Clinical Metagenomics – our Real-Life Experience

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Disclosures

• Abbott Diagnostics and BioMérieux (research support)

• The mNGS assay discussed here is a laboratory-developed test (LDT) validated in the CLIA-certified UCSF Clinical Microbiology Laboratory and is not FDA-approved
Alyass, et al., 2015, *BMC Medical Genomics* 8:33
Precision Diagnosis with Metagenomic Testing can Impact Clinical Decision-Making in Infectious Diseases

CLIA Laboratory

- Agent ID
- Bioinformatics

Turnaround time: hours – days (versus days – weeks)

Lower healthcare costs
Improved patient outcomes

Cost-effective and actionable information for early treatment
Targeting Acute Infectious Diseases in Hospitalized Patients

**Meningitis / Encephalitis**

40 – 60% unknown cause


**Pneumonia**

15 – 25% unknown cause


**Fever / Sepsis**

~20% unknown cause


**Failure to obtain a timely diagnosis leads to delayed / inappropriate therapy, increased mortality, and excess healthcare costs**
Conventional Testing

Metagenomic Next-Generation Sequencing (mNGS)
All Microbes can be Uniquely Identified by mNGS

Bacteria

Viruses

Fungi

Parasites
Precision Diagnosis of a Mysterious Infection

3 hospitalizations over 4 months
>100 inconclusive tests
Brain biopsy and induced coma

(Wilson, et al., 2014, New England Journal of Medicine; photos courtesy of the Osborn family)
The SURPI Bioinformatics Pipeline

“Sequence-based ultra-rapid pathogen identification” (minutes – hours)

- Directly addresses computational analysis bottleneck
- SURPI+ (clinical version) – automated analysis

Naccache, et al., 2014, Genome Research 24(7):1180-1192
Leptospira santarosai
Leptospira borgpetersenii
unclassified
Leptospira interrogans
Propionibacterium acnes
### Chart Review

<table>
<thead>
<tr>
<th>Collect Date/Time</th>
<th>Test Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/25/2017 17:52</td>
<td>Microbiology - Test Not Listed (Special S...)</td>
</tr>
<tr>
<td>01/25/2017 12:42</td>
<td>Microbiology - Test Not Listed (Special S...)</td>
</tr>
<tr>
<td>01/25/2017 12:42</td>
<td>Microbiology - Test Not Listed (Special S...)</td>
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<tr>
<td>01/25/2017 12:42</td>
<td>Microbiology - Test Not Listed (Special S...)</td>
</tr>
<tr>
<td>01/25/2017 12:42</td>
<td>Pathogen Detection, mNGS (metagenom...)</td>
</tr>
<tr>
<td>01/25/2017 12:42</td>
<td>Varicella zoster virus DNA</td>
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<tr>
<td>01/25/2017 12:42</td>
<td>Microbiology - Test Not Listed (Special S...)</td>
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<tr>
<td>01/25/2017 12:42</td>
<td>AFB Non-Respiratory Culture</td>
</tr>
<tr>
<td>01/25/2017 12:42</td>
<td>CSF Fungal Culture for Coccioides</td>
</tr>
<tr>
<td>01/25/2017 12:42</td>
<td>Bacterial Culture and Gram Stain, CSF</td>
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<tr>
<td>01/25/2017 12:42</td>
<td>Cryptococcal Antigen</td>
</tr>
<tr>
<td>01/25/2017 00:00</td>
<td>Metagenomic next-generation sequencing</td>
</tr>
<tr>
<td>01/09/2017 12:00</td>
<td>Respiratory Viral Panel PCR</td>
</tr>
</tbody>
</table>

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Metagenomic next-generation sequencing

**LABORATORY PHYSICIAN INTERPRETATION:**

**Organism Type:**

- **DNA Viruses:**
  - MW polyomavirus
- **RNA Viruses:**
  - Not Detected*
- **Bacteria:**
  - Not Detected
- **Fungi:**
  - Not Detected
- **Parasites:**
  - Not Detected

*Potential limited ability to detect RNA viruses due to insufficient read depth.

MW (Malawi) polyomavirus, also known as MX (Mexico) polyomavirus, was first identified in 2012 in stool samples from children with diarrhea (Siebers, 2012, Journal of Virology, 86(19):10321-10326; Yu, et al., 2012, PLoS ONE (11):e99499). To date, MW polyomavirus has only been detected in the African continent.
Precision Diagnosis of Acute Infectious Diseases (PDAID)

7 hospitals in CA and nationwide
Enroll/consent patients
203 total
CSF collected
Clinical chart review

Meningoencephalitis
40-60% unknown cause

mNGS assay validated in CLIA lab
86% analytic sensitivity, 98% specificity

• Diagnosis of neurologic infection in 21.6% of cases, more than one-half of which were not identified by conventional testing
• 88% clinical sensitivity, 97% specificity (excluding cases dx’ed by serology)

Wilson and Sample, et al., 2017 (manuscript in preparation)
58 y/o immunosuppressed woman with fever, headache, nausea/vomiting

- History of idiopathic pulmonary fibrosis status post bilateral lung transplant in 2011, multiple sclerosis, on chronic immunosuppression
- Admitted to hospital in October 2016 with 8 days of fever, headache ("worst in my life"), nausea/vomiting, neck stiffness, and photophobia
- Neurological symptoms: admitted to "5 years" of word-finding difficulty and slurred speech, 1 year of dizziness/falls, and 1 month of leg weakness; also had first-time seizure in March 2016
- Resident of Orange County; no sick contacts; travel to mountains in Utah in August 2016, Caribbean in 2010, and throughout Europe decades ago
- Fever to 38.3°C, pancytopenic, transaminitis (negative for hepatitis A, B, and C); MRI – white matter intensities related to MS
- Started on empiric antimicrobials: IV vancomycin, ceftazidime, acyclovir, and voriconzole

Murkey, et al., 2017, Open Forum Infectious Diseases, 4(3):ofx121
• Lumbar puncture done, showing a lymphocytic pleocytosis

• WBC 10, 88% lymphocytes, protein 29, glucose 48

Blood
CMV DNA quantitative PCR negative
Cryptococcal Ag negative
EBV PCR detected <10
HSV-1/2 PCR negative
Fungal culture negative
Bacterial culture negative
Toxoplasma gondii DNA PCR negative
MTB Quantiferon-Gold assay negative
Adenovirus DNA PCR negative
Parvovirus B19 DNA PCR negative
West Nile IgG / IgM negative
Rickettsia RMSF and typhus IgG / IgM negative
Varicella zoster DNA PCR negative
Coccidioides IgG and IgM EIA negative
Hepatitis A Ab total negative
Hepatitis A Ab IgM negative

Microbiology (non-HEV)

CSF
Cryptococcal Ag negative
Enterovirus PCR negative
Fungal culture negative
Bacterial Gram stain and culture negative
VZV PCR negative
HSV-1/2 PCR negative
CMV DNA quantitative PCR negative

Nasopharyngeal swab
Respiratory Virus Panel (RVP) PCR negative

MRI brain: Stable periventricular and subcortical and juxtacortical T2/FLAIR white matter intensities w/T1 hypointensity

Imaging

Abdominal ultrasound:
Normal liver size, homogeneous in echogenicity.
Normal spleen size. No ascites. Normally distended gallbladder containing sludge, without stones.

MRI brain: Unchanged

Abdominal ultrasound: Cirrhotic appearing liver without focal lesion, patent hepatic vessels, small volume ascites. Spleen upper normal in size.

Liver ultrasound elastography: shear wave liver stiffness 2.1m/sec consistent with METAVIR score of F3-F4
Hepatitis E virus
mapped to GenBank AB089824, 7,262 bp (Hepatitis E virus genomic RNA, complete genome, isolate: HE-JA10)
assembly 930% complete, 90.2% average pairwise identity
• Patient treated with ribavirin and is clinically improved
• This is a likely case of donor-transmitted HEV (positive anti-HEV antibody testing of donor’s serum)
<table>
<thead>
<tr>
<th>Confirmatory diagnosis using mNGS (n=19, 9.2%)</th>
<th>Diagnosis by mNGS only (n=26, 12.6%)</th>
<th>Orthogonal confirmation post-mNGS testing (22/26 patients, 84.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td><em>Streptococcus agalactiae</em> (also HIV-1 / <em>Cryptococcus</em>)</td>
<td>universal 16S bacterial PCR (clinical, UW)</td>
</tr>
<tr>
<td>HHV-6B</td>
<td><em>Enterobacter aerogenes</em></td>
<td>BioFire FilmArray (clinical, UCD)</td>
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<tr>
<td>HIV-1</td>
<td><em>Streptococcus agalactiae</em></td>
<td>EBV PCR (clinical, UCSF)</td>
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<tr>
<td>enterovirus B</td>
<td>EBV* (also HSV-1)</td>
<td>HHV-7 PCR (clinical, Viracor)</td>
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<tr>
<td>HSV-1</td>
<td><em>HHV-7</em></td>
<td>enterovirus PCR (research, Viracor)</td>
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<tr>
<td>VZV</td>
<td><em>echovirus 6</em> (also HHV-7)</td>
<td>universal 28S fungal PCR (clinical, UW)</td>
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<tr>
<td>Cryptococcus neoformans (also HIV-1)</td>
<td><em>Candida tropicalis</em></td>
<td></td>
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<tr>
<td>HIV-1</td>
<td><em>St. Louis encephalitis virus</em></td>
<td>SLEV PCR (clinical, CDC)</td>
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<tr>
<td>VZV</td>
<td><em>Hepatitis E virus</em></td>
<td>HCV PCR (clinical, CDC)</td>
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<tr>
<td>JC polymavirus</td>
<td><em>Neisseria meningitidis</em></td>
<td><em>N. meningitidis</em> pyrosequencing (clinical, CDPH)</td>
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<tr>
<td>Cryptococcus neoformans (also HIV-1)</td>
<td><em>Human coronavirus 229E</em></td>
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<tr>
<td>VZV</td>
<td><em>Polyomavirus MV</em></td>
<td>MX polyomavirus PCR (research, UCSF)</td>
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<tr>
<td>HHV-6B</td>
<td><em>Angiostrongylus cantonensis</em></td>
<td><em>Angiostrongylus cantonensis</em> PCR (clinical, CDC)</td>
</tr>
<tr>
<td>HIV-1 (also <em>Pectobacterium carotovorum</em>)</td>
<td><em>HHV-7</em></td>
<td>HHV-7 qPCR from plasma (clinical, Viracor)</td>
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<tr>
<td>Cryptococcus neoformans (also HIV-1)</td>
<td><em>Nocardiia farcinica</em></td>
<td><em>Nocardiia</em> PCR (research, UCSF)</td>
</tr>
<tr>
<td>HIV-1</td>
<td><em>HSV-2</em></td>
<td>HSV-2 PCR (clinical, Quest)</td>
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<tr>
<td>EBV</td>
<td><em>VZV</em></td>
<td>VZV RT-PCR (research, UCSF)</td>
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<td>HCV (also HIV-1)</td>
<td><em>HHV-6A</em></td>
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<td>HIV-1</td>
<td><em>EBV</em></td>
<td>EBV PCR (clinical, UCSF)</td>
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<tr>
<td>coxsackievirus B5</td>
<td><em>Streptococcus mitis</em></td>
<td>S. mitis (MALDI from blood culture, SJCRH)</td>
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<tr>
<td></td>
<td><em>HHV-6B</em></td>
<td>HHV-6 qPCR (clinical, Viracor)</td>
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<td></td>
<td><em>echovirus 30</em></td>
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<tr>
<td></td>
<td><em>EBV</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus faecalis</em></td>
<td>positive <em>E. faecalis</em> culture from brain biopsy dural tissue, bone flap, epidural gel foam</td>
</tr>
</tbody>
</table>

* indicates genomic material detected by mNGS.
40 and 45 y/o couple who went on honeymoon to Maui

Couple went on honeymoon to Maui in March of 2017. Upon returning to the United States, both developed fever, transient rash over arms and shoulders, headache, neck stiffness. Workup shows cerebrospinal fluid (CSF) eosinophilia. Upon questioning, they stated that they were ”hiking in the jungle, picking up and eating raw fruits”.
Newlyweds contract rare brain parasite during Hawaiian honeymoon

By Susan Scutti, CNN
Updated 4:14 PM ET, Wed April 12, 2017

Photos: What to know about tapeworms and parasites
Cat-scratch fever, aka Toxoplasmosis, aka T. gondii: Toxoplasmosis infects more than a million people each year in the US. Once you get it, you've usually got it for life, the CDC says.
Accurate Species Classification

With Randall Hayden and Gabriela Marón, St. Jude Children’s Research Hospital
Pathogen Discovery?

During meningocerebralitis episode

Polyomavirus MW/MX

After meningocerebralitis episode
Antibiotic Resistance Prediction

Predicted Antibiotic Resistance - *Enterobacter aerogenes* strain

- *maca* - MDR efflux pump; macrolide-specific efflux system
- *acrB, acrA, tolC* - MDR efflux pump, aminoglycoside, beta-lactam, macrolide resistance
- *mdtG* - MDR efflux pump, resistance fosfomycin
- *mdtL* - MDR efflux pump, resistance chloramphenicol
- *ksgA* - rRNA methylation; kasugamycin resistance
- *mexB* - MDR efflux pump; resistance aminoglycoside, beta-lactam, fluoroquinolone, tetracycline, tigecycline
- *smeB* - MDR efflux pump; resistance fluoroquinolone
- **BL1_cmy2** - AmpC beta-lactamase / class C beta-lactamase - resistance carbapenem, cefoxitin, ceftazidime, ceftriaxone, cephalosporin, cephem. This gene is chromosomally encoded in *Enterobacter aerogenes*
- *emrD* - MDR efflux pump, aminoglycoside resistance
Solving Medical Mysteries
Providing the next generation of clinical testing to diagnose unexplained diseases

http://nextgendiagnostics.ucsf.edu
Next Steps

• **Expand Clinical Assay to New Indications to Reach Broader Patient Populations**
  - Plasma for fever/sepsis
  - BAL fluid for pneumonia
  - Other body fluids (joint fluid, peritoneal fluid, pleural fluid, abscess fluid, etc.)

• **Streamline Clinical Assay to Increase Throughput and Availability**
  - Robotics / automation for sample processing steps
  - Increase personnel capacity and upgrade instrumentation to enable processing of >100 samples/week

• **Sustainable Infrastructure for Clinical Reference Testing**
  - P710 test code for billable metagenomic next-generation sequencing test; approximate charge $2200
  - Application for McKesson Z-Code identified, pre-submission inquiry for FDA approval pending
  - Licensing SURPI+ software via Amazon Web Services (AWS) and DNAnexus, background sample/contamination database, and control reagents via collaboration with the FDA and NIST
  - Clinician feedback via Clinical Microbial Sequencing Board (CMSB)

• **Evaluate Cost / Benefit to Patients**
  - Economic analysis pending (Dr. Brent Fulton, UC Berkeley)

• **Data Mining**
  - Improve our capability of providing “precision diagnosis” to infectious disease patients
Machine Learning-Based Prediction of Causes of Infection from Human Gene Expression Data (RNA-Seq) from CSF from PDAID Patients

90% accuracy in discriminating bacterial from viral infection (preliminary analysis)

- Training set: 25 bacterial positive cases, 48 viral positive cases
- Test set: 6 bacterial positive cases, 9 viral positive cases

<table>
<thead>
<tr>
<th>Model</th>
<th>CV RSME Score</th>
<th>CV RSME STD</th>
<th>CV Accuracy</th>
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</thead>
<tbody>
<tr>
<td>Linear SVM</td>
<td>0.221034</td>
<td>0.226150</td>
<td>0.900000</td>
</tr>
<tr>
<td>Logistic Regression</td>
<td>0.250920</td>
<td>0.265278</td>
<td>0.866667</td>
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<tr>
<td>Polynomial SVM</td>
<td>0.323491</td>
<td>0.220651</td>
<td>0.846667</td>
</tr>
<tr>
<td>Stochastic Gradient Descent</td>
<td>0.241841</td>
<td>0.248018</td>
<td>0.840000</td>
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<tr>
<td>AdaBoost</td>
<td>0.274579</td>
<td>0.290871</td>
<td>0.806667</td>
</tr>
</tbody>
</table>

Tony Li, BS

(with Matt Massie and Anthony Joseph, UC Berkeley)
Identification of *Haemophilus influenzae* Pneumonia / Sepsis in a Leukemic Patient

Cell-free bronchoalveolar lavage and plasma samples reveal a 12p interstitial deletion on cell-free NGS, confirmed by traditional cytogenetic testing.
Nanopore Sequencing for Real-Time Metagenomic Pathogen Detection in Patients with Fever / Sepsis

MinION (Oxford Nanopore Technologies)
## Differential Diagnosis of Tropical Febrile Illness

<table>
<thead>
<tr>
<th>BACTERIAL</th>
<th>VIRAL</th>
<th>OTHER</th>
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</thead>
<tbody>
<tr>
<td>Rickettsioses</td>
<td>Arboviral infections</td>
<td>Malaria / Babesiosis</td>
</tr>
<tr>
<td>Bacillary Dysentery</td>
<td>Viral hepatitis</td>
<td>Amebiasis</td>
</tr>
<tr>
<td>Plague</td>
<td>Enterovirus</td>
<td>Visderal leishmaniasis</td>
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<tr>
<td>Meningococcemia</td>
<td>Measles</td>
<td>Acute schistosomiasis</td>
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<tr>
<td>Typhoid fever</td>
<td>Rubella</td>
<td>Filarial fever</td>
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<tr>
<td>Other bacterial septicemia</td>
<td>Acute Retroviral Syndrome (HIV)</td>
<td>Trypanosomiasis</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Epstein-Barr virus</td>
<td></td>
</tr>
</tbody>
</table>
Assay Turnaround Time is Critical for Sepsis
Nanopore Sequencing

• **Advantages**
  – Real-time sequence analysis
  – Expansion potential (ProMethion, GridION, etc.)
  – Long read capability
  – Can directly sequence RNA and protein in addition to DNA
  – Portable, pocket-size, amenable for field work
  – Potentially fast turnaround times, key for infectious disease sequencing

• **Disadvantages**
  – Cost of sequencing ($500 per flow cell)
  – Error rates still 8-12%
  – Oxford Nanopore Technologies is a startup company (? reliable source); quality of flow cells can be variable
Viral Reads Detected <8 Min into Sequencing Run

(Greninger, et al., 2015, Genome Medicine 7:99)
Low Serum Titers in Acutely Infected ZIKV Patients

**EBOV**

![Histogram for EBOV](image1)


**ZIKV**

![Histogram for ZIKV](image2)

Spiked Primer Strategy for Metagenomic Target Enrichment

- Set of reference genomes
- Partition aligned genomes into overlapping 250-nt segments
- Select forward and reverse spiked 13-nt primers

Thézé, et al., 2017 and Deng, et al., 2017, manuscript in preparation
Targeted Primers Increase Sensitivity But Do Not Impact Off-Target Metagenomic Detection

Thézé, et al., 2017, manuscript in preparation
Protocol Optimization on the MinION Nanopore Sequencer

Wayne Deng, PhD

Dianna Ng, MD

Deng, et al., 2017, manuscript in preparation
A Field-Ready, Portable Nanopore Sequencing Assay
Instituto de Biotecnologia, UNAM
Susana López /Carlos Arias Laboratories, Cuernavaca, Mexico
SURPIrt Setup
(offline use)
# Nanopore Sequencing of Clinical Samples

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Sample Type</th>
<th>Pathogen Titer</th>
<th>Sample-to-Detection Time</th>
<th>Accumulated pathogen reads at time of detection</th>
<th>SURPlrr Result</th>
<th>Conventional Testing Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSF</td>
<td>BAL</td>
<td>High</td>
<td>2 hr, 42 min</td>
<td>31 out of 50,000</td>
<td>Streptococcus pneumoniae</td>
<td>Streptococcus pneumoniae</td>
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<tr>
<td>UCSF</td>
<td>Pleural fluid</td>
<td>Moderate colonies</td>
<td>2 hr, 50 min</td>
<td>31 out of 50,000</td>
<td>Staphylococcus lugdunensis</td>
<td>Staphylococcus lugdunensis</td>
</tr>
<tr>
<td>UCSF</td>
<td>BAL (no amplification)</td>
<td>Moderate colonies</td>
<td>2 hr</td>
<td>31 out of 50,000</td>
<td>Haemophilus influenzae</td>
<td>Negative*</td>
</tr>
<tr>
<td>UCSF</td>
<td>Plasma</td>
<td>Low colonies</td>
<td>3 hr</td>
<td>7 out of 150,000</td>
<td>Haemophilus influenzae</td>
<td>Negative*</td>
</tr>
<tr>
<td>UCSF</td>
<td>Joint fluid</td>
<td>Moderate colonies</td>
<td>3 hr</td>
<td>14 out of 50,000</td>
<td>Staphylococcus aureus</td>
<td>Staphylococcus aureus</td>
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<tr>
<td>UCSF</td>
<td>Plasma</td>
<td>40 parasites/ul</td>
<td>2 hr, 50 min</td>
<td>320 out of 50,000</td>
<td>Babesia microti</td>
<td>Babesia microti</td>
</tr>
<tr>
<td>UCSF</td>
<td>Whole Blood</td>
<td>10 parasites/ul</td>
<td>2 hr, 45 min</td>
<td>15 out of 50,000</td>
<td>Plasmodium falciparum</td>
<td>Plasmodium falciparum</td>
</tr>
<tr>
<td>UCSF</td>
<td>Whole Blood</td>
<td>50 parasites/ul</td>
<td>3 hr</td>
<td>50 out of 50,000</td>
<td>Plasmodium falciparum</td>
<td>Plasmodium falciparum</td>
</tr>
<tr>
<td>UCSF</td>
<td>dengue virus spiked into negative plasma matrix &amp;</td>
<td>$10^2$ copies/mL</td>
<td>3 hr</td>
<td>10 out of 50,000</td>
<td>dengue virus</td>
<td>spiked dengue virus</td>
</tr>
<tr>
<td>UCSF</td>
<td>Zika virus spiked into negative plasma matrix &amp;</td>
<td>$10^2$ copies/mL</td>
<td>3 hr</td>
<td>22 out of 50,000</td>
<td>Zika virus</td>
<td>spiked Zika virus</td>
</tr>
<tr>
<td>Mexico (Cuernavaca)</td>
<td>plasma sample</td>
<td>$10^3$ copies/mL</td>
<td>3 hr</td>
<td>7 out of 50,000</td>
<td>dengue virus</td>
<td>dengue virus</td>
</tr>
<tr>
<td>Mexico (Cuernavaca)</td>
<td>nasal swab sample</td>
<td>$10^5$ copies/mL</td>
<td>2 hr, 30 min</td>
<td>4 out of 50,000</td>
<td>influenza B</td>
<td>influenza B</td>
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<tr>
<td>Democratic Republic of the Congo (Kinshasa)</td>
<td>lambda phage control</td>
<td></td>
<td>2 hr, 40 min</td>
<td>319 out of 368</td>
<td>lambda phage</td>
<td>lambda phage</td>
</tr>
</tbody>
</table>
Nanopore Sequencing in Space

- Equimolar DNA
- ISS1: 8/26
- ISS2: 9/3
- ISS3: 9/7
- ISS4: 9/13
- ISS and Ground (G) synchronous sequencing runs

- G1, G2, G3, G4

- Nanopore sequencing
- Data transfer and basecalling
- Continuous directory scanning
- Computational host subtraction
- Microbial identification
- Real-time graphical visualization
Analysis of Nanopore Data Collected on the ISS

E. coli de novo assembly
(ISN runs #1-8, Canu)
raw 2D reads (n=192,042)

ISS runs #1-8 (pooled SURPlrt analysis)

Viral reads (83,237)

Enterobacteria phage lambda (17,663, 21.2%)
Lambdakovirus genus (8,766, 10.5%)
Enterobacteria genus (215, 0.26%)
Siphoviridae family (57,535, 69.3%)
Escherichia coli (83,052, 30.1%)
Mus musculus (83,332, 30.1%)
Unidentified reads (27,043, 9.8%)
Other (237, 0.08%)
Other (218, 0.08%)
Caudovirales order (56,489, 67.9%)
Enterobacteriaceae (25,212, 30.4%)
Bacteria (83,052, 30.0%)
Acknowledgements

UCSF Chiu Lab and VDDC
Calla Martyn, BS
Scot Federman, BA
Asmeeta Achari, BS
Shaun Arevalo, CLS
Jerome Bouquet, PhD
Guixia Yu, BS
Dianna Ng, MD
Xianding (Wayne) Deng, PhD
Doug Stryke, MS
Matt Massie, BS
Tony Li, BS
Guixia Yu, BS
Steve Miller, MD, PhD

National Autonomous University of Mexico
Carlos Arias, PhD and lab
Susana Lopez, PhD

DeRisi Lab, UCSF
Hannah Sample, BS
Kelsey Zorn, BS
Michael Wilson, MD
Wei Gu, MD/PhD

Funding
• NIH R01 HL105701-01 and R21 AI120977 (Chiu)
• UC Discovery Award
• Abbott Pathogen Discovery Award
• California Initiative to Advance Precision Medicine
• Charles and Helen Schwab Foundation
• George and Judy Marcus Innovation Fund
• National Institutes of Health
• Sandler Foundation
• Steven and Alexandra Cohen Foundation
• UCSF Medical Center (Clinical Laboratories)

Oxford University, UK
Julien Theze, PhD
Oliver Pybus, PhD

NASA
Aaron Burton, PhD
Sarah Castro-Wallace, PhD
David Smith, PhD

Weill Cornell Medical College
Christopher Mason, PhD
Alexa McIntyre, BS

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