacy and Security**
- **Financial Considerations**
- **Qualifications of Personnel**
- **Other Approval and Registrations**

8.2 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove (Help Text updated 9/13):

We hypothesize that many clinical illnesses in the hospital (meningitis, encephalitis, sepsis, and pneumonia) are caused by infectious agents but remain undiagnosed because current laboratory testing lacks sensitivity and scope. Clinical implementation of an mNGS assay in a licensed diagnostic laboratory (the UCSF Clinical Microbiology Laboratory) will result in more rapid and accurate diagnoses, decreased costs, and improved clinical outcomes.

8.3 AIMS: List the specific aims:

This study is a prospective, multi-institutional study with the following specific aims:

1. Compare the diagnostic yield of a newly clinically validated metagenomic next-generation sequencing (mNGS) assay to standard microbiologic testing in 300 consented and enrolled patients presenting with (1) acute meningitis and/or encephalitis, (2) sepsis, or (3) pneumonia at 3 hospitals in California
2. To collect clinical specimens for mNGS testing in a licensed diagnostic laboratory and excess specimens or blood for orthogonal laboratory testing and/or research from patients with the aforementioned illnesses.
3. To interpret clinical mNGS results in the context of a precision medicine board and clinical interface
4. To evaluate impact of the mNGS assay on costs and clinical outcomes

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

This is a 1-year prospective cohort study which will enroll 300 patients at UCSF, UCLA, and UC Davis with encephalitis, meningitis, sepsis, or pneumonia. Patients will be enrolled if the clinical mNGS assay correpsonding to the appropriate sample type -- cerebrospinal fluid (CSF) for encephalitis / meningitis (anticipated launch date 3/2016), plasma for sepsis (7/2016), and bronchoalveolar lavage (BAL) fluid for pneumonia (12/2016 --- has been validated in the CLIA laboratory (the UCSF Clinical Microbiology Laboratory). Accordingly, we anticipate that the majority of patients enrolled in the study will be encephalitis and meningitis patients. Patients will be consented for (1) clinical mNGS testing and review of their electronic medical record (clinical, laboratory, and radiological data) and publication of their case histories and (2) collection of blood and additional clinical samples that have not been validated for clincial mNGS testing (e.g. brain biopsy) for the purpose of orthogonal clinical testing to confirm mNGS results and biobanking to facilitate research on additional novel assay development (e.g. autoantibody and host gene transcriptome profiling). If additional clinical samples are to be used only for research purposes and not for orthogonal clinical testing, then only available excess / surplus sample will be collected. As the research on transcriptome profiling will involve deposition of deidentified genetic data into public databases, patients will be explicitly consented for release of their deidentified genetic information.
After clinical mNGS testing is performed and results communicated to the patient and clinical provider, a "precision medicine board" consisting of clinicians, laboratory directors, and research investigators will be available to interpret mNGS results and recommend further diagnostic testing, management, and treatment. This board for infectious diseases is analogous to the tumor board in oncology. We will also extract data from the electronic medical record and evaluate the impact of the mNGS assay on costs and clinical outcomes as compared to a subset of historical controls obtained by retrospective chart review of similar cases in the past for which the mNGS assay was not available.

8.5 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.

We aim to provide the first-ever demonstration of precision medicine for diagnosis of acute infectious diseases in hospitalized patients, with the goal of directly impacting clinical care and improving patient outcomes. Existing methods fail to diagnose many life-threatening infections in a clinically relevant timeframe, resulting in excessive health care costs and unnecessary morbidity and mortality.
Failure to obtain a laboratory-confirmed diagnosis for many acute infectious diseases directly contributes to poor patient outcomes and a high cost burden to the health care system. Key areas of unmet clinical need targeted by this proposal include neurological infections (encephalitis and meningitis), pneumonia, and sepsis. The principal advantage of this approach is the ability to detect all viruses, bacteria, fungi, and parasites in a single, standardized universal test, the clinically validated mNGS assay, directly from diverse sample types such as cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL), and plasma. This approach is comprehensive because all pathogens with the exception of prions are based on nucleic acid (DNA/RNA). Thus, a single shotgun sequencing test is able to simultaneously screen nearly all pathogens directly from clinical samples, bypassing the "one bug, one test" traditional paradigm of infectious disease diagnosis and maximizing the potential impact on patients with acute, life-threatening infections, where time is of the essence.
Currently, up to 50% of hospitalized patients with pneumonia, sepsis, and encephalitis / meningitis are treated empirically without a confirmed etiologic diagnosis, resulting in delayed or ineffective treatments, increased mortality, and excess healthcare costs. For encephalitis, the annual disease burden in the U.S. exceeds 20,000 hospitalizations with a high rate of long-term sequelae and mortality and $2.0 billion cost to the healthcare system. Pneumonia and sepsis are associated with >43,000 avoidable deaths, 2.3 million excess patient days, and $8.1 billion in added costs each year. Metagenomic NGS, by providing a more timely diagnosis in infected patients and the ability to "rule-out" infectious etiologies in patients with non-infectious illness, has the potential to significantly reduce healthcare costs by decreasing hospital lengths of stay and eliminating unnecessary treatments, procedures, and testing. Our NGS assay also aligns perfectly with the Centers for Disease Control and Prevention (CDC) and President's Obama's National Action Plan to Combat Antibiotic-Resistant Bacteria by enabling an early, specific diagnosis that may obviate the need for empiric antibiotics and inform targeted, appropriate treatment, with the potential to ultimately decrease antibiotic resistance in hospitals.

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

At UCSF, we have pioneered the use of unbiased metagenomic next-generation sequencing (mNGS) for detection of all potential pathogens in a single assay, and have demonstrated its utility in saving the life of a critically ill 14-year old boy with previously unrecognized neuroleptospirosis in a case report published in the *New England Journal of Medicine.* We have further demonstrated the value of our mNGS assay by identifying clinically significant pathogens in over 1,000 patients with severe, undiagnosed pulmonary, blood and neurological infections. We have also previously developed an automated sample-to-answer pathogen identification pipeline named SURPI ("Sequence-based Ultra-Rapid Pathogen Identification") to accelerate the speed of the bioinformatics analysis and ensure that NGS results will be available in a fast enough time frame to impact patient care.

8.7 * 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

8.8 * 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)

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

8.9 * PROCEDURES / METHODS: (REQUIRED)

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

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

Examples may include:

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

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

The investigators will seek to identify and enroll patients with a clinical syndrome that may have an acute infectious etiology. Consent will follow procedures outlined under application section for recruitment and consent.
The study investigators or site coordinator will review the medical record and abstract clinical, laboratory, and radiographic data.
A RedCap survey will be used to collect basic demographic information, exposure/travel history, and clinical information such as imaging results, labs, treatment history and clinical phenotype. The patient may be asked directly by the study investigator or site coordinator to provide exposure/travel history,

however, most data will be obtained by reviewing the medical record.
All patients will have had the validated mNGS assay ordered clinically by a provider and the appropriate sample (CSF, plasma, or BAL fluid) collected for clinical testing at UCSF. Specimens will be shipped and processed at UCSF.
An additional sample (e.g. biopsy sample) that has not been clinically validated for mNGS testing may also be collected for orthogonal diagnostic testing to confirm mNGS results and/or for research purposes. If this additional sample is to be used only for research purposes, only available excess / surplus sample will be collected. Specimens will be shipped to UCSF.
A tissue bank will be established at UCSF for future research.
Research candidates will be asked to consent for collection of a venous blood sample of up to 30 ml or 1-3 tubes. Blood collected will be processed to isolate peripheral blood mononuclear cells (PBMCs) and serum for (1) orthogonal clinical validation of the mNGS assay, and/or (2) research analysis.
Blood draws will only be performed on patients who consent and who are 13 years and older. Blood collections may be done on patients who are younger than 13, but only by adding 1-2 tubes to an already scheduled blood draw, thus avoiding venipuncture solely for the research collection.
Subjects will also be consented to be re-contacted to provide short and longer-term follow-up to confirm final diagnosis and outcome.

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

Given that many patients will be severely ill, we will utilize the standardized form, Capacity Assessment Record for Research Informed Consent, to insure that subject capacity is assessed in a systematic manner.
Patients will be requested to participate in a short questionnaire. This questionnaire will be administered verbally at the time of consent and completed by either the patient or surrogate. This is a RedCap questionnaire entitled 'Clinical Case History'. The patient will only be requested to provide information for the following sections: patient information, exposures 1 month before onset, and travel 1 year before onset. The patient or surrogate will not see the remaining sections of the survey. The treating physician will be requested to complete the remainder of the survey. The information to be completed by the treating physician will have already been gathered as part of the patient's routine work-up.

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

☑ Blood
☑ Tissue (describe below):

- [ ] Existing/archival materials (name source below):
- [x] Other (describe below):

Describe and/or name source:

clinical mNGS testing at the UCSF Clinical Microbiology Laboratory: cerebrospinal fluid, plasma, bronchoalveolar lavage fluid
blood draw: blood for PBMCs and serum/plasma
additional specimen types for orthogonal clinical validation or research (surplus): biopsy tissue, nasal swabs, cyst / abscess fluid

8.14 * 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

8.15 * DESTINATION: Specimens will ultimately be stored (check all that apply): (REQUIRED)

Outside Entity:

- [ ] Cooperative group bank
- [ ] NIH
- [ ] Other university
- [ ] Industry sponsor
- [ ] Other

UCSF:

- [x] UCSF repository/bank being established under this protocol
- [x] Existing UCSF specimen repository/bank with CHR approval
- [ ] Other location at UCSF (please describe)

Provide the name of the bank and iRIS approval number (if not being banked at UCSF under this protocol). If you checked 'Other,' please provide the location or lab:

Chiu Laboratory Biobank:

H9187-32565-02 Chiu, Charles Y MD
Pathogen Detection and Discovery in Hospitalized Patients with Unexplained Acute or Chronic Illness

Clinical Microbiology Laboratory Biobank:

H52699-34941-01 Miller, Steven A
Improved diagnosis of infectious meningitis / encephalitis using multiplex molecular methods

H52699-35006-01 Miller, Steven A
Identification and characterization of infectious causes for respiratory infection

8.16 UCSF-BANK PHYSICAL LOCATION: The repository/bank is physically located at (list the address and room number for all locations):

1. UCSF Clinical Microbiology Laboratory (Directors: Steve Miller and Charles Chiu), 185 Berry Street, Suite 290, San Francisco, CA 94107
1. Chiu Lab, 185 Berry Street, Room 185, San Francisco, CA 94107
2.DeRisi Lab, 1700 4th Street, QB3 Room BH 401, San Francisco, CA 94158
3. Pleasure Lab, 675 Nelson Rising Ln. Room 260, San Francisco, CA 94158

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

(•) Yes ( ) No

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

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

8.20 * 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':

indefinitely

8.21 * UCSF-BANKED SPECIMENS - LINKING 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.
- [x] 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:

none. Only researchers directly involved in this study will have access to identifiers.

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

- [x] Name
- [x] Date of birth
- [ ] Social Security number
- [x] Medical record number

- [x] Address
- [x] Phone number
- [ ] Email address
- [ ] Other dates (dates of surgery, visit dates)

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

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

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

- ○ Yes
- ◉ No

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

The UCSF Clinical Microbiology Laboratory will process the clinical sample under validated standardized operating procedures. Bioinformatics analysis will be performed using the SURPI pipeline (Naccache, et al., 2014). We will also occasionally need to perform orthogonal clinical testing (serological, PCR testing) or research polymerase chain reaction (PCR) testing for confirmation of results. All data will be deidentified prior to submission and submitted to dbGaP (database of Genotypes and Phenotypes), an NIH database which archives deidentified data beyond a controlled-access firewall and makes such data only accessible to a limited number of investigators (see http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap).
For the additional excess clinical samples used for research for the purposes of new assay development, we will perform additional analyses including autoantibody profiling, human transcriptome profiling, and probe-based sequencing enrichment.

8.26 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):

- Goldberg B, Sichtig H, Geyer C, Ledeboer N, and Weinstock GM. (2015) Making the leap from research laboratory to clinic: challenges and opportunities for next-generation sequencing in infectious disease diagnostics. *mBio* 6(6):e01888-15.
- Naccache SN, Federman S, Veeraraghavan N, Zaharia M, Lee D, Samayoa E, Bouquet J, Greninger AL, Luk, KC, Enge B, Wadford DA, Messenger SL, Genrich GL, Pellegrino K, Grard G, Leroy E, Schneider BS, Fair JN, Martinez MA, Isa P, Crump JA, DeRisi JL, Sittler T, Hackett, Jr. J, Miller S, and Chiu CY. (2014) A cloud-compatible bioinformatics pipeline for ultra-rapid pathogen identification from next-generation sequencing of clinical samples. *Genome Research* 24(7):1180-9. (PMCID: PMC4079973).
- Wilson MR, Naccache SN, Samayoa E, Biagtan M, Bashir H, Yu G, Salamat SM, Somasekar S, Federman S, Miller S, Sokolic R, Garabedian E, CAndotti F, Buckley RH, Reed KD, Meyer TL, Seroogy CM, Galloway R, Henderson SL, Gern JE, DeRisi JL, and Chiu CY. (2014) Actionable diagnosis of neuroleptospirosis by next-generation sequencing. *New England Journal of Medicine* 370:2408-2017. (PMCID: PMC4134948).
- Greninger AL, Naccache SN, Messacar K, Clayton A, Yu G, Somasekar S., Federman S, Stryke D, Anderson C, Yagi S, Messenger S, Wadford D, Xia D, Watt JP, Van Haren K, Dominguez SR, Glaser C, Aldrovandi G, and Chiu CY. (2015) A novel outbreak enterovirus D68 strain associated with acute flaccid myelitis cases in the United States from 2012-2014: a retrospective cohort study. *Lancet Infectious Diseases* S1473-3099(15)70093-93. E-pub ahead of print.

- Naccache SN, Peggs KS, Mattes FM, Phadke R, Garson JA, Grant P, Samayoa E, Federman S, Miller S, Lunn MP, Gant V, and Chiu CY. (2015) Diagnosis of neuroinvasive astrovirus infection in an immunocompromised adult with encephalitis by unbiased next-generation sequencing. *Clinical Infectious Diseases* 60(6):919-23. (PMCID: PMC4345816).

9.0 Drugs and Devices

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

○ Yes ◉ No

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

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

◉ Yes ○ No

9.4 * NSR: Are you requesting a Non-Significant Risk (NSR) determination for an investigational device: (REQUIRED)

Note: an NSR determination is different from an Investigational Device Exemption (IDE). Check the Help link for more guidance on what types of devices can qualify for an NSR determination.

○ Yes ◉ No

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

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

Please see the UCSF IRB website for more details about the use of devices in research, including the Investigator Checklist for Significant Risk, Non-Significant Risk, and/or IDE Exempt Device Studies

Verification of IDE numbers: If the sponsor's protocol does not list the IDE number, you must submit documentation from the sponsor or FDA identifying the IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet.

If you have any correspondence from the FDA or sponsor regarding this device, please attach it to the application.

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	mNGS IVD for diagnosis of infectious diseases	No	Yes	

Manufacturer/Supplier of Device	University of California, San Francisco
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	The in vitro diagnostic under study (mNGS for diagnosis of infectious disease) will be performed as a laboratory-developed test in the UCSF clinical laboratory. As a laboratory-developed test, FDA approval or IDE registration are not required. The primary purpose of the test is to diagnose patients enrolled in the study.
In the opinion of the sponsor, select the level of risk associated with this device	Significant Risk

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

◉ Yes ○ No

10.0 Sample Size and Eligibility Criteria

10.1 ENROLLMENT TARGET: How many people will you enroll:

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

10.2 TOTAL PARTICIPANTS: For multicenter studies, how many people will be enrolled in total:

300

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

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

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

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

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

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

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

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

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

10.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on patient care units at UCSF medical facilities: (REQUIRED)

○ Yes ◉ No

11.0 Recruitment and Consent

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

- [x] Medical records review
- [ ] 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)
- [ ] Referrals from the community / word of mouth
- [ ] Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- [ ] Online recruiting tool such as TrialSpark
- [ ] CTSI Recruitment Services unit
- [ ] Other method (describe below)

11.2 * 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)

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

Treating clinicians on the infectious disease, neurology, and critical care services will refer patients with infectious disease syndromes. At that point, the Study Investigator, co-Investigators or Study Coordinator will review the patient's clinical information to determine whether they are eligible for the study. The Study Investigator, co-Investigator or Study Coordinator will then approach and consent the patient (or his/her surrogate decision maker) for the study.
Similarly, the Study Investigator, co-Investigator, or Study Coordinator will screen patients in APeX for eligiblility. If patients meet criteria, the primary treating team will be contacted for permission to approach and discuss the study with the potential research candidate. The Study Investigator, co-Investigator or Study Coordinator will approach for possible consent.
A RedCap Referral survey will be used to assist with determining patient eligibilty. This will be submitted to either the CRC, PI, or co-PI to review and determine eligibility prior to approaching patients for consent.

11.4 * 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)

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

- [x] In person
- [x] Phone
- [ ] 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.

11.6 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)

Potential participants will be identified by treating clinicians who have ordered the clinical UCSF mNGS and referred the patient to opt into research participation. Study team members will also review medical records for potential subjects that meet criteria.
Subjects will be approached by their treating clinician(s) in the context of their ongoing clinical care (e.g. at the treating medical center).

11.7 * 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)
- [ ] Provide online 'eConsent' using DocuSign or another E-Signature system
- [ ] Click through a link in a survey or email after reading about the study and then complete the study online (electronic consent)
- [ ] 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)
- [x] 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.

11.8 * 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.**

As this study coincides with the release of the new UCSF metagenomic Next-Generation Sequencing (mNGS) test, candidates and/or surrogates will be approached for possible consent to the study after the mNGS clinical test has been ordered by the treating team.

UCSF Research Candidate with Capacity to Consent

The PI or other study key personnel will approach the research candidate and invite them to learn more about the study. The PI or study key personnel will describe the study and the research candidate will be given ample time to ask questions and consider their choice. Written informed consent will only be obtained when the candidate feels comfortable proceeding with the study. A photocopy of the signed consent documents will be provided to the candidate after they have been signed.

Specimens may be sent to the Clinical Microbiology Lab at UCSF for mNGS prior to the patient being approached for possible consent. However, ancillary specimens will not be obtained prior to candidate consent.

UCSF Surrogate Consent

Some research candidates will not be able to provide informed consent due to altered mental status or cognitive impairment caused by their illness. Surrogates who are local and able to meet the study personnel at bedside will be consented in person. The study PI or other key personnel will approach the surrogate at the hospital to explain the research study and invite them to give consent on behalf of the research candidate. The surrogate will be given ample time to discuss and ask questions. They surrogate will complete the "Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research". When ready to sign the documents, they will sign the consent documents and be provided a photocopy of the signed forms.

Surrogates who are not local or unable to meet the study personnel at the hospital, may be contacted

and invited to learn more about the study over the phone. Surrogate contact information will be gathered from either the electronic medical record, the treating physician, or by contacting the nurse, case manager or other hospital staff involved in caring for the research candidate. The PI or other study personnel will reach out to the surrogate by phone to explain the research study and invite them to give consent on behalf of the research candidate. If the surrogate provides verbal consent, ancillary specimens may be collected after this initial contact with the surrogate, including a blood draw. At the time of initial verbal consent either the study personnel will schedule a meeting with the surrogate at a later date at the hospital to review and sign the consent documents or they will be sent a package with 2 copies (one to be returned and one for the participant to keep) of each of the following documents: the study consent forms, bill of rights, HIPPA authorization form and self-certification of surrogate form. A stamped envelope will also be provided to return the signed documents in. If requested, an electronic copy will also be sent to the surrogate. The surrogate will be given ample time to consider and discuss the study. No ancillary samples will be collected until verbal consent is received.
Ancillary specimens may be collected and processed after verbal consent. Signed consent will be obtained after obtaining verbal consent. If signed consent is not received by the surrogate within 4 months of receiving the specimen(s), the participant will be considered not enrolled and PHI will be removed from records/ destroyed and banked specimens will be destroyed.
Specimens may be sent to the Clinical Microbiology Lab at UCSF for mNGS prior to the patient being approached for possible consent.

Outside Relying Site Research Candidate with Capacity to Consent

Outside relying sites will similarly ordering the clinical mNGS test and subsequently or simultaneously be approaching candidates for possible consent to the research study.
The relying outside site PI or other study key personnel will approach the research candidate and invite them to learn more about the study. The PI or study key personnel will describe the study and the research candidate will be given ample time to ask questions and consider their choice. Written informed consent will only be obtained when the candidate feels comfortable proceeding with the study. A photocopy of the signed consent documents will be provided to the candidate after they have been signed.
Specimens may be sent to the Clinical Microbiology Lab at UCSF for mNGS prior to the patient being approached for possible consent. However, ancillary specimens will not be obtained prior to candidate consent.

Outside Relying Site Surrogate Consent

Some research candidates at outside sites will not be able to provide informed consent due to altered mental status or cognitive impairment caused by their illness. Surrogates who are local to the relying sites and able to meet the local study personnel at bedside will be consented in person. The local study PI or other key personnel will approach the surrogate at the hospital to explain the research study and invite them to give consent on behalf of the research candidate. The surrogate will be given ample time to discuss and ask questions. They surrogate will complete the "Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research". When ready to sign the documents, they will sign the consent documents and be provided a photocopy of the signed consent form, HIPPA auth, and Bill Rights. One version of the consent document will be used at all sites.
Surrogates who are not local or unable to meet the local study personnel at the hospital, may be contacted and invited to learn more about the study over the phone. Surrogate contact information will be gathered from either the electronic medical record, the treating physician, or by contacting the nurse, case manager or other hospital staff involved in caring for the research candidate. The local PI or other study personnel will reach out to the surrogate by phone to explain the research study and invite them to give consent on behalf of the research candidate. If the surrogate provides verbal consent, ancillary specimens may be collected after this initial contact with the surrogate, including a blood draw. At the time of initial verbal consent either the study personnel will schedule a meeting with the surrogate at a later date at the hospital to review and sign the consent documents or they will be sent a package with 2 copies (one to be returned and one for the participant to keep) of each of the following documents: the study consent forms, bill of rights, HIPPA authorization form and self-certification of surrogate form. A stamped envelope will also be provided to return the signed documents in. If requested, an electronic copy will also be sent to the surrogate. The surrogate will be given ample time to consider and discuss the study. No ancillary samples will be collected until verbal consent is received.
Ancillary specimens may be collected and processed after verbal consent. Signed consent will be obtained after obtaining verbal consent. If signed consent is not received by the surrogate within 4 months of receiving the specimen(s), the participant will be considered not enrolled and PHI will be removed from records/ destroyed and banked specimens will be destroyed.

Outside non-relying site consent

Non-relying sites will consent research candidates and/or surrogates according to local IRB protocols.

Re-Consent for participants that gain capacity to consent after enrollment

Research candidates who were enrolled by surrogate consent while in the hospital will be re-contacted in the case they re-gain capacity to give informed consent. We anticipate this to occur once the patient is no longer hospitalized. Therefore, re-consent will be initiated with a phone call to explain the study to the

research participant and give them the option to remain in the study or to withdraw. If the participant wishes to be withdrawn, banked specimens will be destroyed and no further research will be conducted using the specimens. However, any research already done using the specimens or data will be kept and analyzed as part of the study. If the participant wishes to remain in the study, they will be asked to sign new consent forms. Documents (2 of each: consent form, HIPPA authorization, and Bill of Rights) will be mailed to the participant. One copy will be for the participant to keep for their personal records and the second to sign and return.

* 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)**

At UCSF,
Hannah Sample, BS -- Study Coordinator, ~2 year experience in obtaining informed consent for research studies
Amy Berger, MD -- internal medicine physician, hospitalist training, ~3 years experience in obtaining informed consent for research studies
other faculty, fellows, residents on the Molecular Medicine, Neurology, Infectious Diseases consult services -- clinical providers at UCSF who have been trained by the investigators on the details of the CIAPM study and with at least 5 years experience in obtaining informed consent for research studies

11.9 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED)

Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

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

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

Subjects will be asked to explain back the risks, benefits and study protocols. All prospective subjects will have a detailed neurological exam, part of which will entail a mental status exam in which multiple cognitive domains are assessed. In addition, we will administer the attached Capacity Assessment Record for Research Informed Consent. This document will insure that we assess and document whether the potential research subject is able to make a choice whether to participate in the research protocol, whether he/she shows understanding of the research protocol and its elements, including the risks/benefits of participation, whether he/she is able to provide rational reasons for participating or not participating the research protocol and whether he/she shows an appreciation of the personal risks/benefits of participating or not participating in the protocol.

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

About 30-60 mins for consent. The rest of the study procedures involve processing and analysis but not subject time. The 30-60 minutes for a follow up telephone call to confirm long-term outcome and final diagnosis.
A blood draw shoud take about 5 minutes.

IMPORTANT TIP: Ensure this information is consistent with the

information provided in the consent form.

12.0 Waiver of Consent/Authorization for Recruitment Purposes

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

12.1 * 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.

12.2 * 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.

12.3 * 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.

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

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [x] 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.

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

Name, MRN, dates, clinical history for the purposes of establishing eligibility based on suspected diagnosis and clinical syndrome. Phone numbers may also be collected in order to contact non-local surrogates or research candidates.

Note: HIPAA requires that you collect the minimum necessary.

12.6 * 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:

Data on subjects who are not eligible or do not wish to participate will be destroyed. Patient name and MRN will be kept on record in the secure research database so that patients who have declined participation will not be approached again.

13.0 Surrogate Consent

13.1 PSYCHIATRIC SCREEN: Are any subjects inpatients on a psychiatric ward or mental health facility, or on psychiatric hold:

(•) No

If Yes, use of surrogate consent for research is NOT allowed in California.

13.2 AREAS OF RESEARCH: Is this study related to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of the research subjects:

(•) Yes

13.3 JUSTIFICATION: Explain why use of surrogates is necessary for completion of this study:

Many subjects to be enrolled in this study may be incapacitated with a serious illness, sedated, or otherwise unable to provide informed consent. For enrollment in this study, the use of surrogates with durable power of attorney will be necessary for these subjects.

13.4 COGNITIVE ASSESSMENT: Describe the plans for assessing the decision-making capacity of prospective subjects:

We will assess the decision-making capacity of prospective subjects by their condition (sedated, intubated, or otherwise incapacitated patients will not be able to make decisions), including severity of illness, and a clinician determination of whether they are able to provide informed consent.

13.5 POST-ENROLLMENT CONSENT PLANS: Describe the plans for obtaining consent from subjects who regain ability to consent after a surrogate has given initial consent:

If subjects regain ability to consent after a surrogate has given initial consent, and are otherwise accessible (e.g. still in the hospital), we will make every effort to obtain informed consent from the subject directly.

13.6 SURROGATE CONSENT REQUIREMENTS: Check to acknowledge:

- [x] Research takes place in California. All surrogates will complete the "Self-Certification of Surrogate Decision Makers for Participation in Research" form.
- [x] Conscious subjects will be notified of the decision to contact a surrogate. If subjects object to study participation, they will be excluded even if their surrogate has given consent.
- [x] Surrogates will not receive any financial compensation for providing consent.
- [x] If a higher-ranking surrogate is identified at any time, the investigators will defer to the higher-ranking surrogate's decision regarding the subject's participation in the research.

For research taking place outside of California, explain how investigators will confirm that surrogates are legally authorized representatives:

14.0 Risks and Benefits

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

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

14.2 RISKS: Describe any anticipated risks and discomforts not listed above:

1. We will be analyzing surplus CSF, blood, other bodily fluids and biopsy tissue, which will not be able to be returned to the subject for further clinical analysis.
2. It is possible that a pathogen will be identified using this approach, that upon additional clinical

confirmation by the treating team, may need to be reported to public health authorities by law, which could have implications for patient privacy.
3. There is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record. Taking part in a genetic study may also have a negative impact or unintended consequences on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk. Although your name will not be with the sample, it will have other facts about you such as information about your medical history, age and gender. These facts are important because they will help us learn if the factors that cause neurologic disease to occur or get worse are the same or different based on these facts. Thus it is possible that study finding could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.
4. Drawing blood may cause temporary discomfort from the needle stick, bruising, and very rarely infection.

14.3

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

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

All clinical specimens will be obtained by trained clinical personnel according to standard operating procedures, and the procedures will only be performed as clinically indicated.

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

These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities.

Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

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

As described in the "Qualifications of Key Study Personnel" section, all research staff involved in this project have extensive experience with research and patient care and understand the importance of minimizing risks to study subjects. As described in the "Privacy" section, we have numerous protections in place to insure subject privacy.

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

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

☐ 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
- [x] 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

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

The risk to subjects is minimal, principally loss of privacy (although every effort will be made to maintain confidentiality, especially of genetic information). Knowledge may be gained from the clinically validated mNGS test about the infectious cause of their illness.

15.0 Confidentiality, Privacy, and Data Security

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

- [x] Conduct conversations about the research in a private room
- [ ] 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)

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

○ Yes ◉ No

15.3 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

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

Specimens and data will be coded. The "key" to this code will kept in RedCap. RedCap will only be accessible to key study personnel and no identifying information will be shared with researchers not directly involved in the study and who are listed as study personnel on this application.

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

(•) Yes ( ) No

The confidentiality and privacy section of the consent form should include this as a possible risk of participation.

* Describe the types of reportable information the research team may encounter and provide the details of the reporting plan: **(REQUIRED)**

If there is suspicion for a concerning pathogen, the PI will contact the treating physician and/or clinical laboratory to discuss the finding. Public health reporting may be indicated if confirmed by the clincial lab and treating physician. The PI will not report research findings for public health reporting as these are research findings.

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

( ) Yes (•) No

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

(•) Yes ( ) No

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

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

Explain under what circumstances research results may be shared:

Results from the clinical mNGS test (CSF, plasma, or BAL) will be reported in the electronic medical record and communicated to the treating clinician as this is a clinically validated test performed in the UCSF Clinical Microbiology Laboratory.
For research results from non-validated specimen types (e.g. brain biopsy), a narrative results report will be discused with the treating clinician detailing the candidate pathogen(s) found, research assay methods, and limitations. The discussion will include any testing available in CLIA-certified laboratories for confirmation of the research result, if applicable. The results will be marked specifically as "Research use only not to be used for clinical purposes" and "Any results (positive or negative) do not exclude any other causes for patient illness". Thus, these research results will not be used for clinical purposes but may be communicated to clinicians to guide additional CLIA-certified diagnostic testing.

15.8 * IDENTIFIERS: Will any personal identifiers be collected: (REQUIRED)

(•) Yes ( ) No

Check all the identifiers that may be included:

- [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
- [x] Facial photos or other identifiable images
- [ ] Any other unique identifier

If publications from this study may include ANY photos or images of patients - even without faces - either collected for research or from the medical records, you are required to have each patient sign the 'Consent for Photography / Authorization for Publication' form prior to submittal for publication. Failure to obtain consent for publication may result in a finding of Serious Non-compliance by the IRB and civil and criminal penalties, *including fines up to $1.5 million dollars* for violation of the HIPAA privacy protections if a participant complains.

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

(•) Yes ( ) No

15.9 DATA DISCLOSURE: Will identifiable information be shared with outside groups:

( ) Yes (•) No

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

Collection methods:

- [x] Paper-based (surveys, logs, diaries, etc.)
- [x] Electronic case report forms (CRFs), such as OnCore or another clinical trial management portal
- [x] Web-based online surveys or computer-assisted interview tool
- [ ] Mobile applications (mobile or tablet-based)
- [ ] Wearable devices

- [ ] Audio/video recordings
- [ ] Other:

* What online survey tool will you use: **(REQUIRED)**

- [ ] Qualtrics (Recommended)
- [x] 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)**

- [x] UCSF
- [ ] SF VAMC
- [ ] Amazon (Amazon Cloud)
- [ ] Other academic institution
- [x] 3rd party vendor (business entity)
- [ ] Other (explain below)

* Do you have a contract or Data Use Agreement with a 3rd party for research data collection, storage, access, and ownership: **(REQUIRED)**

(•) Yes ( ) No

15.12 DATA SECURITY: Indicate how data are kept secure and protected from improper use and disclosure (check all that apply):

NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- [ ] Data are stored securely in My Research
- [ ] Data are coded; data key is destroyed at end of study
- [x] Data are coded; data key is kept separately and securely
- [x] Data are kept in a locked file cabinet
- [x] Data are kept in a locked office or suite
- [x] Electronic data are protected with a password
- [x] Data are stored on a secure network
- [x] Data are collected/stored using REDCap or REDCap Survey
- [ ] Data are securely stored in OnCore

15.13 * DATA SECURITY: Confirm below that you will keep data confidential: (REQUIRED)

I will keep any data sets that include identifiers secure and protected from improper use and disclosure by using methods such as:

- **Physical Security – Keeping data in locked file cabinets, locked offices, locked suites, and physically securing computers and servers.**
- **Electronic Security – Following UCSF minimum security standards for electronic information resources, which includes (but is not limited to): not storing identifiers on portable devices like laptops or flash drives if they are unencrypted, encrypting portable devices, and storing**

data in password-protected files and on secure networks.

(●) Yes

15.15 HIPAA APPLICABILITY: Study data will be:

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

16.0 Financial Considerations

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

( ) Yes (●) No

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

( ) Yes (●) No

17.0 Qualifications of Key Study Personnel

17.1

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. Also identify each person who will be involved in the consent process. Click the orange question mark for more information and examples.
Under qualifications, please include:

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

November, 2015 - NEW Definition of Key Study Personnel and CITI

Training Requirements:

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.

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.

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. Chiu, Charles Y MD	Principal investigator, Supervision of next generation sequencing techniques and bioinformatic analysis of sequencing data, patient consent	UCSF Associate Professor of Laboratory Medicine and Medicine/Infectious Diseases; Director, UCSF-Abbott Viral Diagnostics and Discovery Center; Associate Director, UCSF Clinical Microbiology; expert in pathogen discovery techniques, next generation sequencing and bioinformatics
Dr. DeRisi, Joseph, PhD	Supervision of next generation sequencing techniques and bioinformatic analysis of sequencing data, patient consent	UCSF Professor and Chair of Biochemistry and Biophysics, expert in pathogen discovery techniques, next generation sequencing and bioinformatics
Dr. Gelfand, Jeffrey MD	Patient recruitment, consent, study design	UCSF Assistant Professor of Neurology, UCSF Multiple Sclerosis Center, expert on neuroimmunological diseases, Masters in Clinical Research
Dr. Wilson, Michael MD	Study design, perform next generation sequencing on clinical specimens and bioinformatics analysis, patient consent	UCSF Assistant Professor in Residence in Neurology, UCSF MS Center, expert in neuro-infectious diseases
Langelier, Charles R	Study design, perform next generation sequencing on clinical specimens and	UCSF Infectious Diseases fellow

	bioinformatics analysis, patient consent	
Chow, Felicia, MD	Study design, patient recruitment, data analysis, patient consent	UCSF Assistant Professor of Neurology, Neurologist expert in neuro-infectious diseases
Dr. Pleasure, Samuel M.D., PhD	Study design, autoantibody screening, patient consent	UCSF Professor of Neurology, Neurologist expert in neuroimmunological diseases, Neuroanatomist
Dr. Geschwind, Michael, MD, PhD	Study design, data acquisition and analysis, patient consent	UCSF Professor of Neurology, neurologist expert in rapdily progressive dementia
Sample, Hannah	Study coordinator; Patient recruitment and consent; specimen processing; study database management	UCSF clinical research coordinator
Dr. Chow, Eric, PhD	perform next generation sequencing on clinical specimens, data analysis	Director - Center for Advanced Technology UCSF Dept. of Biochemistry and Biophysics
Samayoa, Erik L	perform next generation sequencing on clinical specimens	CLIA Lab technician, Chiu Lab
Naccache, Samia N	perform next generation sequencing on clinical specimens and bioinformatics analysis; data manager; CLIA technician running the mNGS assay	PhD Bioinformatician, CLIA Lab technician, Chiu Lab
Miller, Steven	Supervision of next generation sequencing techniques and bioinformatic analysis of sequencing data	UCSF Associate Professor of Laboratory Medicine, Director, UCSF Clinical Microbiology
Federman, Scot M	next-generation sequencing data analysis; running SURPI bioinformatics pipeline	UCSF Programmer/Analyst III, UCSF Department of Laboratory Medicine
Stryke, Doug	next-generation sequencing data analysis; running SURPI bioinformatics pipeline	UCSF Programmer Analyst, UCSF Department of Laboratory Medicine
Berger, Amy	study design; enrolling patients for NGS study; obtaining consent	UCSF Resident Physician
Mccaleb, Kristen L	Study coordinator; Patient recruitment and consent; specimen processing; study database management	UCSF Special Projects Manager, UCSF Office of the Executive Vice Chancellor & Provost
Pham, Elizabeth		

	CLIA technician running the clinical mNGS assay	UCSF Clin Lab Scientist UCSF Department Laboratory Medicine
Samayoa, Erik L	CLIA technician running the clinical mNGS assay	UCSF Clin Lab Scientist UCSF Department Laboratory Medicine
Yu, Guixia	Sample biobanking and aliquotting; running confirmatory research assays for the mNGS clinical test	UCSF SRA, UCSF Department of Laboratory Medicine

18.0 Other Approvals and Registrations

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

○ Yes ◉ No

18.2 * HUMAN GENE TRANSFER: Does this study involve human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to IRB approval): (REQUIRED)

○ Yes ◉ No

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 #:

Chiu lab: BUA 49187-BU-01-INC; CLIA certificate 05D1024215

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

19.0 End of Study Application

19.1

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 wants your feedback about this new form. Please click the link to take a brief survey about the new application form.

Study Application (Version 1.16)

1.0 General Information

*Enter the full title of your study:		
Precision Diagnosis of Acute Infectious Diseases		
*Enter the study number or study alias		
PDAID * This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.		

2.0 Add Department(s)

2.1 List departments and/or research programs associated with this study:

Primary Dept?	Department Name
○	**UCSF** - *115001* - M_Biochemistry and Biophysics
○	**UCSF** - *135118* - M_CTSI-SOS
◉	**UCSF** - *144075* - M_Laboratory Medicine
○	**UCSF** - *138300* - M_MEDICINE
○	**UCSF** - *140020* - M_Neurology

3.0 Assign key study personnel(KSP) access to the study

3.1 *Please add a Principal Investigator for the study:

Chiu, Charles Y 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

Berger, Amy
Other Investigator
Chow, Eric D PhD, PhD
Other Investigator
Chow, Felicia, MD
Other Investigator
Derisi, Joseph L. PhD
Co-Principal Investigator
Gelfand, Jeffrey MD
Other Investigator
Geschwind, Michael MD, PhD
Other Investigator
Langelier, Charles R
Other Investigator
Miller, Steven
Co-Principal Investigator
Naccache, Samia N
Other Investigator
Samayoa, Erik L
Other Investigator
Wilson, Michael R, MD
Co-Principal Investigator

B) Research Support Staff

Federman, Scot M
Biostatistician
Naccache, Samia N
Data Manager
Pham, Elizabeth
Technician
Samayoa, Erik L
Technician
Sample, Hannah
Study Coordinator
Stryke, Doug
Biostatistician
Weininger, Joshua K
Study Coordinator
Yu, Guixia
Technician
Zorn, Kelsey C
Study Coordinator

3.3 *Please add a Study Contact:

Chiu, Charles Y MD
Derisi, Joseph L. PhD

Mann, Jennifer
Miller, Steven
Sample, Hannah
Wilson, Michael R, MD

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):

Hauser, Stephen M.D.
Department Chair
Lowell, Clifford A MD
Department Chair

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 June 2017

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.

Currently, up to 50% of hospitalized patients with pneumonia, sepsis, and encephalitis / meningitis are treated without a laboratory-confirmed cause of their disease, resulting in delayed and ineffective therapy, increased mortality, and excess healthcare costs. Here ***we aim to use metagenomic next-generation sequencing (mNGS) to provide the first-ever demonstration of precision medicine for the diagnosis of acute infectious diseases in hospitalized patients, with immediate impact on clinical care and patient outcomes.*** Clinical validation of the mNGS assay in a licensed clinical diagnostic laboratory (the UCSF Clinical Microbiology Laboratory) is complete for cerebrospinal fluid (CSF) for the diagnosis of encephalitis / meningitis as of June 2016. Validation is ongoing on plasma for sepsis, and bronchoalveolar lavage (BAL) fluid for pneumonia is anticipated complete by June 2017, and Dec 2017, respectively. In June 2016, we launched a prospective clinical study enrolling patients from 4 UC hospitals (UCSF, UCLA, and UC Davis) to evaluate the performance of the clinically validated mNGS assay relative to routine microbiological testing. Patients will be consented for (1) review of their medical chart and eventual publication, (2) blood draw for orthogonal laboratory testing and/or research, and (3) collection and mNGS analysis of excess material from related sample types that have not been clinically validated (e.g. brain biopsy). We will specifically evaluate how the mNGS results obtained from the clinically validated test affect patient management and clinical outcomes. Ultimately, we aim to deliver a clinically reimbursable, self-sustaining genomic test for infectious diseases that will improve patient outcomes long past the 1-year study time frame.

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: (Click the Help link for definitions and guidance): (REQUIRED)

- (•) Biomedical research
- ( ) 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 * RADIATION EXPOSURE: 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): (REQUIRED)

- ( ) Yes (•) No

4.6 * RISK LEVEL: (REQUIRED)
What is your estimation of the risk level, including all screening procedures and study activities (Help Text updated 9/13):

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

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

- ( ) Full Committee
- (•) Expedited
- ( ) Exempt

4.8 * 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
- [x] 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.)
- [x] 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)
- [x] Category 7: Low risk behavioral research or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies

4.11 * 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:

pending

If you don't yet have the NCT#, type 'Pending.'

4.12 * CLINICAL TRIAL PHASE (REQUIRED)
Check the applicable phase(s) (Help Text updated 9/13):

- [ ] Phase I
- [ ] Phase II
- [ ] Phase III
- [ ] Phase IV

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

(•) Yes ( ) No

4.14 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 CHR approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Services (CRS) Advisory Committee
- [ ] CTSI Consultation Services
- [ ] Departmental scientific review
- [x] Other:

* Specify **Other: (REQUIRED)**

California Initiative to Advance Precision Medicine

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

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

4.16 * 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

The Conflict of Interest Advisory Committee (COIAC) office may contact you for additional information.

5.0 Funding

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

( ) Yes (•) No

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

( ) Yes (•) No

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

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution	Contract Type:	UCSF RAS "P number" or eProposal number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	CALIF Governors Ofc of Planning & Resrch	02	UCSF	Grant	P0509948	

Sponsor Name:	CALIF Governors Ofc of Planning & Resrch
Sponsor Type:	02
Sponsor Role:	Funding
Grant/Contract Number:	P0509948
Awardee Institution:	UCSF
Is Institution the Primary Grant Holder:	Yes
Contract Type:	Grant
UCSF RAS "P number" or eProposal number:	P0509948
UCSF RAS System Award Number ("A" + 6 digits):	
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	Clinical Implementation of Metagenomic Next-Generation Sequencing for Precision Diagnosis of Acute Infectious Diseases
PI Name: (If PI is not the same as identified on the study.)	Charles Y Chiu
Significant Discrepancy:	

If the funding is coming through UCSF and you don't know the A or P number, you can search the eProposal side for the contract or grant (this does NOT replace adding the sponsor by name above AND entering the A or P number):

Project Status	Proposal Number	Project Title	Principal Investigator
		CIAPM Full Proposal	Charles Y Chiu MD
Submitted to Sponsor	P0509948	Clinical implementation of metagenomic next-generation sequencing for precision diagnosis of acute infectious diseases	
		ChiuC New NSF BIGDATA 22Mar201 ...	Charles Y Chiu MD

Submitted to Sponsor	P0522592	BIGDATA: IA: Collaborative Research: Patient Data-Driven Machine Learning for Diagnosis of Infectious Diseases Dr. Gu_new K08_due 10/12/2017_ ... Wei Gu, MD/PhD
Submitted to Sponsor	P0526430	Noninvasive Risk Stratification of Prostate Cancer Using Cell-Free Nucleic Acids

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

- [x] Funded by gift (specify source below)
- [ ] Funded by UCSF or UC-wide program (specify source below)
- [x] Specific departmental funding (specify source below)
- [ ] Unfunded (miscellaneous departmental funding)
- [ ] Unfunded student project

* List the gift, program, or departmental funding source: **(REQUIRED)**

Sandler-Bowes Foundation Award, UCSF Clinical Laboratory

6.0 Sites, Programs, Resources, and External IRB Review

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

- [x] UCSF (including Laurel Heights and all the other sites outside the main hospitals)
- [x] Parnassus
- [x] Mission Bay
- [x] China Basin
- [ ] Mount Zion
- [ ] Helen Diller Family Comprehensive Cancer Center
- [ ] Langley Porter Psychiatric Institute
- [x] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Blood Centers of the Pacific (BCP)
- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno Community Medical Center
- [ ] Gallo
- [ ] Gladstone
- [ ] Jewish Home
- [ ] Institute on Aging (IOA)
- [ ] SF Dept of Public Health (DPH)

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

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

UCSF/Clinical Microbiology Laboratory
185 Berry Street, Suite #290
San Francisco, CA 94107

UCSF/Chiu Lab
185 Berry Street, China Basin 185
San Francisco, CA 94107

UCSF/DeRisi Lab
1700 4th Street
QB3 Room BH 401
San Francisco, CA 94158

UCSF/Pleasure Lab
Department of Neurology
675 Nelson Rising Lane, Room 260-270
San Francisco, CA 94158

UCSF/Oksenberg Lab
Department of Neurology
675 Nelson Rising Lane, Room 240-242
San Francisco, CA 94158

UCSF/ Center for Advanced Technology
Genentech Hall, Second floor, room S252
600 16th St.
San Francisco, CA 94158

UCLA Medical Center

UCD Medical Center

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

(•) Yes ( ) No

Please identify which procedures may be done off-site:

UC Davis and UCLA Medical Centers will serve as a major patient recruitment sites for the DAID study outside of UCSF. UCD, UCLA, UCSD as well as all other clinical outside sites will be identifying eligible patients and once consented, collecting patient clinical data and biospecimens relevant to the study. All biospecimens will be shipped to UCSF and relevant clinical data will be uploaded into a RedCap project maintained by the UCSF coordinating team and relying sites for their respective research candidates.

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 multicenter research trial? By multi-center trial, we mean a study where the protocol is developed by an industry sponsor, consortium, a disease-group, etc., who then selects sites across the nation or in different countries to participate in the trial. The local sites do not have any control over the design of the protocol.

- ◉ Yes ○ No

Is UCSF the coordinating center:

- ◉ Yes ○ No

6.7 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 its affiliates are the coordinating center.

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

6.8 OTHER UC COLLABORATORS: Check any other UC campuses with which you are collaborating on this research study:

- [x] UC Berkeley
- [x] UC Davis
- [ ] Lawrence Berkeley National Laboratory (LBNL)
- [ ] UC Irvine
- [x] UC Los Angeles
- [ ] UC Merced

- [ ] UC Riverside
- [x] UC San Diego
- [ ] UC Santa Barbara
- [ ] UC Santa Cruz

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

- ○ Yes
- ◉ No

6.11 UC RELIANCES: Are any of the above UC campuses requesting to rely on UCSF's IRB:

- [x] Yes
- [ ] No

7.0 Outside Site Information

7.1 Outside Site Information

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.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

University of California, Los Angeles

Contact name:

Dr. Jeffrey Klausner

Email:

JDKlausner@mednet.ucla.edu

Phone:

415 876 8901

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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

◉ Yes ○ No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

UC Reliance Registry Application #1595

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

◉ Yes ○ No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

◉ Yes ○ No

Note: your application cannot be processed without the training certificates.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

University of California, Davis

Contact name:

Dr. Christopher Polage

Email:

crpolage@ucdavis.edu

Phone:

(916) 734-3655

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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

◉ Yes ○ No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

UC Reliance Registry #1595

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

(•) Yes ( ) No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

(•) Yes ( ) No

Note: your application cannot be processed without the training certificates.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Syapse

Contact name:

Adam Jonas

Email:

adamj@syapse.com

Phone:

608.320.1042

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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

(●) Yes ( ) No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

Andi Barsan
Andrew Fisher
Maylee Wu
Preeti Bhat
Taylor Horwood
Tom Lemberg
Adam Jonas
Sonny Van
Stephen Mitchell
Syapse team is responsible for 1) facilitating the reporting of metagenomic NGS data, 2) correlating clinical data extracted from the Electronic Medical Record, alongside mNGS data from research samples in a easily searchable database. In addition, Syapse provides the software platform to enable the Precision Medicine Consult service; where subject matter experts can offer clinical guidance to providers, in the context of mNGS and other clinical information.

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

(●) Yes ( ) No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

(●) Yes ( ) No

Note: your application cannot be processed without the training certificates.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

UC Berkeley

Contact name:

Brent Fulton

Email:

fultonb@berkeley.edu

Phone:

510-643-4102

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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

(•) Yes ( ) No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

Brent Fulton, PhD, MBA

- Analysis of cost data for patients enrolled study (may have identifiers)
- Oversee analysis of de-identified cost data (Truven data set)

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

(•) Yes ( ) No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

(•) Yes ( ) No

Note: your application cannot be processed without the training certificates.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Children's National Medical Center

Contact name:

Roberta DeBiasi

Email:

RDebiasi@childrensnational.org

Phone:

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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

◉ Yes ○ No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

Maggie Ryan

- Patient recruitment and consent
- Data entry
- Clincian engagement

Roberta DeBiasi, MD

- Local patient recruitment / enrollment / consenting
- Collect clinical data from local medical records
- Coordinate specimen handling and shipping to UCSF for processing
- Participate in weekly Clinical Microbial Sequencing Board to discuss clincal data from mNGS assay

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

◉ Yes ○ No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

(•) Yes ( ) No

Note: your application cannot be processed without the training certificates.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Children's Hospital Los Angeles

Contact name:

Jeffrey M. Bender, MD

Email:

jbender@chla.usc.edu

Phone:

323-361-2509

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.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Milliman

Contact name:

Susan Pantely

Email:

susan.pantely@milliman.com

Phone:

415-394-3756

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.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

St. Jude Children's Research Hospital, Inc.

Contact name:

Randall T. Hayden, M.D.

Email:

randall.hayden@stjude.org

Phone:

901-595-3525

For Federally-funded studies only, corresponding FWA#:

00000068

*** 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.

Request for UCSF to Serve As the IRB of Record

The non-affiliated site has reviewed UCSF's guidance "When UCSF Can Serve as IRB of Record" and made an initial determination that UCSF's IRB can serve as the IRB of record:

◉ Yes ○ No

If **not**, do NOT submit your application until after the other site has completed this step.

List the collaborators and describe the scope of work that will be carried out at the non-affiliated site:

Kim Allison, BSN, RN : Manager, Clinical Research Operations
Ronald Dallas, PhD : Clinical Research Scientist
Victoria Darling, BS : Clinical Research Assistant
Randall Hayden, MD : Member, St. Jude Faculty; Director of Clinical & Molecular Microbiology

Gabriela Maron, MD, MS : Assistant Member, St. Jude Faculty
Naomi Ragsdale, BSN, RN : Clinical Research Associate
Tracey Stewart, BSN, RN : Director, Clinical Trials Management
Lauren Stronski, BSN, RN : Clinical Research Associate
Jennifer Vest, BSN, RN : Clinical Research Associate

Scope of work: the team at St. Jude will screen inpatients and submit referrals for this demonstration project. If inclusion criteria is met, the St. Jude's team will consent patients and families and send specimens to UCSF for processing. They will also be responsible for clinical data collection and input into the UCSF RedCap database. Furthermore, the clinicians and treating teams of patients included in this study will participate in weekly Clinical Microbial Sequencing Board discussions.

A letter from the non-affiliated site deferring IRB approval to the UCSF IRB is attached:

(●) Yes ( ) No

Note: your application cannot be processed without this letter.

Collaborators' training certificates for Human Subjects Training Course are attached:

(●) Yes ( ) No

Note: your application cannot be processed without the training certificates.

Click here to view this form.

Outside Site Information

Non-UCSF affiliated site information:

Site name:

Children's Hospital Colorado

Contact name:

Kevin Messacar, MD

Email:

Kevin.Messacar@childrenscolorado.org

Phone:

(720) 777-6627

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 This new consolidated section requests information about:

- **Hypothesis**
- **Aims**
- **Study Design**
- **Background and Significance**
- **Preliminary Studies**
- **Procedures**
- **Statistical Methods**
- **References**

Later sections include:

- **Drugs and Devices**
- **Sample Size, Eligibility, and Subjects**
- **Recruitment and Consent**
- **Risks and Benefits**
- **Data and Safety Monitoring Plan**
- **Confidentiality, Privacy and Security**
- **Financial Considerations**
- **Qualifications of Personnel**
- **Other Approval and Registrations**

8.2 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove (Help Text updated 9/13):

We hypothesize that many clinical illnesses in the hospital (meningitis, encephalitis, sepsis, and pneumonia) are caused by infectious agents but remain undiagnosed because current laboratory testing lacks sensitivity and scope. Furthermore, we hypothesize clinical implementation of an mNGS assay in a

licensed diagnostic laboratory (the UCSF Clinical Microbiology Laboratory) during the duration of the demonstration project will result in more rapid and accurate diagnoses, decreased costs, and improved clinical outcomes.

8.3 AIMS: List the specific aims:

This study is a prospective, multi-institutional study with the following specific aims post secimen validation:

1. Compare the diagnostic yield of a newly clinically validated metagenomic next-generation sequencing (mNGS) assay to standard microbiologic testing in 300 consented and enrolled patients presenting with (1) acute meningitis and/or encephalitis, (2) sepsis, or (3) pneumonia at 4 hospitals in California and 1 in Washington, DC.
2. To collect clinical specimens for mNGS testing in a licensed diagnostic laboratory and excess specimens or blood for orthogonal laboratory testing and/or research from patients with the aforementioned illnesses.
3. To interpret clinical mNGS results in the context of a precision medicine board and clinical interface
4. To evaluate impact of the mNGS assay on costs and clinical outcomes

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

This is a 1-year prospective cohort study which will enroll 300 patients at 5+ hospitals with encephalitis, meningitis, sepsis, or pneumonia. Patients will be enrolled if the clinical mNGS assay correpsonding to the appropriate sample type -- cerebrospinal fluid (CSF) for encephalitis / meningitis (launched 6/2016), plasma for sepsis (anticipated 6/2017), and bronchoalveolar lavage (BAL) fluid for pneumonia (anticipated 12/2017) --- has been validated in the CLIA laboratory (the UCSF Clinical Microbiology Laboratory). Accordingly, we anticipate that the majority of patients enrolled in the study will be encephalitis and meningitis patients. Patients will be consented for (1) clinical mNGS testing and review of their electronic medical record (clinical, laboratory, and radiological data) and publication of their case histories and (2) collection of blood and additional clinical samples that have not been validated for clincial mNGS testing (e.g. brain biopsy) for the purpose of orthogonal clinical testing to confirm mNGS results and biobanking to facilitate research on additional novel assay development (e.g. autoantibody and host gene transcriptome profiling). If additional clinical samples are to be used only for research purposes and not for orthogonal clinical testing, then only available excess / surplus sample will be collected. As the research on transcriptome profiling will involve deposition of deidentified genetic data into public databases, patients will be explicitly consented for release of their deidentified genetic information.

After clinical mNGS testing is performed and results communicated to the patient and clinical provider, a "precision medicine board" consisting of clinicians, laboratory directors, and research investigators will be available to interpret mNGS results and recommend further diagnostic testing, management, and treatment. This board for infectious diseases is analogous to the tumor board in oncology. Members from the treating team will be invited to paricipate in a voluntary survey both pre and post mNGS results being reported. See survey in 'Other Study Documents'. We will also extract data from the electronic medical record and evaluate the impact of the mNGS assay on costs and clinical outcomes as compared to a subset of historical controls obtained by retrospective chart review of similar cases in the past for which the mNGS assay was not available.

8.5 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.

We aim to provide the first-ever demonstration of precision medicine for diagnosis of acute infectious diseases in hospitalized patients, with the goal of directly impacting clinical care and improving patient outcomes. Existing methods fail to diagnose many life-threatening infections in a clinically relevant timeframe, resulting in excessive health care costs and unnecessary morbidity and mortality.

Failure to obtain a laboratory-confirmed diagnosis for many acute infectious diseases directly contributes to poor patient outcomes and a high cost burden to the health care system. Key areas of unmet clinical need targeted by this proposal include neurological infections (encephalitis and meningitis), pneumonia, and sepsis. The principal advantage of this approach is the ability to detect all viruses, bacteria, fungi, and parasites in a single, standardized universal test, the clinically validated mNGS assay, directly from diverse sample types such as cerebrospinal fluid (CSF), bronchoalveolar lavage (BAL), and plasma. This approach is comprehensive because all pathogens with the exception of prions are based on nucleic acid (DNA/RNA). Thus, a single shotgun sequencing test is able to simultaneously screen nearly all pathogens directly from clinical samples, bypassing the "one bug, one test" traditional paradigm of infectious disease diagnosis and maximizing the potential impact on patients with acute, life-threatening infections, where time is of the essence.

Currently, up to 50% of hospitalized patients with pneumonia, sepsis, and encephalitis / meningitis are treated empirically without a confirmed etiologic diagnosis, resulting in delayed or ineffective treatments, increased mortality, and excess healthcare costs. For encephalitis, the annual disease burden in the U.S. exceeds 20,000 hospitalizations with a high rate of long-term sequelae and mortality and $2.0 billion cost to the healthcare system. Pneumonia and sepsis are associated with >43,000 avoidable deaths, 2.3 million excess patient days, and $8.1 billion in added costs each year. Metagenomic NGS, by providing a more timely diagnosis in infected patients and the ability to "rule-out" infectious etiologies in patients with non-infectious illness, has the potential to significantly reduce healthcare costs by decreasing hospital lengths of stay and eliminating unnecessary treatments, procedures, and testing. Our NGS assay also aligns perfectly with the Centers for Disease Control and Prevention (CDC) and President's Obama's National Action Plan to Combat Antibiotic-Resistant Bacteria by enabling an early, specific diagnosis that may obviate the need for empiric antibiotics and inform targeted, appropriate treatment, with the potential to ultimately decrease antibiotic resistance in hospitals.

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

At UCSF, we have pioneered the use of unbiased metagenomic next-generation sequencing (mNGS) for detection of all potential pathogens in a single assay, and have demonstrated its utility in saving the life of a critically ill 14-year old boy with previously unrecognized neuroleptospirosis in a case report published in the *New England Journal of Medicine.* We have further demonstrated the value of our mNGS assay by identifying clinically significant pathogens in over 1,000 patients with severe, undiagnosed pulmonary, blood and neurological infections. We have also previously developed an automated sample-to-answer pathogen identification pipeline named SURPI ("Sequence-based Ultra-Rapid Pathogen Identification") to accelerate the speed of the bioinformatics analysis and ensure that NGS results will be available in a fast enough time frame to impact patient care.

8.7 * 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

8.8 * 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)

- [x] Interviews, questionnaires, surveys
- [ ] Educational or cognitive tests
- [ ] Focus groups
- [ ] Observation

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

8.9 * PROCEDURES / METHODS: (REQUIRED)

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

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

Examples may include:

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

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

The investigators will seek to identify and enroll patients with a clinical syndrome that may have an acute infectious etiology. Consent will follow procedures outlined under application section for recruitment and consent.

The study investigators or site coordinator will review the medical record and abstract clinical, laboratory, and radiographic data.

A RedCap survey will be used to collect basic demographic information, exposure/travel history, and clinical information such as imaging results, labs, treatment history and clinical phenotype. The patient may be asked directly by the study investigator or site coordinator to provide exposure/travel history, however, most data will be obtained by reviewing the medical record.

All patients will have had the validated mNGS assay ordered clinically by a provider and the appropriate sample (CSF, plasma, or BAL fluid) collected or added onto an existing collection for clinical testing at

UCSF. Specimens will be shipped and processed at UCSF.

An additional sample (e.g. biopsy sample) that has not been clinically validated for mNGS testing may also be collected for orthogonal diagnostic testing to confirm mNGS results and/or for research purposes. Specimens must be excess / surplus sample to be used for research. Specimens will be shipped to UCSF.

A tissue bank will be established at UCSF for future research.

Research candidates will be asked to consent for collection of a venous blood sample of up to 30 ml or 1-3 tubes. Blood collected will be processed to isolate peripheral blood mononuclear cells (PBMCs) and serum for (1) orthogonal clinical validation of the mNGS assay, and/or (2) research analysis.

Blood draws will only be performed on patients who consent and who are 13 years and older. Blood collections may be done on patients who are younger than 13, but only by adding 1-2 tubes to an already scheduled blood draw, thus avoiding venipuncture solely for the research collection.

Subjects will also be consented to be re-contacted to provide short and longer-term follow-up to confirm final diagnosis and outcome.

Sub-study: Plasma Validation for Patients with Sepsis
Plasma specimens from blood culture-positive patients are needed for validation of the mNGS assay for pathogen detection from plasma in the CLIA-certified clinical laboratory. A sub-study, limited in duration, will be implemented at UCSF for specimen acquisition.

Specimens will be collected in coordination with the staff on the adult intensive care units at at 9ICU and 13ICU as well as the Adult Acute Care Unit on 15L. One tube of blood (4 – 10 mL) will be collected at the time that blood cultures are ordered and sent as part of a workup for sepsis. This battery of tests and work-up is sometimes completed prior to transfer to the 9 or 13 adult ICU (i.e. in the emergency department) or will be initiated in the ED or the Adult Acute Care unit on 15L.

Plasma specimens will be transferred on ice to the Clinical Microbiology Laboratory at China Basin, aliquoted by certified personnel, and frozen for validation studies. Within one week of the blood collection occurring, an informational letter will be mailed to the address available in Apex. By default, patients will be included in the study. If the patient or their family requests to be withdrawn, the sample held in the Clinical Microbiology Laboratory at China Basin will be discarded and their research records will be updated to reflect this.

Sub-cohort of the validation cohort for plasma validation (sepsis):
In addition to the above mentioned cohort of patients who will be recruited to accrue validation plasma samples, there will be a smaller number of cases from whom there will be interest to obtain remnant specimens from the clinical lab (i.e. biopsy tissue, blood, other bodily fluid) in addition to an optional blood draw for comparative study. These patients will be identified by either direct physician referral or by working with the Microbiology/Pathology departments to identify tissue and/or bodily fluid from patients of interest (i.e. culture positive abscess fluid). These patients will be approached for informed consent and may be on units outside of the above mentioned units. Consent will be coordinated with permission from the treatment team before approaching potential research candidates.

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

Given that many patients will be severely ill, we will utilize the standardized form, Capacity Assessment Record for Research Informed Consent, to insure that subject capacity is assessed in a systematic manner.

Patients will be requested to participate in a short questionnaire. This questionnaire will be administered verbally at the time of consent and completed by either the patient or surrogate. This is a RedCap questionnaire entitled 'Clinical Case History'. The patient will only be requested to provide information for the following sections: patient information, exposures 1 month before onset, and travel 1 year before onset. The patient or surrogate will not see the remaining sections of the survey. The treating physician will be requested to complete the remainder of the survey. The information to be completed by the treating physician will have already been gathered as part of the patient's routine work-up.

Providers will be requested for feedback before and after mNGS for pathogen detection results are reported. Providers caring for the research participant will be identified through Apex and emailed and

invitation to participate. Participation is not required, but encouraged. Once mNGS results are posted, a second survey is sent to the same providers and any new treating team members identified by reviewing the care team in Apex.

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

- [x] Blood
- [x] Tissue (describe below):
- [ ] Existing/archival materials (name source below):
- [x] Other (describe below):

Describe and/or name source:

clinical mNGS testing at the UCSF Clinical Microbiology Laboratory: cerebrospinal fluid, plasma, bronchoalveolar lavage fluid

blood draw: blood for PBMCs and serum/plasma

additional specimen types for orthogonal clinical validation or research (surplus): biopsy tissue, nasal swabs, cyst / abscess fluid

8.14 * 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

8.15 * DESTINATION: Specimens will ultimately be stored (check all that apply): (REQUIRED)

Outside Entity:

- [ ] Cooperative group bank
- [ ] NIH
- [ ] Other university
- [ ] Industry sponsor
- [ ] Other

UCSF:

- [x] UCSF repository/bank being established under this protocol
- [x] Existing UCSF specimen repository/bank with CHR approval
- [ ] Other location at UCSF (please describe)

Provide the name of the bank and iRIS approval number (if not being banked at UCSF under this protocol). If you checked 'Other,' please provide the location or lab:

Chiu Laboratory Biobank:

H9187-32565-02 Chiu, Charles Y MD
Pathogen Detection and Discovery in Hospitalized Patients with Unexplained Acute or Chronic Illness

Clinical Microbiology Laboratory Biobank:

H52699-34941-01 Miller, Steven A
Improved diagnosis of infectious meningitis / encephalitis using multiplex molecular methods

H52699-35006-01 Miller, Steven A
Identification and characterization of infectious causes for respiratory infection

8.16 UCSF-BANK PHYSICAL LOCATION: The repository/bank is physically located at (list the address and room number for all locations):

1. UCSF Clinical Microbiology Laboratory (Directors: Steve Miller and Charles Chiu), 185 Berry Street, Suite 290, San Francisco, CA 94107
1. Chiu Lab, 185 Berry Street, Room 185, San Francisco, CA 94107
2.DeRisi Lab, 1700 4th Street, QB3 Room BH 401, San Francisco, CA 94158
3. Pleasure Lab, 675 Nelson Rising Ln. Room 260, San Francisco, CA 94158

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

(•) Yes ( ) No

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

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

8.20 * 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':

indefinitely

8.21 * UCSF-BANKED SPECIMENS - LINKING 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.
- [x] 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:

none. Only researchers directly involved in this study will have access to identifiers.

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

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

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

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

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

( ) Yes (•) No

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

The UCSF Clinical Microbiology Laboratory will process the clinical sample under validated standardized operating procedures. Bioinformatics analysis will be performed using the SURPI pipeline (Naccache, et al., 2014). We will also occasionally need to perform orthogonal clinical testing (serological, PCR testing) or research polymerase chain reaction (PCR) testing for confirmation of results. Orthogonal testing will be performed to confirm positive mNGS results or by recommendations from the Clinical Microbial Sequencing Board. All data will be deidentified prior to submission and submitted to dbGaP (database of Genotypes and Phenotypes), an NIH database which archives deidentified data beyond a controlled-access firewall and makes such data only accessible to a limited number of investigators (see http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap).

For the additional excess clinical samples used for research for the purposes of new assay development, we will perform additional analyses including autoantibody profiling, human transcriptome profiling, and probe-based sequencing enrichment.

8.26 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):

- Goldberg B, Sichtig H, Geyer C, Ledeboer N, and Weinstock GM. (2015) Making the leap from research laboratory to clinic: challenges and opportunities for next-generation sequencing in infectious disease diagnostics. *mBio* 6(6):e01888-15.
- Naccache SN, Federman S, Veeraraghavan N, Zaharia M, Lee D, Samayoa E, Bouquet J, Greninger AL, Luk, KC, Enge B, Wadford DA, Messenger SL, Genrich GL, Pellegrino K, Grard G, Leroy E, Schneider BS, Fair JN, Martinez MA, Isa P, Crump JA, DeRisi JL, Sittler T, Hackett, Jr. J, Miller S, and Chiu CY. (2014) A cloud-compatible bioinformatics pipeline for ultra-rapid pathogen identification from next-generation sequencing of clinical samples. *Genome Research* 24(7):1180-9. (PMCID: PMC4079973).
- Wilson MR, Naccache SN, Samayoa E, Biagtan M, Bashir H, Yu G, Salamat SM, Somasekar S, Federman S, Miller S, Sokolic R, Garabedian E, CAndotti F, Buckley RH, Reed KD, Meyer TL, Seroogy CM, Galloway R, Henderson SL, Gern JE, DeRisi JL, and Chiu CY. (2014) Actionable diagnosis of neuroleptospirosis by next-generation sequencing. *New England Journal of Medicine* 370:2408-2017. (PMCID: PMC4134948).
- Greninger AL, Naccache SN, Messacar K, Clayton A, Yu G, Somasekar S., Federman S, Stryke D, Anderson C, Yagi S, Messenger S, Wadford D, Xia D, Watt JP, Van Haren K, Dominguez SR, Glaser C, Aldrovandi G, and Chiu CY. (2015) A novel outbreak enterovirus D68 strain associated with acute flaccid myelitis cases in the United States from 2012-2014: a retrospective cohort study. *Lancet Infectious Diseases* S1473-3099(15)70093-93. E-pub ahead of print.
- Naccache SN, Peggs KS, Mattes FM, Phadke R, Garson JA, Grant P, Samayoa E, Federman S, Miller S, Lunn MP, Gant V, and Chiu CY. (2015) Diagnosis of neuroinvasive astrovirus infection in an immunocompromised adult with encephalitis by unbiased next-generation sequencing. *Clinical Infectious Diseases* 60(6):919-23. (PMCID: PMC4345816).

9.0 Drugs and Devices

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

○ Yes ◉ No

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

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

(•) Yes ( ) No

9.4 * NSR: Are you requesting a Non-Significant Risk (NSR) determination for an investigational device: (REQUIRED)

Note: an NSR determination is different from an Investigational Device Exemption (IDE). Check the Help link for more guidance on what types of devices can qualify for an NSR determination.

(•) Yes ( ) No

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

The metagenomic Next-Gen Sequencing (mNGS) assay for pathogen detection was validated for clinical use as a laboratory-developed (LDT) test in the CLIA-certified UCSF Clinical Microbiology Laboratory. Validation studies demonstrated that the test has acceptable performance characteristics for use in patient diagnosis. These studies included evaluation of assay sensitivity, specificity, precision, accuracy, stability and interference. Accuracy was compared to a composite clinical reference standard consisting of all microbiologic and serologic testing performed on the cerebrospinal samples. Because not all samples had the appropriate conventional testing done to be able to confirm or refute mNGS findings, additional discrepancy testing was performed as needed. After discrepancy testing, the performance of acceptable samples yielded an overall sensitivity of 86.1% and specificity of 97.9%. Due to the difficulty in making an etiologic diagnosis in many cases of meningitis / encephalitis, a test sensitivity of 80-90% with specificity >95% is very useful in patient management decisions.

Over the course of the Precision Diagnosis of Acute Infectious Diseases demonstration project,, each case is discussed with a team of leading experts in neurology, infectious disease and microbiology (CMSB, “clinical microbial sequencing board”). The mNGS findings are put into clinical context, and appropriate treatment and management decisions are recommended to treating physicians. This helps to ensure that proper management decisions are made and that the assay results are interpreted according to the clinical context, thus mitigating risk that may be associated with diagnostics provided outside of the healthcare system associated with the patient.

During the demonstration project, positive findings by mNGS are evaluated using orthogonal testing (clinical testing is preferred if available, or research-based PCR confirmatory testing) to assess the possibility of false-positive results. However, as this assay utilizes significant advances in pathogen detection technology, there is the potential to detect the presence of a pathogen that may not yet be detectable via other diagnostic assays (i.e. detecting a virus before antibody production).

Potential false-negative mNGS results (negative mNGS assay but positive by conventional testing) are also reviewed with additional discrepancy testing performed, as necessary.

The results of the mNGS assay do not solely determine the need for therapy or other patient interventions. Conventional test results and mNGS results are used in the proper clinical context to guide therapy decisions. Given the overall mNGS test performance during clinical laboratory validation studies, expert review and case discussion, and the use of discrepancy testing as needed, the mNGS assay (device) as performed poses a non-significant risk to patients.

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

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

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

Please see the UCSF IRB website for more details about the use of devices in research, including the Investigator Checklist for Significant Risk, Non-Significant Risk, and/or IDE Exempt Device Studies

Verification of IDE numbers: If the sponsor's protocol does not list the IDE number, you must submit documentation from the sponsor or FDA identifying the IDE number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet.

If you have any correspondence from the FDA or sponsor regarding this device, please attach it to the application.

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	mNGS IVD for diagnosis of infectious diseases	No	Yes	

Manufacturer/Supplier of Device	University of California, San Francisco
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	The in vitro diagnostic under study (mNGS for diagnosis of infectious disease) will be performed as a laboratory-developed test in the UCSF clinical laboratory. As a laboratory-developed test, FDA approval or IDE registration are not required. The primary purpose of the test is to diagnose patients enrolled in the study.

In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

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

○ Yes ◉ No

10.0 Sample Size and Eligibility Criteria

10.1 ENROLLMENT TARGET: How many people will you enroll:

500

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

200- neurology patients
300- sub-study for plasma validation of mNGS for pathogen detection (sepsis patients w/ no patient contact)

10.2 TOTAL PARTICIPANTS: For multicenter studies, how many people will be enrolled in total:

600

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

300 participants is the target enrollment for this project to demonstrate the utility of this new diagnostic assay. We anticipate the majority of patients to be hospitalized at UCSF (200), with another 100 enrolled at UCLA and UCD.

The sub-study for specimen acquisition for plasma validation will obtain samples from approximately 300 patients receiving sepsis work-up. A small number (approximately 10) of plasma samples on correlated blood culture negatives will be held for validation studies. Plasma samples correlated to positive blood cultures will be held for validation studies (approximately 30). The remaining plasma specimens will not be held (approximately 260).

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

- ☑ 0-6 years
- ☑ 7-12 years
- ☑ 13-17 years
- ☑ 18-64 years
- ☑ 65+

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

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

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

- [x] Children / Minors
- [x] Subjects unable to consent for themselves
- [x] Subjects unable to consent for themselves (emergency setting)
- [x] Subjects with diminished capacity to consent
- [x] Subjects unable to read, speak or understand English
- [x] Pregnant women
- [ ] Fetuses
- [x] Neonates
- [ ] Prisoners
- [x] 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:

The majority of the subjects involved in this study will have neurological illness, with the minority having sepsis.

Central nervous system infections and autoimmune diseases can affect cognition. Therefore, subjects who are unable to consent for themselves, an appropriate surrogate will be approached and given the opportunity to consent on the patient's behalf.

Undiagnosed CNS infections and autoimmune diseases are a major problem in pediatrics. Therefore we do not wish to exclude pediatrics or neonates.

While we anticipate very few if any pregnant women to be in this study, we would like to include them in the case that a pregnant women were to develop neuroinflammatory disease requiring hospitalization.

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**.

Capacity assessment and consent from surrogate decision-maker if subjects do not have capacity for consent. If capacity improves, subjects will be re-contacted for their consent. For age < 18 years, the protocol requires assent (if the patient has capacity) as well as parental/guardian consent.

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

Inclusion criteria for this study is any patient with acute onset of encephalitis and/or meningitis (phase 1), sepsis (phase 2), and pneumonia (phase 3). Information will be gathered about these patients. Some data may be collected on family members or other sick contacts of the patient. This will only be for information gathering that may help explain or identify the infectious etiology.

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

We will not include patients with a psych hold (5150 or 5250), prisoners or UC employees or students or close associates of the key personnel on the study.

10.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on patient care units at UCSF 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.

11.0 Inclusion of Minors in Research

11.1 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:

The greatest risk to the patients is the potential loss of privacy.

It is possible, although unlikely, that this research could indicate an infection where infection control measures are needed in order to protect public health. In these cases, we will contact the treating team of the participant and the hospital infection control physicians. These people will be responsible for determining how to proceed with the participant's care, which could include sending additional tests and/or moving the participant to a separate hospital room to keep a possible infection from spreading.

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

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

○ Yes ◉ No

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

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

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

Minors will be approached for assent. Parents or legal guiardians will approached for informed, signed consent.

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

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

Provide a brief justification for the waiver:

As this study will be primarily enrolling participants with neurological disease, it is anticipated that many, if not most, children will be too ill to engage in an assent discussion with the research staff. If it is determined by the treating team, family members, and/or the study personnel, the assent discussion may be waived. However, parental and/or guardian consent will always be obtained prior to enrollment.

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

- [x] Permission form addressed to the parents
- [x] 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)
- [x] 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:

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

(•) Yes ( ) No

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

This study is minimal risk and access to the clinical diagnostic test, currently only available in congruence with research participation, and its associated potential benefit to the patient, outweigh the risks.

12.0 Recruitment and Consent

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

- [x] Medical records review
- [ ] 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)
- [ ] Referrals from the community / word of mouth
- [ ] Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- [ ] Online recruiting tool such as TrialSpark
- [ ] CTSI Recruitment Services unit
- [ ] Other method (describe below)

12.2 * 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)
- [x] University of California Research Exchange (UC ReX)
- [ ] Other method (describe below)

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

Treating clinicians on the infectious disease, neurology, and critical care services will refer patients with infectious disease syndromes. At that point, the Study Investigator, co-Investigators or Study Coordinator will review the patient's clinical information to determine whether they are eligible for the study. The Study Investigator, co-Investigator or Study Coordinator will then approach and consent the patient (or his/her surrogate decision maker) for the study.

Similarly, the Study Investigator, co-Investigator, or Study Coordinator will screen patients in APeX for eligibility. If patients meet criteria, the primary treating team will be contacted for permission to approach and discuss the study with the potential research candidate. The Study Investigator, co-Investigator or Study Coordinator will approach for possible consent.

A RedCap Referral survey will be used to assist with determining patient eligibility. This will be submitted to either the CRC, PI, or co-PI to review and determine eligibility prior to approaching patients for consent.

Sepsis sub-study: eligibility will be determined by meeting clinical criteria for sepsis or sirs (i.e. low blood pressure, increased heart rate, fever, etc). Blood samples will be collected near the time of the first blood culture, non-acute/well-established/managed cases of sepsis will not be included.

12.4 * 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)

12.5 * 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.

12.6 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)

Potential participants will be identified by treating clinicians who have ordered the clinical UCSF mNGS and referred the patient to opt into research participation. mNGS test ordering may happen before or after enrollment criteria is reviewed, or before or after patient consent. Patients will only be included in the study and have mNGS performed if they meet criteria and consent to the study. Study team members will also review medical records for potential subjects that meet criteria and engaging treating teams to determine eligibility.

Subjects will be approached by their treating clinician(s) in the context of their ongoing clinical care (e.g. at the treating medical center).

Sepsis sub-study: information letter will be mailed within one week of blood draw occuring.

Providers will be recruited for feedback (pre and post mNGS results) by an emailed survey. Treating team members will be identified by reviewing the EMR of the study participants.

12.7 * 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)
- [ ] Provide online 'eConsent' using DocuSign or another E-Signature system
- [ ] 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)
- [x] 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)
- [x] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

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

12.8 * 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.**

As this study coincides with the release of the new UCSF metagenomic Next-Generation Sequencing (mNGS) test, candidates and/or surrogates will be approached for possible consent to the study after the mNGS clinical test has been ordered by the treating team.

UCSF Research Candidate with Capacity to Consent

The PI or other study key personnel will approach the research candidate and invite them to learn more about the study. The PI or study key personnel will describe the study and the research candidate will be given ample time to ask questions and consider their choice. Written informed consent will only be obtained when the candidate feels comfortable proceeding with the study. A photocopy of the signed consent documents will be provided to the candidate after they have been signed.

Specimens may be sent to the Clinical Microbiology Lab at UCSF for mNGS prior to the patient being approached for possible consent. However, ancillary specimens will not be obtained prior to candidate consent.

Some research candidates will be discharged or transferred before informed consent may be obtained. In these instances, the site PI or other study key personnel will reach out the research candidate by phone and invite them to participate in the study. If the candidate is interested to participate and verbally OKs sending their specimen for testing and the review of medical records, they will be included in the study.

Copies of the consent forms will then be mailed or sent via DocuSign to the candidate to sign and return. If signed documentation is not received within 4 months from enrollment, the candidate will be withdrawn from the study.

UCSF Surrogate Consent

Some research candidates will not be able to provide informed consent due to altered mental status or cognitive impairment caused by their illness. Surrogates who are local and able to meet the study personnel at bedside will be consented in person. The study PI or other key personnel will approach the surrogate at the hospital to explain the research study and invite them to give consent on behalf of the research candidate. The surrogate will be given ample time to discuss and ask questions. They surrogate will complete the “Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research”. When ready to sign the documents, they will sign the consent documents and be provided a photocopy of the signed forms.

Surrogates who are not local or unable to meet the study personnel at the hospital, may be contacted and invited to learn more about the study over the phone. Surrogate contact information will be gathered from either the electronic medical record, the treating physician, or by contacting the nurse, case manager or other hospital staff involved in caring for the research candidate. The PI or other study personnel will reach out to the surrogate by phone to explain the research study and invite them to give consent on behalf of the research candidate. If the surrogate provides verbal consent, ancillary specimens may be collected after this initial

contact with the surrogate, including a blood draw. At the time of initial verbal consent the study personnel will invite the surrogate to meeti at the hospital to review and sign the consent documents.

If they are unable to meet in person, copies of the consent forms will then be mailed or sent via DocuSign to the surrogate to sign and return. The surrogate will be given ample time to consider and discuss the study. No ancillary samples will be collected until verbal consent is received.

Ancillary specimens may be collected and processed after verbal consent. Signed consent will be obtained after obtaining verbal consent. If signed consent is not received by the surrogate within 4 months of receiving the specimen(s), the participant will be considered not enrolled and PHI will be removed from records/ destroyed and banked specimens will be destroyed.

Specimens may be sent to the Clinical Microbiology Lab at UCSF for mNGS prior to the patient being approached for possible consent.

Outside Relying Site Research Candidate with Capacity to Consent
Outside relying sites will similarly ordering the clinical mNGS test and subsequently or simultaneously be approaching candidates for possible consent to the research study.

The relying outside site PI or other study key personnel will approach the research candidate and invite them to learn more about the study. The PI or study key personnel will describe the study and the research candidate will be given ample time to ask questions and consider their choice. Written informed consent will only be obtained when the candidate feels comfortable proceeding with the study. A photocopy of the signed consent documents will be provided to the candidate after they have been signed.

Specimens may be sent to the Clinical Microbiology Lab at UCSF for mNGS prior to the patient being approached for possible consent. However, ancillary specimens will not be obtained prior to candidate consent.

Some research candidates will be discharged or transferred before informed consent may be obtained. In these instances, the site PI or other study key personnel will reach out the research candidate by phone and invite them to participate in the study. If the candidate is interested to participate and verbally Okays sending their specimen for testing and the review of medical records, they will be included in the study.

Copies of the consent forms will then be mailed or sent via DocuSign to the candidate to sign and return. If signed documentation is not received within 4 months from enrollment, the candidate will be withdrawn from the study.

Outside Relying Site Surrogate Consent
Some research candidates at outside sites will not be able to provide informed consent due to altered mental status or cognitive impairment caused by their illness. Surrogates who are local to the relying sites and able to meet the local study personnel at bedside will be consented in person. The local study PI or other key personnel will approach the surrogate at the hospital to explain the research study and invite them to give consent on behalf of the research candidate. The surrogate will be given ample time to discuss and ask questions. They surrogate will complete the “Self-Certification of Surrogate Decision Makers for Potential Subject's Participation in University of California Research”. When ready to sign the documents, they will sign the consent documents and be provided a photocopy of the signed consent form, HIPPA auth, and Bill Rights. One version of the consent document will be used at all sites.

Surrogates who are not local or unable to meet the local study personnel at the hospital, may be contacted and invited to learn more about the study over the phone. Surrogate contact information will be gathered from either the electronic medical record, the treating physician, or by contacting the nurse, case manager or other hospital staff involved in caring for the research candidate. The local PI or other study personnel will reach out to the surrogate by phone to explain the research study and invite them to give consent on behalf of the research candidate. If the surrogate provides verbal consent, ancillary specimens may be collected after this initial contact with the surrogate, including a blood draw. At the time of initial verbal consent the study personnel will invite the surrogate to meeti at the hospital to review and sign the consent documents.

If they are unable to meet in person, copies of the consent forms will then be mailed or sent via DocuSign to the surrogate to sign and return. The surrogate will be given ample time to consider and discuss the study. No ancillary samples will be collected until verbal consent is received.

Ancillary specimens may be collected and processed after verbal consent. Signed consent will be obtained after obtaining verbal consent. If signed consent is not received by the surrogate within 4 months of receiving the specimen(s), the participant will be considered not enrolled and PHI will be removed from records/ destroyed and banked specimens will be destroyed.

Outside non-relying site consent
Non-relying sites will consent research candidates and/or surrogates according to local IRB protocols.

Re-Consent for participants that gain capacity to consent after enrollment
Research candidates who were enrolled by surrogate consent while in the hospital will be re-contacted in the case they re-gain capacity to give informed consent. We anticipate this to occur once the patient is no longer hospitalized. Therefore, re-consent will be initiated with a phone call to explain the study to the research participant and give them the option to remain in the study or to withdraw. If the participant wishes to be withdrawn, banked specimens will be destroyed and no further research will be conducted using the specimens. However, any research already done using the specimens or data will be kept and analyzed as part of the study. If the participant wishes to remain in the study, they will be asked to sign new consent forms. Documents (2 of each: consent form, HIPPA authorization, and Bill of Rights) will be mailed to the participant. One copy will be for the participant to keep for their personal records and the second to sign and return.

Sepsis sub-study:
All patients from whom a blood sample has been collected (regarless of use in research) will be mailed an information letter within one week of blood sample collection. Letter will include study contact information and a return envelope. If the patient wishes to be excluded from the study, they will check 'withdraw' on the information letter and return in the envelope provided. By default, cases will be included if criteria is met unless otherwise requested by the patient or appropriate surrogate.

Sub-cohort of the validation cohort for plasma validation (sepsis):

Same as *'UCSF Research Candidate with Capacity to Consent'* and *'UCSF Surrogate Consent'* as described above (substituting research mNGS for clinical mNGS).

* 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)**

At UCSF,
Hannah Sample, BS -- Study Coordinator, ~2 year experience in obtaining informed consent for research studies
Amy Berger, MD -- internal medicine physician, hospitalist training, ~3 years experience in obtaining informed consent for research studies
other faculty, fellows, residents on the Molecular Medicine, Neurology, Infectious Diseases consult services -- clinical providers at UCSF who have been trained by the investigators on the details of the CIAPM study and with at least 5 years experience in obtaining informed consent for research studies

12.9 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED)

Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed

consent for more detail on how to conduct the assessment.

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

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

Subjects will be asked to explain back the risks, benefits and study protocols. All prospective subjects will have a detailed neurological exam, part of which will entail a mental status exam in which multiple cognitive domains are assessed. In addition, we will administer the attached Capacity Assessment Record for Research Informed Consent. This document will insure that we assess and document whether the potential research subject is able to make a choice whether to participate in the research protocol, whether he/she shows understanding of the research protocol and its elements, including the risks/benefits of participation, whether he/she is able to provide rational reasons for participating or not participating the research protocol and whether he/she shows an appreciation of the personal risks/benefits of participating or not participating in the protocol.

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

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

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

We expect non-English speaking consent to be a minority of our cohort. Given the minimal risk this study poses, we fell that this approach will be sufficient. An interpreter (either available by phone or in-person) will be used for consenting and all follow-up contact.

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

- ○ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether they want documentation linking them with the research. 46.117(c) (1)
- ◉ The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. 46.117(c) (2)

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

About 30-60 mins for consent. The rest of the study procedures involve processing and analysis but not subject time. The 30-60 minutes for a follow up telephone call to confirm long-term outcome and final diagnosis.

A blood draw shoud take about 5 minutes.

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

13.0 Waiver of Consent/Authorization for Recruitment Purposes

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

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

(•) Yes

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

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

(•) Yes

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

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

(•) Yes

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

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

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [x] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers

- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

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

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

Name, MRN, dates, clinical history for the purposes of establishing eligibility based on suspected diagnosis and clinical syndrome. Phone numbers may also be collected in order to contact non-local surrogates or research candidates.

Note: HIPAA requires that you collect the minimum necessary.

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

Data on subjects who are not eligible or do not wish to participate will be destroyed. Patient name and MRN will be kept on record in the secure research database so that patients who have declined participation will not be approached again.

14.0 Waiver of Consent/Authorization

(August, 2013)

14.1 * IMPACT OF WAIVER ON RIGHTS AND WELFARE: I affirm that subjects' rights and welfare will not be adversely affected by waiving informed consent:

- (•) Yes

14.2 * PRACTICABILITY: It is not practicable to conduct the research without the waiver of consent / authorization because (check all that apply):

- [ ] Many subjects are no longer being followed at the institution or are deceased
- [ ] The attempt to contact subjects poses a greater risk than this study
- [x] The large number of records required makes it impracticable to contact all potential subjects
- [ ] The researchers do not know the identity of the study subjects and therefore cannot contact them
- [ ] The data being used was collected under a different IRB-approved study and subjects gave their consent for data to be used in research of this type

14.3 * INFORMING SUBJECTS POST-PARTICIPATION: Will subjects be provided with pertinent information after their participation:

○ Yes ◉ No

14.4 * IDENTIFIERS: Are you recording identifiers in the research records: (REQUIRED)

◉ Yes ○ No

* Describe your plan to destroy the identifiers at the earliest opportunity consistent with the research or provide a health or research justification for retaining the identifiers, or indicate and explain that retention is required by law: **(REQUIRED)**

For mNGS sepsis validation sub-study: MRNs will be recorded in order to link to blood culture results.

15.0 Surrogate Consent

15.1 PSYCHIATRIC SCREEN: Are any subjects inpatients on a psychiatric ward or mental health facility, or on psychiatric hold:

◉ No

If Yes, use of surrogate consent for research is NOT allowed in California.

15.2 AREAS OF RESEARCH: Is this study related to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of the research subjects:

◉ Yes

15.3 JUSTIFICATION: Explain why use of surrogates is necessary for completion of this study:

Many subjects to be enrolled in this study may be incapacitated with a serious illness, sedated, or otherwise unable to provide informed consent. For enrollment in this study, the use of surrogates with durable power of attorney will be necessary for these subjects.

15.4 COGNITIVE ASSESSMENT: Describe the plans for assessing the decision-making capacity of prospective subjects:

We will assess the decision-making capacity of prospective subjects by their condition (sedated, intubated, or otherwise incapacitated patients will not be able to make decisions), including severity of illness, and a clinician determination of whether they are able to provide informed consent.

15.5 POST-ENROLLMENT CONSENT PLANS: Describe the plans for obtaining consent from subjects who regain ability to consent after a surrogate has given initial consent:

For all sites, UCSF study staff will coordinate re-consent procedures.

Research candidates who were enrolled by surrogate consent while in the hospital will be re-contacted in case they re-gain capacity to give informed consent. We anticipate this to occur once the patient is no longer hospitalized. If, based on chart review, the participant has clearly regained capacity to consent, study staff will reach out by phone to discuss the study and give them the option to remain in the study

or to withdraw. If the participant wishes to be withdrawn, banked specimens will be destroyed and no further research will be conducted using the specimens. However, any research already done using the specimens or data will be kept and analyzed as part of the study. If the participant wishes to remain in the study, they will be asked to sign new consent forms. Documents (2 of each: consent form, HIPPA authorization, and Bill of Rights) will be mailed to the participant. One copy will be for the participant to keep for their personal records and the second to sign and return.

If study staff are not able to reach the participant via phone, a letter ('re-consent letter') will be mailed to the address of record, along with 2 copies of the consent forms. One copy will be for the participant to keep for their personal records and the second to sign and return. No further attempts to reach the participant will be made after 1 phone call and 1 letter.

If it is not clear from review of the medical chart whether the participant has regained the ability to consent, contact will be initiated with the surrogate decision maker via phone. Staff will call the surrogate to inquire about the participant's mental status. If they have regained mental capacity, staff will reach out to the participant directly for consent following the procedures outlined above.

If the surrogate is not reachable via phone call, staff will mail a letter inquiring as to the mental status of the participant along with a form to complete summarizing the participant's status ('surrogate check in letter', 'participant status form'). If the 'participant status form' comes back indicating that the participant has regained mental capacity, staff will reach out to the participant directly for consent following the procedures outlined above. No further attempts to reach the surrogate or participant will be made after 1 phone call and 1 letter.

Study staff will not attempt to contact surrogates or participants if they become aware (through chart review or physician notification) that the patient has passed away.

15.6 SURROGATE CONSENT REQUIREMENTS: Check to acknowledge:

- [x] Research takes place in California. All surrogates will complete the "Self-Certification of Surrogate Decision Makers for Participation in Research" form.
- [x] Conscious subjects will be notified of the decision to contact a surrogate. If subjects object to study participation, they will be excluded even if their surrogate has given consent.
- [x] Surrogates will not receive any financial compensation for providing consent.
- [x] If a higher-ranking surrogate is identified at any time, the investigators will defer to the higher-ranking surrogate's decision regarding the subject's participation in the research.

For research taking place outside of California, explain how investigators will confirm that surrogates are legally authorized representatives:

Non California sites: Children's National Medical Center & St. Jude Children's Research Hospital :

Children enrolled at these site will be consented by the parents or legal guardians. The appropriate surrogates will be indentified by the local treating team caring for the patients.

16.0 Risks and Benefits

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

- [ ] For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- [ ] Risks associated with radiation exposure for imaging studies specifically for research purposes
- [ ] Risks associated with the administration of contrast agent for imaging studies
- [ ] Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout

period is required by the study protocol)

- ☐ For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- ☐ For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- ☐ Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- ☑ Risk of pain or physical discomfort caused by the research intervention
- ☐ Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

16.2 RISKS: Describe any anticipated risks and discomforts not listed above:

1. We will be analyzing surplus CSF, blood, other bodily fluids and biopsy tissue, which will not be able to be returned to the subject for further clinical analysis.

2. It is possible that a pathogen will be identified using this approach, that upon additional clinical confirmation by the treating team, may need to be reported to public health authorities by law, which could have implications for patient privacy.

3. There is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record. Taking part in a genetic study may also have a negative impact or unintended consequences on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk. Although your name will not be with the sample, it will have other facts about you such as information about your medical history, age and gender. These facts are important because they will help us learn if the factors that cause neurologic disease to occur or get worse are the same or different based on these facts. Thus it is possible that study finding could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.

4. Drawing blood may cause temporary discomfort from the needle stick, bruising, and very rarely infection.

16.3

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**

All clinical specimens will be obtained by trained clinical personnel according to standard operating procedures, and the procedures will only be performed as clinically indicated.

16.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants:

These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities.

Depending on the nature of the research study, investigators should consider the proximity or

availability of critical resources that may be essential to the safety and welfare of participants, such as

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

As described in the "Qualifications of Key Study Personnel" section, all research staff involved in this project have extensive experience with research and patient care and understand the importance of minimizing risks to study subjects. As described in the "Privacy" section, we have numerous protections in place to insure subject privacy.

16.5 * 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

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

The risk to subjects is minimal, principally loss of privacy (although every effort will be made to maintain confidentiality, especially of genetic information). Knowledge may be gained from the clinically validated mNGS test about the infectious cause of their illness.

17.0 Confidentiality, Privacy, and Data Security

17.1 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.
- ☑ 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)

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

○ Yes ◉ No

17.3 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

17.4 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:

Specimens and data will be coded. The "key" to this code will kept in RedCap. RedCap will only be accessible to key study personnel and no identifying information will be shared with researchers not directly involved in the study and who are listed as study personnel on this application.

17.5 * 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

The confidentiality and privacy section of the consent form should include this as a possible risk of participation.

* Describe the types of reportable information the research team may encounter and provide the details of the reporting plan: **(REQUIRED)**

If there is suspicion for a concerning pathogen, the PI will contact the treating physician and/or clinical laboratory to discuss the finding. Public health reporting may be indicated if confirmed by the clincial lab and treating physician. The PI will not report research findings for public health reporting as these are research findings.

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

○ Yes ◉ No

17.7 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:

Research results from non-validated specimen types (e.g. brain biopsy), a narrative results report will be discused with the treating clinician detailing the candidate pathogen(s) found, research assay methods, and limitations. The discussion will include any testing available in CLIA-certified laboratories for confirmation of the research result, if applicable. The results will be marked specifically as "Research use only not to be used for clinical purposes" and "Any results (positive or negative) do not exclude any other causes for patient illness". Thus, these research results will not be used for clinical purposes but may be communicated to clinicians to guide additional CLIA-certified diagnostic testing.

17.8 * IDENTIFIERS: Will any personal identifiers be collected: (REQUIRED)

(•) Yes ( ) No

Check all the identifiers that may be included:

- [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
- [x] Facial photos or other identifiable images
- [ ] Any other unique identifier

If publications from this study may include ANY photos or images of patients - even without faces - either collected for research or from the medical records, you are required to have each patient sign the 'Consent for Photography / Authorization for Publication' form prior to submittal for publication. Failure to obtain consent for publication may result in a finding of Serious Non-compliance by the IRB and civil and criminal penalties, *including fines up to $1.5 million dollars* for violation of the HIPAA privacy protections if a participant complains.

* Could study records include *ANY* photos or images (even 'unidentifiable'

ones): **(REQUIRED)**

◉ Yes ○ No

17.9 DATA DISCLOSURE: Will identifiable information be shared with outside groups:

○ Yes ◉ No

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

Collection methods:

- ☑ Paper-based (surveys, logs, diaries, etc.)
- ☑ Electronic case report forms (CRFs), such as OnCore or another clinical trial management portal
- ☑ Web-based online surveys or computer-assisted interview tool
- ☐ Mobile applications (mobile or tablet-based)
- ☐ Wearable devices
- ☐ Audio/video recordings
- ☐ Other:

* What online survey 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)**

- ☑ UCSF
- ☐ SF VAMC
- ☐ Amazon (Amazon Cloud)
- ☐ Other academic institution
- ☑ 3rd party vendor (business entity)
- ☐ Other (explain below)

* Do you have a contract or Data Use Agreement with a 3rd party for research data collection, storage, access, and ownership: **(REQUIRED)**

◉ Yes ○ No

17.12 DATA SECURITY: Indicate how data are kept secure and protected from improper use and disclosure (check all that apply):

NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- [ ] Data are stored securely in My Research
- [ ] Data are coded; data key is destroyed at end of study
- [x] Data are coded; data key is kept separately and securely
- [x] Data are kept in a locked file cabinet
- [x] Data are kept in a locked office or suite
- [x] Electronic data are protected with a password
- [x] Data are stored on a secure network
- [x] Data are collected/stored using REDCap or REDCap Survey
- [ ] Data are securely stored in OnCore

17.13 * DATA SECURITY: Confirm below that you will keep data confidential: (REQUIRED)

I will keep any data sets that include identifiers secure and protected from improper use and disclosure by using methods such as:

- **Physical Security – Keeping data in locked file cabinets, locked offices, locked suites, and physically securing computers and servers.**
- **Electronic Security – Following UCSF minimum security standards for electronic information resources, which includes (but is not limited to): not storing identifiers on portable devices like laptops or flash drives if they are unencrypted, encrypting portable devices, and storing data in password-protected files and on secure networks.**

- (•) Yes

17.15 HIPAA APPLICABILITY: Study data will be:

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

Unless a waiver of Authorization is granted, in addition to the consent form, participants will need to sign UCSF Research Subject Authorization Form (HIPAA Form). NEW REQUIREMENT - This form should be uploaded in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to obtain HIPAA Authorization for research is one of the most common findings from QIU Routine Site Visits. Your IRB approval letter will include instructions about HIPAA requirements specific to your study.

If derived from a medical record, identify source:

APeX

17.16 * 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)

- [x] Drug or alcohol abuse, diagnosis or treatment
- [x] HIV/AIDS testing information
- [ ] Genetic testing information
- [x] 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.

18.0 Financial Considerations

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

○ Yes ◉ No

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

○ Yes ◉ No

19.0 Qualifications of Key Study Personnel

19.1

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. Also identify each person who will be involved in the consent process. Click the orange question mark for more information and examples.
Under qualifications, please include:

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

November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

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.

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.

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. Chiu, Charles Y MD	Principal investigator, Supervision of next generation sequencing techniques and bioinformatic analysis of sequencing data, patient consent	UCSF Associate Professor of Laboratory Medicine and Medicine/Infectious Diseases; Director, UCSF-Abbott Viral Diagnostics and Discovery Center; Associate Director, UCSF Clinical Microbiology; expert in pathogen discovery techniques, next generation sequencing and bioinformatics
Dr. DeRisi, Joseph, PhD	Supervision of next generation sequencing techniques and bioinformatic analysis of sequencing data, patient consent	UCSF Professor and Chair of Biochemistry and Biophysics, expert in pathogen discovery techniques, next generation sequencing and bioinformatics
Dr. Gelfand, Jeffrey MD	Patient recruitment, consent, study design	UCSF Assistant Professor of Neurology, UCSF Multiple Sclerosis Center, expert on neuroimmunological diseases, Masters in Clinical Research
Dr. Wilson, Michael MD	Study design, perform next generation sequencing on clinical specimens and bioinformatics analysis, patient consent	UCSF Assistant Professor in Residence in Neurology, UCSF MS Center, expert in neuro-infectious diseases
Langelier, Charles R	Study design, perform next generation sequencing on clinical specimens and bioinformatics analysis, patient consent	UCSF Infectious Diseases fellow
Chow, Felicia, MD	Study design, patient recruitment, data analysis, patient consent	UCSF Assistant Professor of Neurology, Neurologist expert in neuro-infectious diseases

Dr. Pleasure, Samuel M.D., PhD	Study design, autoantibody screening, patient consent	UCSF Professor of Neurology, Neurologist expert in neuroimmunological diseases, Neuroanatomist
Dr. Geschwind, Michael, MD, PhD	Study design, data acquisition and analysis, patient consent	UCSF Professor of Neurology, neurologist expert in rapdily progressive dementia
Sample, Hannah	Study coordinator; Patient recruitment and consent; specimen processing; study database management	UCSF clinical research coordinator
Dr. Chow, Eric, PhD	perform next generation sequencing on clinical specimens, data analysis	Director - Center for Advanced Technology UCSF Dept. of Biochemistry and Biophysics
Samayoa, Erik L	perform next generation sequencing on clinical specimens	CLIA Lab technician, Chiu Lab
Naccache, Samia N	perform next generation sequencing on clinical specimens and bioinformatics analysis; data manager; CLIA technician running the mNGS assay	PhD Bioinformatician, CLIA Lab technician, Chiu Lab
Miller, Steven	Supervision of next generation sequencing techniques and bioinformatic analysis of sequencing data	UCSF Associate Professor of Laboratory Medicine, Director, UCSF Clinical Microbiology
Federman, Scot M	next-generation sequencing data analysis; running SURPI bioinformatics pipeline	UCSF Programmer/Analyst III, UCSF Department of Laboratory Medicine
Stryke, Doug	next-generation sequencing data analysis; running SURPI bioinformatics pipeline	UCSF Programmer Analyst, UCSF Department of Laboratory Medicine
Berger, Amy	study design; enrolling patients for NGS study; obtaining consent	UCSF Resident Physician
Pham, Elizabeth	CLIA technician running the clinical mNGS assay	UCSF Clin Lab Scientist UCSF Department Laboratory Medicine
Samayoa, Erik L	CLIA technician running the clinical mNGS assay	UCSF Clin Lab Scientist UCSF Department Laboratory Medicine
Yu, Guixia	Sample biobanking and aliquotting; running confirmatory research assays	UCSF SRA, UCSF Department of Laboratory Medicine

	for the mNGS clinical test		
Zorn, Kelsey C	Consent patients, assist with specimen collection, data management	UCSF Clinical Research Coordinator, Dept of Biochemistry and Biophysics	

20.0 Other Approvals and Registrations

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

○ Yes ◉ No

20.2 * HUMAN GENE TRANSFER: Does this study involve human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to IRB approval): (REQUIRED)

○ Yes ◉ No

20.4 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 #:

Chiu lab: BUA 49187-BU-01-INC; CLIA certificate 05D1024215

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

21.0 End of Study Application

21.1

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 wants your feedback about this new form. Please click the link to take a brief survey about the new application form.

4. SUMMARY OF CHANGES TO THE ORIGINAL STUDY PROTOCOL

	Approval date	Summary of modifications
1.2	3/01/16	Initial approval of study application. UCSF as IRB of record, UC Davis and UCLA approved as relying sites.
1.3	5/25/16	Changes to consent documents: • removed language that allowed for participants to have the UCSF mNGS test done without participation in the research study. This initial demonstration project will limit access only those who are in the study (meet criteria and are willing to consent). Changes to Application: • section 3- updated study personnel • section 7 updated personnel for outside site; Syapse • section 11 included referral form that we will use to determine eligibility for study Attached docs: • referral survey • CITI training certification for new Syapse team member • revised consents
1.4	6/10/16	Updated study personnel
1.5	6/20/16	This modification is being submitted because of a glitch in the iRIS system. Our vulnerable populations were accidentally removed from the application. They have been added again here on the new form. Discussion has been had with Karen Chao and Liz Tioupine. Section 1: DAID-> PDAID Section 3: removed Kristen McCaleb Section 5: CIAPM is listed as funding (this has always been the case) Section 6: removed SFGH, this is still in process, will add them at a later date Section 9: changed to No, this has never been true and was an error. Section 10: added justification for enrollment numbers Added minors, pregnant women, non-English speakers, patients unable to consent themselves, and the economically disadvantaged (this was in the original application form, but glitched out with section 9.6 being selected 'yes') Section 11: inclusion of minors Section 12: added UC ReX Section 12: consent method for non-English speakers Section 16: Added where we are obtaining PHI Section 16/ 14: defined PHI, sensitive data Section 18: removed Kristen McCaleb
1.7	8/19/16	This modification includes changes to the consent documents, the addition of one study personnel, and includes consenting subjects who have been discharged or transferred. <u>Changes to consent:</u> No major changes Minor changes in language, presentation, and organization These changes are being submitted via the request of our UCLA collaborators in hopes it will make the consent more understandable for study participants <u>Changes to application:</u> Section 3: two team members added Section 12: adding consent for patients who have been transferred or discharged Section 18: qualifications for KSP

1.9	1//3/17	Section 4.1—updated information to reflect finished validation of CSF (June 2016) and pending validation of serum and BAL. Section 4.9—yes, Clinical Trial, pending final posting. Section 4- indicated 'yes' to financial conflict of interest 1) The SURPI-PLUS software used for analysis of sequencing data in the study has been disclosed to the UCSF Industry and Technology Alliances (UCSF ITA) and is under copyright as disclosure SF2014-090 2)The SURPI-PLUS algorithms, including analysis, interpretation, and visualization components, is the subject of a patent application titled "Pathogen Detection Using Next-Generation Sequencing", filed 9/21/2016, and superseding the non-provisional U.S. patent application No. 62/221,574 filed 9/21/2015. 3)The terms "SURPI", "SURPI+", "SURPI-PLUS", and "SURPIrt" have been trademarked by UCSF, filed with the United States Patent and Trademark Office with statement of use 7/19/16 4)The positive and negative controls used in the assay have been disclosed as case number SF2016-185, entitled "Microbial Standard Reference Materials for Pathogen Detection" Section 6.1 added SFGH Section 6.3 updated information on sites Section 7.1- updated information for CNMC, Dr. Goldberg has recused as site PI, Dr. DeBiasi will now be site PI 7.1 added Milliman, St. Jude and Children's Hospital Colorado Section 8- updated information stated Section 9.3 non-significant risk information Section 11- added wards of the state. There is a current patient who is a foster child, whom we would like to enroll in the study as they have acute encephalitis and access to the clinical diagnostic could potentially benefit this patient. Section 12- updated wording Section 12.8 added DocuSign for remote consenting Section 14.6 updated surrogate consent info Section 16.7 removed info about clinical test, not relevant for IRB _____CONSENT_____ CNMC: removed Dr. Goldberg as contact from these documents, updated to include DeBiasi's contact information (all 3 CNMC consents) UCSF consents: removed Dr. Goldberg (CNMC collaboration is using a separate consent), updated statement that addressed accuracy of test to state "clinical utility" of test. Added statement regarding patent. _____ATTACHED DOCUMENTS_____ attached are IAA for ST. Jude, CITI certs for St. Jude team and CNMC team, as well as letter of support from Milliman (not engaged in human subjects research). Also attached IRB documents for Children's Hospital Colorado (independent IRB review and approval for collaboration)
1.10	2/22/17	Section 3- updated staff (originally added in study management prior to modification) Section 3.3- added another contact (Jenn Mann) Section 4.1 3 UCs-> 4UCs (adding UCSD) Section 5.3 This change may have been an error—the P number is now pulled into the application Section 6.3 adding UCSD Section 6.8- checked UCSD Consent form: added UCSD contact info to adult/adolescent form
1.16	8/17/17	<u>Application:</u> 8.4 added provider survey to procedures 15.5 updated and detailed re-consent procedure for patients who were enrolled via surrogate <u>Consent Documents:</u> 1. Submitting an adult consent form for St Jude (currently only a minors consent form is available for St Jude) <u>Other Study Documents:</u> 1-2. Submitting the provider pre and post test result surveys 3. Added phone script for re-consent to surrogate 4. Added phone script for re-consent to participant 5. Added re-consent letter to participants

		6. Added re-consent letter to surrogates 7. Added Status Update Form
1.17	12/18/17	Section 3: removed Jenn Mann as study contact, other personnel changes pulled from study management tab Section 7.1 Outside sites—added new coordinator for CNM Other Documents: CITI cert for new CNMC coordinator who will be doing data collection / chart review

5. REGULATORY COMMITTEE APPROVALS

The UCSF Clinical Microbiology Laboratory, a CLIA-licensed facility, operates under CLIA with certificate 05D1024215 and undergoes regular inspections by CAP and CLIA. The Chiu research laboratory is able to analyze research samples collected from patients under active BUA (Biological Use Authorization) 49187-BU-01-INC.

This was a multisite study with the following IRB approvals:

UC Reliance 1595-3

- Coordinating Center
    - University of California, San Francisco
    - 15-18425
- Relying Sites through UC BRAID
    - University of California, Davis
    - University of California, Los Angeles
    - University of California, Berkeley
    - University of California, San Diego

Relying Sites (UCSF IRB, not under UC BRAID)

- Children's National Medical Center
- Zuckerberg San Francisco General Hospital
- St Jude Children's Research Hospital

Collaborating Sites with independent IRB review

- Children's Hospital Los Angeles
- Children's Hospital Colorado

This study was submitted as version 1.0 on 12/8/15 and approved by the UCSF IRB as study number 15-18425 after proposed clarifications to the protocol as version 1.2 on 3/1/2016. The first study patients were enrolled on 6/15/2016 under protocol version 1.4 which was approved on 6/10/16.

6. STATISTICAL ANALYSIS PLAN

6.1. Original Statistical Analysis Plan

This was a one-year, multicenter, prospective cohort study in which subjects were enrolled based on a particular exposure (i.e. idiopathic meningitis +/- encephalitis and/or myelitis) and then followed over time to assess for the occurrence of the outcome (i.e. results of CSF mNGS testing). Prospective enrollees were identified by physician referral, computerized provider order entry, patient chart review, or screening of daily EMR reports (Supplementary Appendix). Given funding and clinical testing capacity constraints, sample size estimates (n=300) were based on convenience without formal statistical considerations. The target condition was idiopathic meningitis, encephalitis, and/or myelitis in patients undiagnosed at time of enrollment. The index test was the CSF mNGS assay, and the reference standard was a composite of conventional testing and orthogonal confirmatory testing of mNGS-only positive results, either with respect to all clinical testing or direct detection (i.e. non-serologic) testing of CSF only.

Performance measures (sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)) were calculated using standard formulas for proportions, and 95% confidence intervals for these proportions were determined using Wilson's method. The primary analysis was a comparison of the performance of the mNGS assay versus conventional (direct detection) testing using the composite results of direct detection testing of CSF, including orthogonally confirmed mNGS results, as the reference standard. Secondary analyses included 2x2 contingency analyses of other comparative performance measures and calculations of diagnostic yield (the number and proportion of infectious diagnoses made by mNGS or conventional testing).

The original statistical analysis plan may also be viewed as part of original IRB protocol on page 27.

6.2. Final Statistical Analysis Plan

This was a one-year, multicenter, prospective cohort study in which subjects were enrolled based on a particular exposure (i.e. idiopathic meningitis +/- encephalitis and/or myelitis) and then followed over time to assess for the occurrence of the outcome (i.e. results of CSF mNGS testing). Prospective enrollees were identified by physician referral, computerized provider order entry, patient chart review, or screening of daily EMR reports (Supplementary Appendix). Given funding and clinical testing capacity constraints, sample size estimates (n=300) were based on convenience without formal statistical considerations. The target condition was idiopathic meningitis, encephalitis, and/or myelitis in patients undiagnosed at time of enrollment. The index test was the CSF mNGS assay, and the reference standard was a composite of conventional testing and orthogonal confirmatory testing of mNGS-only positive results, either with respect to all clinical testing or direct detection (i.e. non-serologic) testing of CSF only.

As gold standard reference results for diagnosis of meningitis and encephalitis was not available (due to the varying extent of diagnostic testing done at each hospital, lack of detailed performance characteristics for each test performed locally, and lack of availability of comprehensive gold standard testing for meningitis and encephalitis), obtaining unbiased estimates of sensitivity and specificity was not possible. Thus, the comparative performance measures of mNGS relative to conventional testing are reported as positive percent agreement (PPA) and negative percent agreement (NPA) to the composite reference standard, in accordance with statistical guidance from the FDA. PPA and NPA were calculated

using standard formulas for proportions, and 95% confidence intervals for these proportions were determined using Wilson's method.

The primary analysis was a comparison of the performance of the mNGS assay versus conventional (direct detection) testing using the composite results of direct detection testing of CSF, including orthogonally confirmed mNGS results. Secondary analyses included 2x2 contingency analyses of the PPA and NPA of the mNGS assay relative to other combinations of conventional diagnostic testing including serology and test results from other tissue types.

The final statistical analysis plan may also be viewed as part of the final IRB protocol on page 78.

6.3. Summary of Changes to the Statistical Analysis Plan

In the Institutional Review Board (IRB)-approved protocol titled "Study Protocol for the PDAID Trial", clinical trials registration number NCT02910037, one of the primary outcomes is described as an assessment of clinical mNGS assay performance (sensitivity, specificity, positive predictive value, and negative predictive value). These performance measures are also mentioned in the document as an explanation for why the use of the device in the study (the clinical mNGS assay) poses a non-significant risk.

During the course of peer review, it was brought up that obtaining unbiased estimates of sensitivity and specificity was not possible as gold standard reference results for diagnosis of meningitis and encephalitis were not available. Thus, the comparative performance measures of mNGS relative to conventional testing are calculated and reported in the paper as positive percent agreement (PPA) and negative percent agreement (NPA) to the composite reference standard, in accordance with statistical guidance from the FDA ("Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests – Guidance for Industry and FDA Staff", Food and Drug Administration, U.S. Department of Health and Human Services, issued March 13th, 2007).

7. APPENDIX

7.1. Enrollment Flow Chart