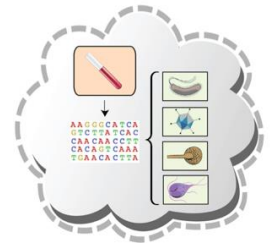




University of California
San Francisco



Clinical Metagenomics – our Real-Life Experience

Charles Chiu, MD / PhD

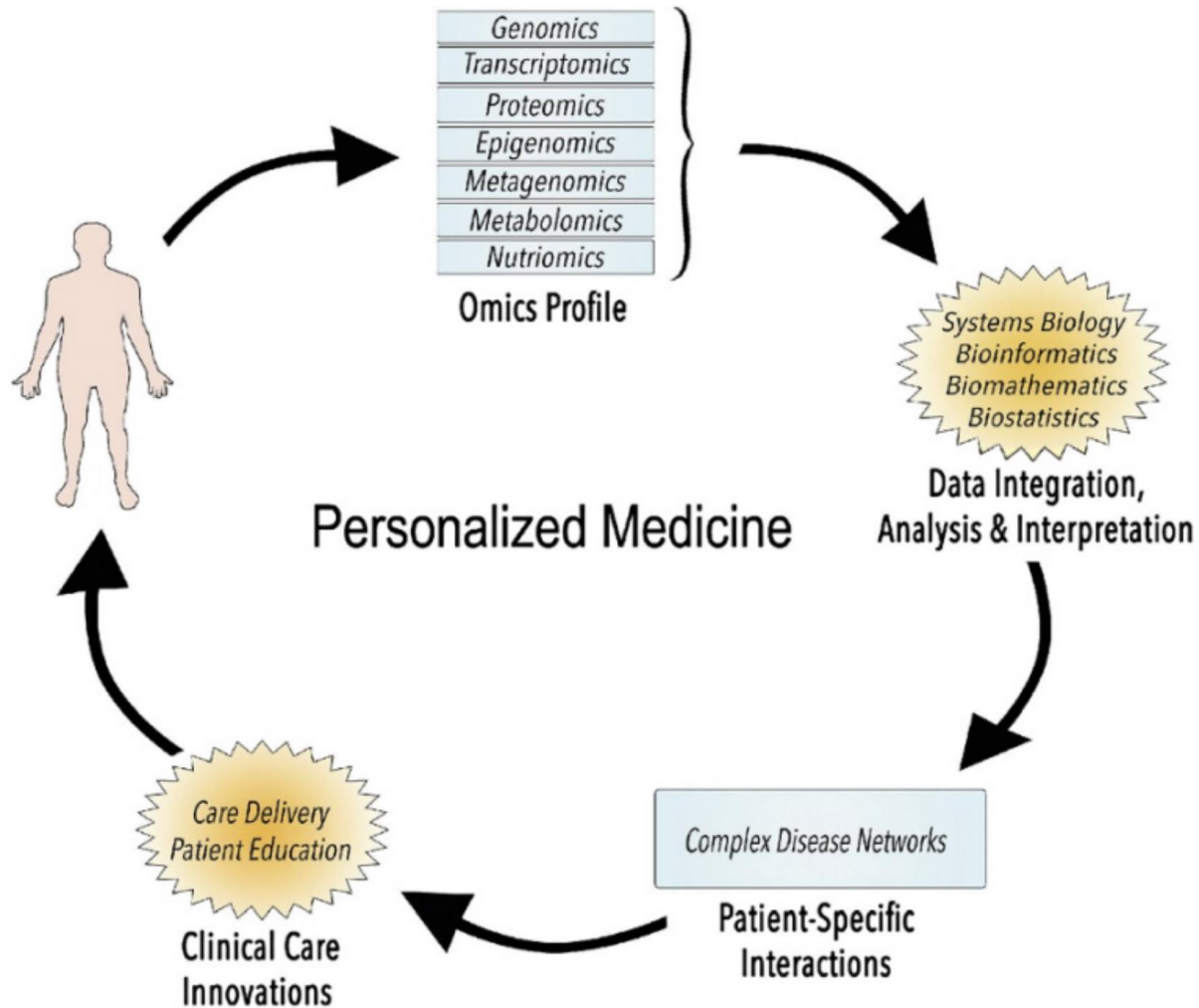
Associate Professor, Department of Laboratory Medicine and Medicine / Infectious
Diseases

Director, UCSF-Abbott Viral Diagnostics and Discovery Center

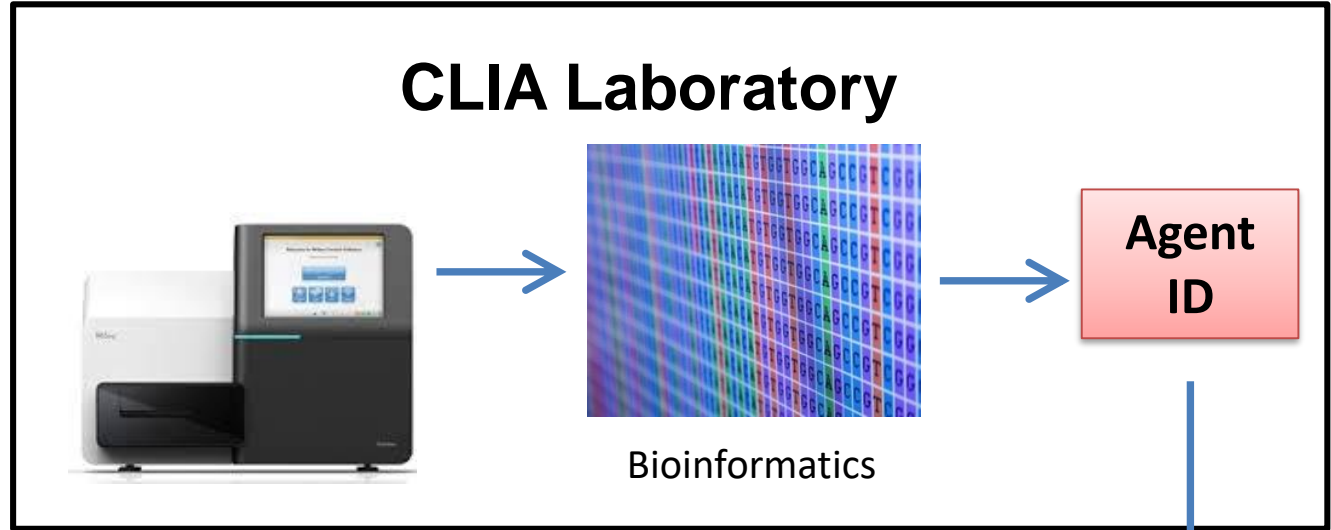
Associate Director, UCSF Clinical Microbiology Laboratory

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



Precision Diagnosis with Metagenomic Testing can Impact Clinical Decision-Making in Infectious Diseases



Lower healthcare costs



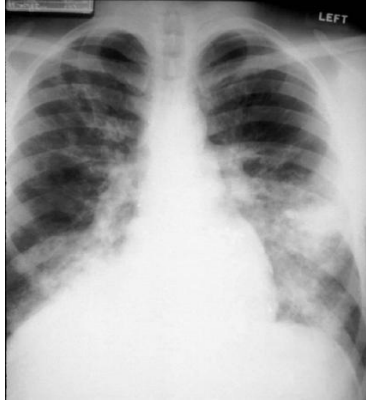
Improved patient outcomes

Cost-effective and actionable information for early treatment



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

Targeting Acute Infectious Diseases in Hospitalized Patients



Pneumonia

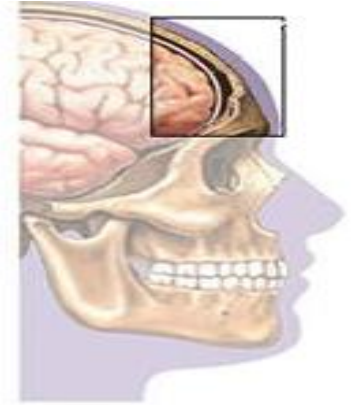
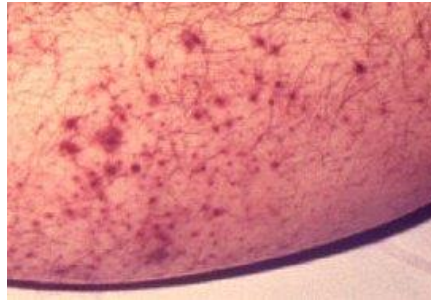
15 – 25% unknown cause

- Van Gageldonk-Lafeber, (2005) *CID* 41:490-497
- Louie, et al., (2005) *CID* 41:822-828
- Ewig, et al. (2002) *Eur Respir J* 20:1254-1262

Meningitis / Encephalitis

40 – 60% unknown cause

- Glaser, et al., (2006) *CID* 43:1565-1577
- Vora, et al., (2010) *Neurology* 82:443-451



Fever / Sepsis

~20% unknown cause

- Eber, et al. (2010) *Arch Intern Med* 170:347-353

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

**Conventional
Testing**



**Metagenomic Next-Generation
Sequencing
(mNGS)**

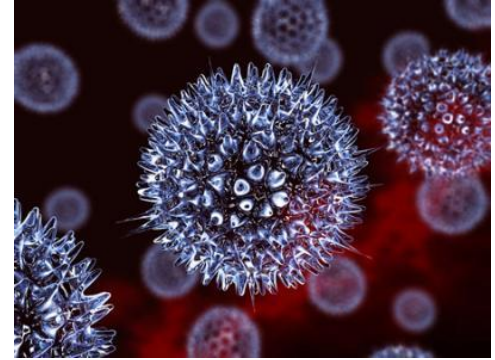


All Microbes can be Uniquely Identified by mNGS

Bacteria



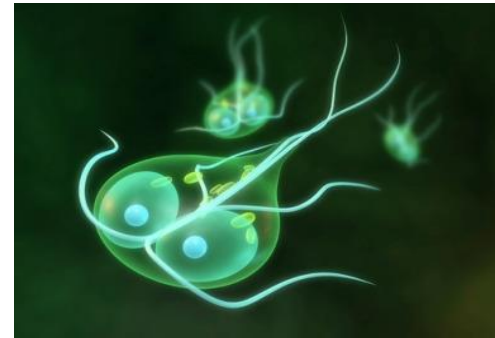
Viruses



Fungi



Parasites



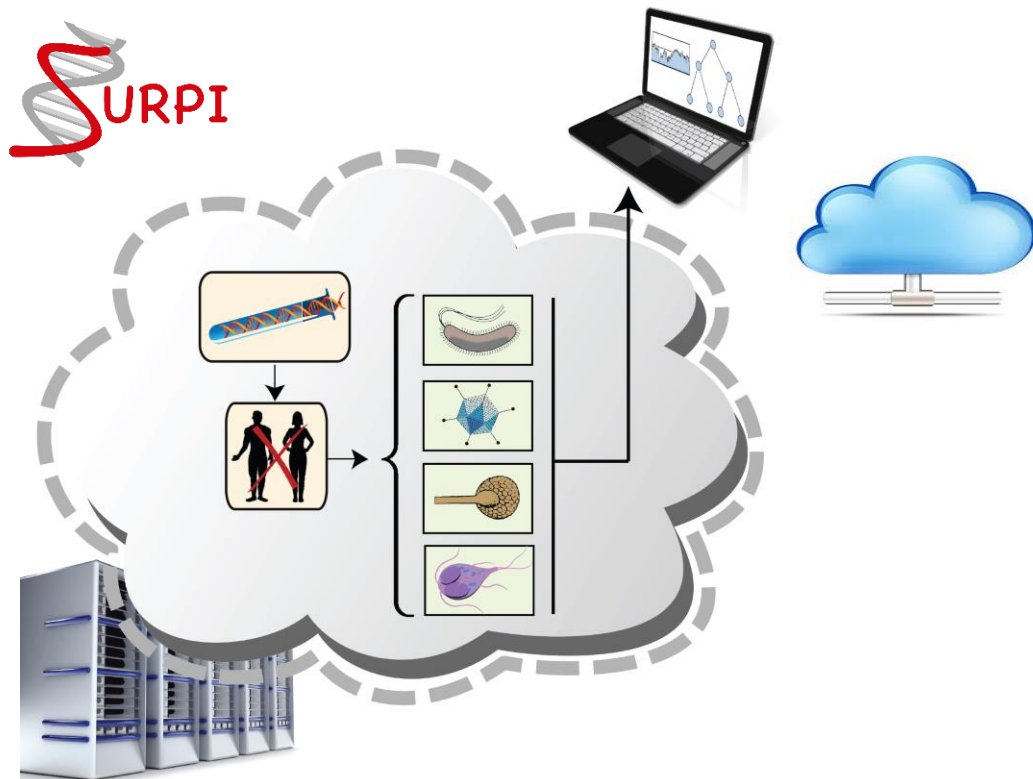
Precision Diagnosis of a Mysterious Infection



(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***

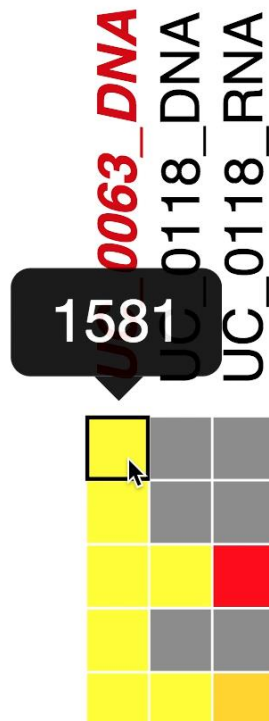
Leptospira santarosai

Leptospira borgpetersenii

unclassified

Leptospira interrogans

Propionibacterium acnes





Results Report in Electronic Medical Record

Epic Hyperspace - INFECTIOUS DISEASE SVC - UCSF Production

Patient Lists In Basket Patient Station Chart Today's Pts PagerBox Schedule Encounter Remind Me Carelinks

Print Log Out

Male, 5 years

Pref Lang, Interp?: English, No DOB: 11/12/... Weight: 18.5 kg... Allergies: Other Code: Full... 1st Call: None Precautions:... PCP: PROVIDER, NO...
CSN: None Dose Wt: None AD: None RN: None Research: N... Refer: None
Height: None POLST: No Attending/TT: None

Chart Review

Encounters Notes Labs **Micro** Pathology Imaging Cardiology Procedures Scan Clin AD/POLST/Legal Scan Admin Letters Referrals Meds Other Orders Episodes LDAs

Preview Refresh (2:00 PM) Select All Deselect All Review Selected Lab Flowsheet Route

Filters Hide Canceled John Muir Results UCSF Results In process Ordered / Future

Medications and orders also exist in active treatment plans: **IVIG, CATHETER MAINTENANCE**

Collect Date/Time	Test	S
01/25/2017 17:52	Microbiology - Test Not Listed (Special S...	S
01/25/2017 12:42	Microbiology - Test Not Listed (Special S...	C
01/25/2017 12:42	Microbiology - Test Not Listed (Special S...	C
01/25/2017 12:42	Pathogen Detection, mNGS (metagenomi...	C
01/25/2017 12:42	Varicella zoster virus DNA	C
01/25/2017 12:42	Microbiology - Test Not Listed (Special S...	C
01/25/2017 12:42	AFB Non-Respiratory Culture	C
01/25/2017 12:42	CSF Fungal Culture for Coccidioides	C
01/25/2017 12:42	Bacterial Culture and Gram Stain, CSF	C
01/25/2017 12:42	Cryptococcal Antigen	C
01/25/2017 00:00	Metagenomic next-generation sequencing	
01/09/2017 12:00	Respiratory Viral Panel PCR	N

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 (Siebrasse, 2012, Journal of Virology, 86(19):10321-10326; Yu, et al., 2012, PloS ONE (11):e49449). To date, MW polyomavirus has only been

Precision Diagnosis of Acute Infectious Diseases (PDAID)



California Initiative to Advance
Precision Medicine



Meningoencephalitis

40-60% unknown cause



Clinical microbial
sequencing board

7 hospitals in CA and nationwide
Enroll/consent patients

203 total

CSF collected
Clinical chart review

mNGS assay validated in CLIA lab

86% analytic sensitivity, 98% specificity

Clinical report in
patient EMR **APeX**

CLINICAL LAB SEQUENCING

Receive Sample

Isolate DNA & RNA

Construct mNGS
Library

Generate
Sequence Data

COMPUTATIONAL ANALYSIS

Filter
High-Quality
Sequences

Computationally
subtract
human background
sequences

Identify
Pathogens

Report Results
in Patient
Medical Record

SURPI⁺



- 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 voriconazole

- Lumbar puncture done, showing a lymphocytic pleocytosis
- WBC 10, 88% lymphocytes, protein 29, glucose 48

Microbiology (non-HEV)

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

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.

Blood

Hepatitis A IgM negative
 Hepatitis B core IgM negative
 Hepatitis B surface antigen negative
 Hepatitis C Antibody negative
 HBV DNA PCR negative
 Cryptococcal antigen negative
 HIV 4th generation Ag/Ab negative
 JCV Ab 2.31 [>0.40 positive]
 RPR negative
 Aspergillus antigen EIA negative
Coccidioides IgG/IgM EIA negative
Toxoplasma gondii DNA PCR negative

Peritoneal fluid

Bacterial gram stain and culture negative

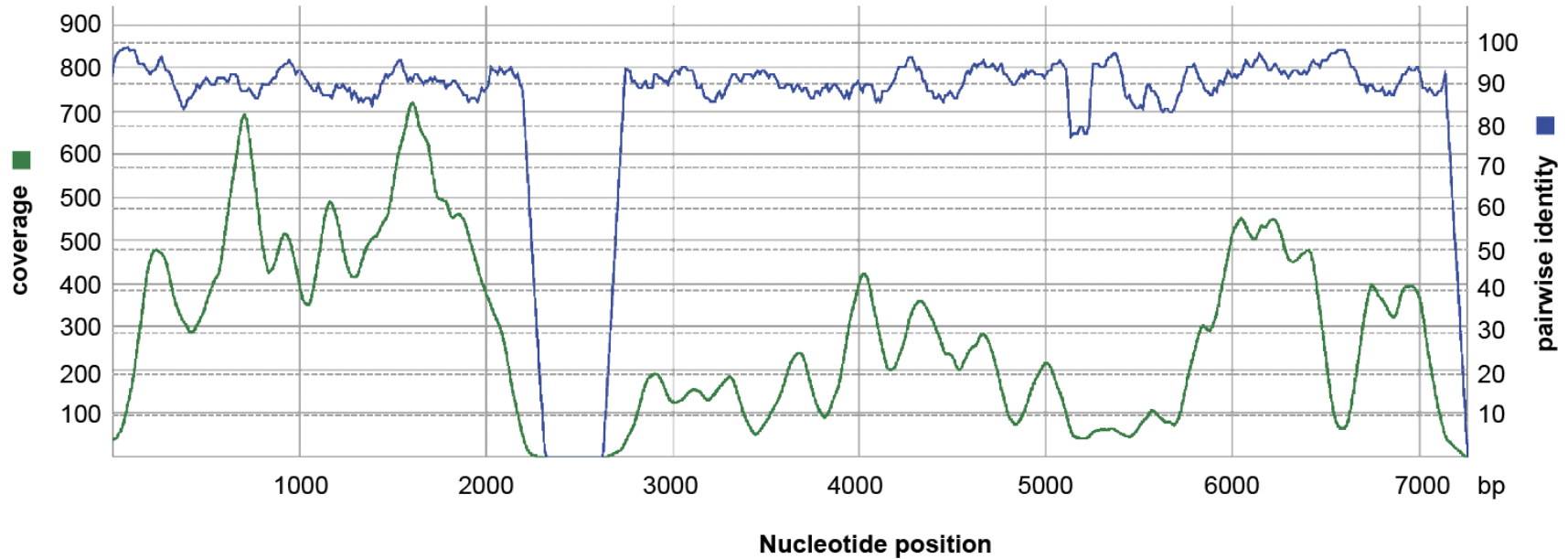
MRI brain: Unchanged

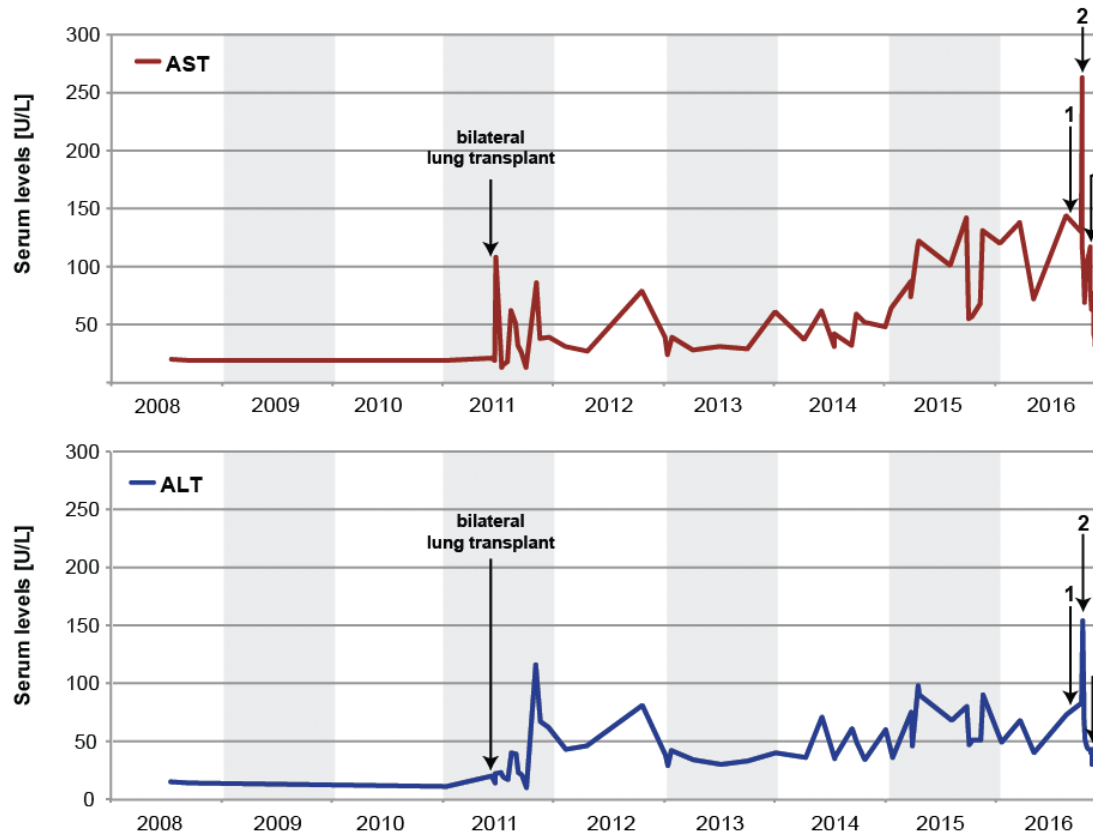
Abdominal ultrasound: Cirrhotic appearing liver without focal lesion, patent hepatic vessels, small volume ascites. Spleen upper normal in size.

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)

Confirmatory diagnosis using mNGS (n=19, 9.2%)	Diagnosis by mNGS only (n=26, 12.6%)	Orthogonal confirmation post-mNGS testing (22/26 patients, 84.6%)
EBV	<i>Streptococcus agalactiae</i> (also HIV-1 / <i>Cryptococcus</i>)	–
HHV-6B	<i>Enterobacter aerogenes</i> *	universal 16S bacterial PCR (clinical, UW)
HIV-1	<i>Streptococcus agalactiae</i> *	BioFire FilmArray (clinical, UCD)
enterovirus B	EBV* (also HSV-1)	EBV PCR (clinical, UCSF)
HSV-1	HHV-7*	HHV-7 PCR (clinical, Viracor)
VZV	echovirus 6* (also HHV-7)	enterovirus PCR (research, UCSF)
<i>Cryptococcus neoformans</i> (also HIV-1)	<i>Candida tropicalis</i> *	universal 28S fungal PCR (clinical, UW)
HIV-1	St. Louis encephalitis virus*	SLEV PCR (clinical, CDC)
VZV	Hepatitis E virus*	HEV PCR (clinical, CDC)
JC polyomavirus	<i>Neisseria meningitidis</i> *	<i>N. meningitidis</i> pyrosequencing (clinical, CDPH)
<i>Cryptococcus neoformans</i> (also HIV-1)	Human coronavirus 229E	–
VZV	Poliovirus MM*	MM polyomavirus PCR (research, UCSF)
HHV-6B	Angiostrongylus cantonensis*	<i>A. cantonensis</i> PCR (clinical, CDC)
HIV-1 (also <i>Pectobacterium carotovorum</i>)	Angiostrongylus cantonensis*	<i>A. cantonensis</i> PCR (clinical, CDC)
<i>Cryptococcus neoformans</i> (also HIV-1)	HHV-7*	HHV-7 qPCR from plasma (clinical, Viracor)
HIV-1	<i>Nocardia farcinica</i> *	<i>Nocardia</i> PCR (research, UCSF) ^a
EBV	HSV-2* (also HIV-1)	HSV-2 PCR (clinical, Quest)
HCV (also HIV-1)	VZV*	VZV RT-PCR (research, UCSF) ^b
HIV-1	HHV-6A* ^c	–
coxsackievirus B5	EBV*	EBV PCR (clinical, UCSF)
	<i>Streptococcus mitis</i> *	<i>S. mitis</i> (MALDI from blood culture, SJCRH) ^d
	HHV-6B*	HHV-6 qPCR (clinical, Viracor)
	echovirus 30*	–
	EBV	EBV PCR (clinical, UCSF)
	<i>Enterococcus faecalis</i> *	positive <i>E. faecalis</i> culture from brain biopsy dural tissue, bone flap, epidural gel foam ^d

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.

Top stories



Police seek suspect in Facebook homicide video



Opinion: Turkey's democracy died today

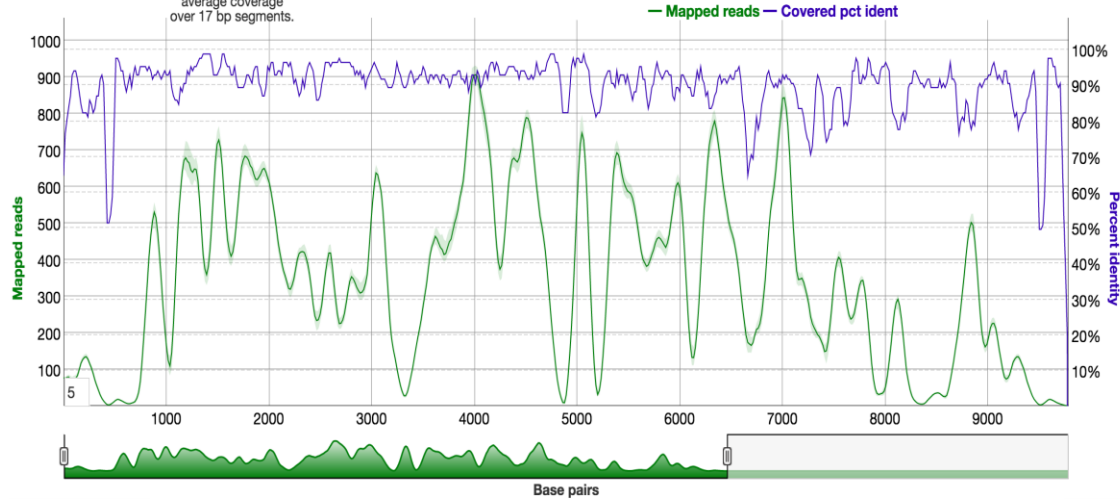


HIV Resistance Prediction

Human immunodeficiency virus 1 (gi|296556485|, 14825 bp)

Human immunodeficiency virus type 1, NYS/BRU (LAV-1) recombinant clone pNL4-3

Assembled from 25015 reads; plotting average coverage over 17 bp segments.



Toggle Log/Linear Y-axis

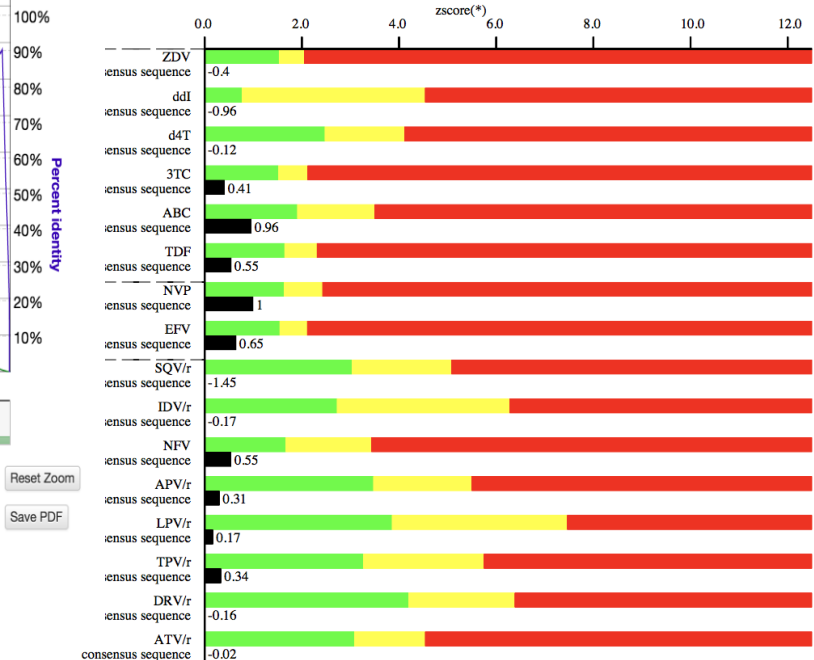
Download Consensus

Reset Zoom

Save PDF

	Reference length bp	Coverage in bp	Percent coverage	Avg coverage depth	Covered pct ident
Overall	14825	9599	64.75	225.97	90.67
Displayed	9790	9599	98.05	342.19	90.67

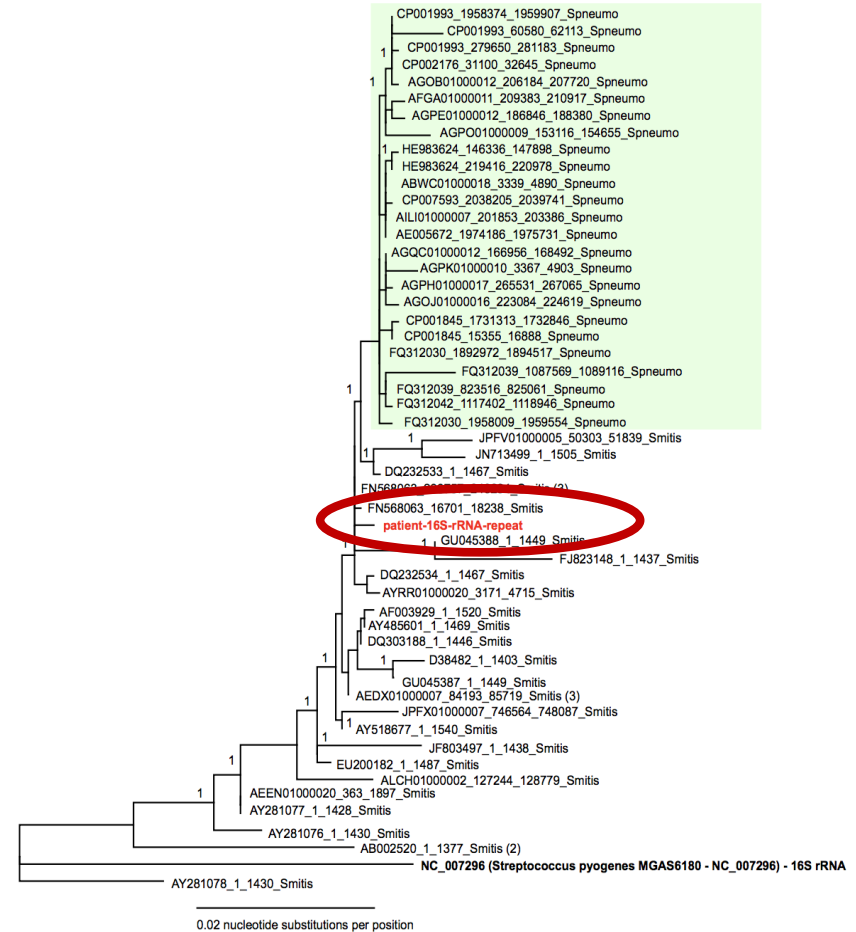
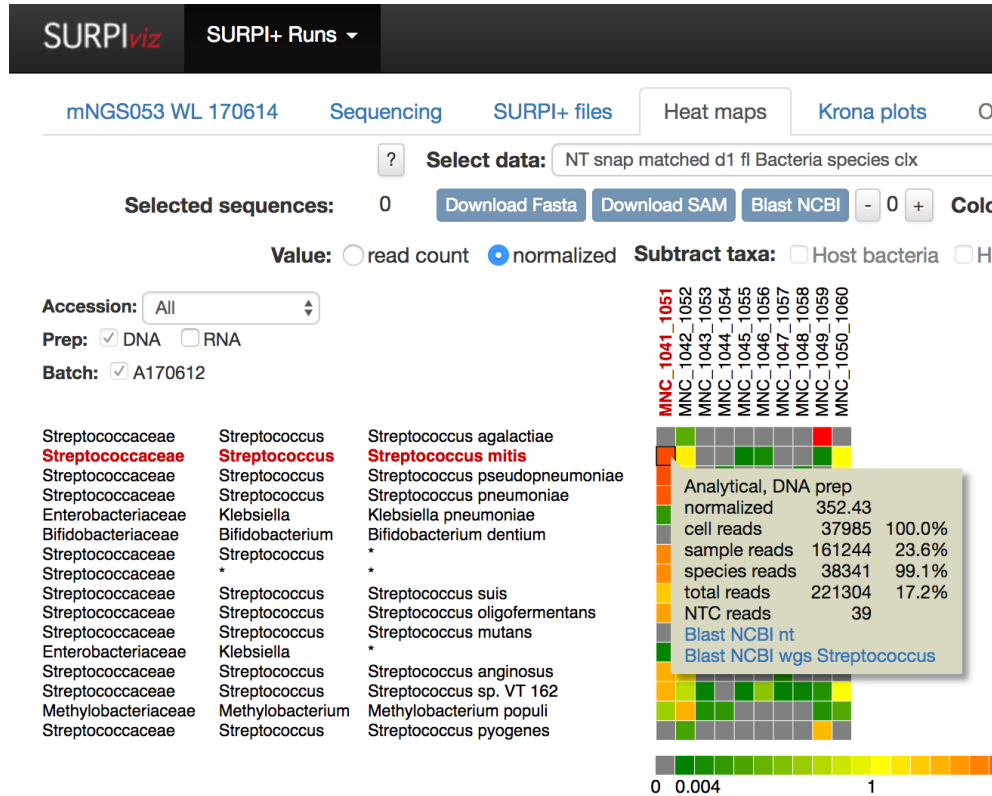
Patient:	Study Id:		
Birth date:	Viral load:		
Sample received:	Sample collected:		
Sample ID:	consensus sequence	Predicted subtype:	B (100%)
Sample type:	Report date: April 29, 2017		
Physician:	Reported by:		



■ susceptible ■ intermediate ■ resistant

(*)number of standard deviations above mean of drug naive patients. Negative z-scores may indicate hypersusceptibility.

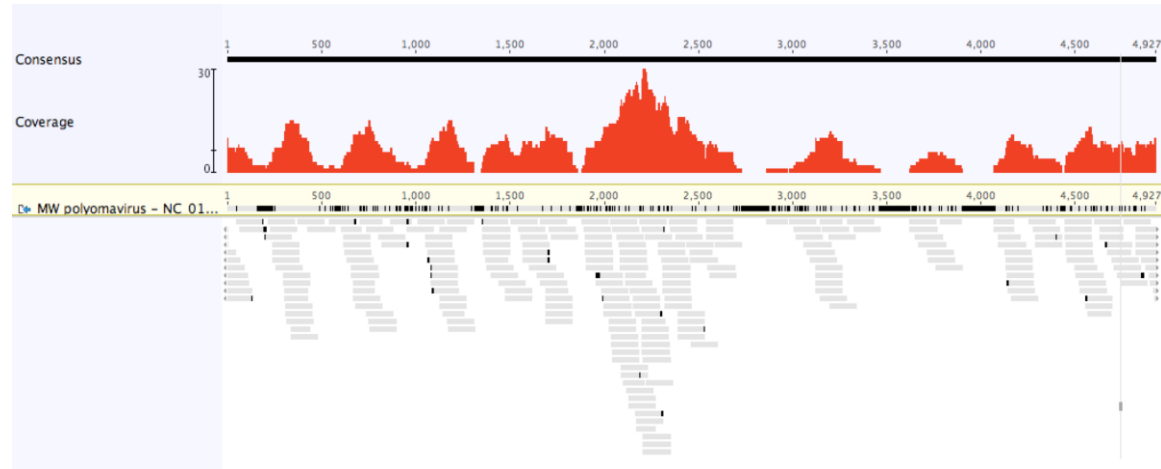
Accurate Species Classification



Pathogen Discovery?

*During
meningoencephalitis
episode*

Polyomavirus MW/MX



*After
meningoencephalitis
episode*

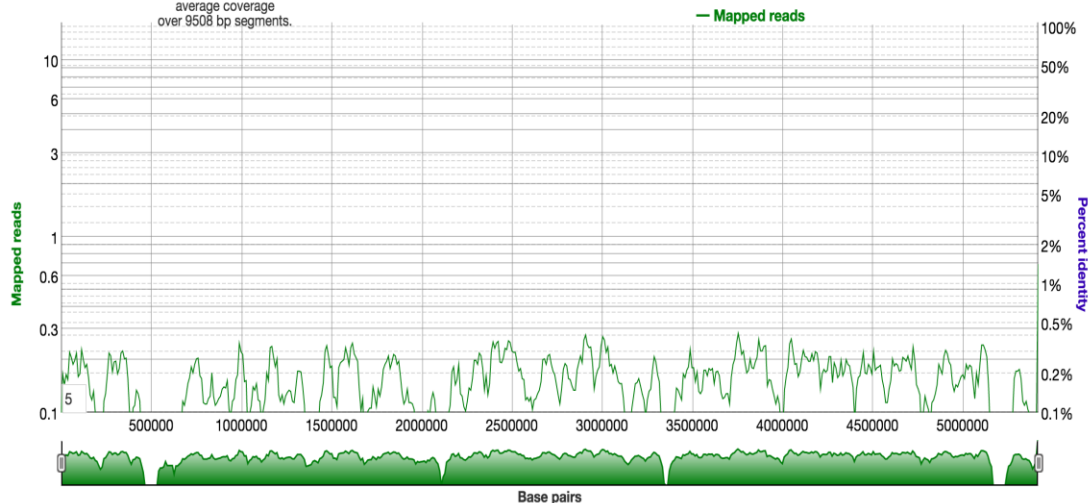


Antibiotic Resistance Prediction

Enterobacter aerogenes EA1509E (gi|443901024|, 5419609 bp)

Enterobacter aerogenes EA1509E complete genome

Assembled from 5112 reads; plotting average coverage over 9508 bp segments.



Toggle Log/Linear Y-axis

Download Consensus

Reset Zoom

Save PDF

	Reference length bp	Coverage in bp	Percent coverage	Avg coverage depth	Covered pct ident
Overall	5419609	314743	5.81	0.15	64.17
Displayed	5419609	314743	5.81	0.15	64.17

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 aminoglycotide, 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, cephamycins; this gene is chromosomally encoded in *Enterobacter aerogenes*
- *emrd* - MDR efflux pump, aminoglycoside resistance

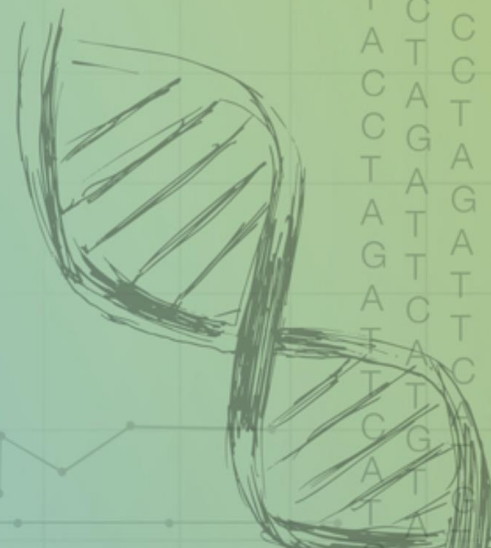
<http://nextgendiagnosics.ucsf.edu>

Solving Medical Mysteries

Providing the next generation of clinical testing to diagnose unexplained diseases

LEARN ABOUT OUR TECHNOLOGY

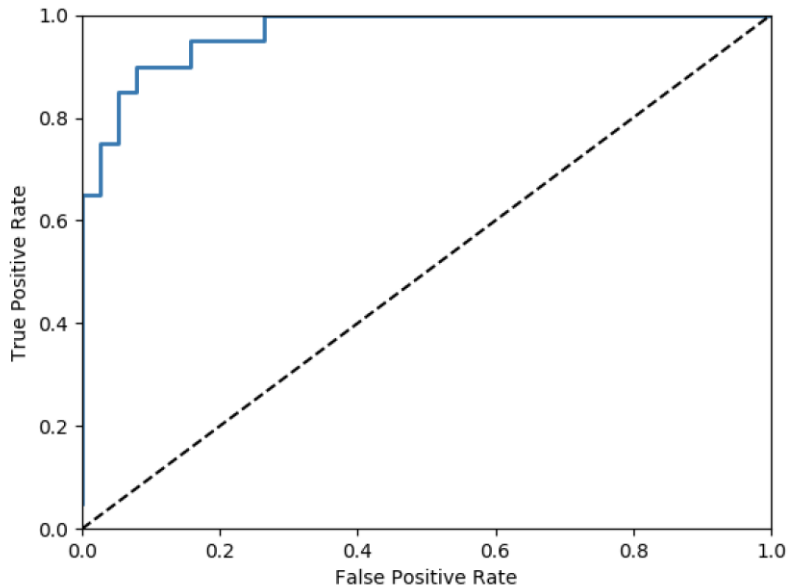
ORDER TEST



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

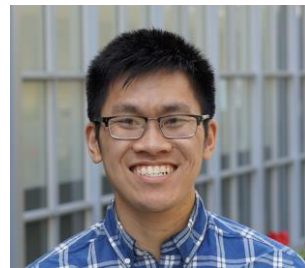
Machine Learning-Based Prediction of Causes of Infection from Human Gene Expression Data (RNA-Seq) from CSF from PDAID Patients



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

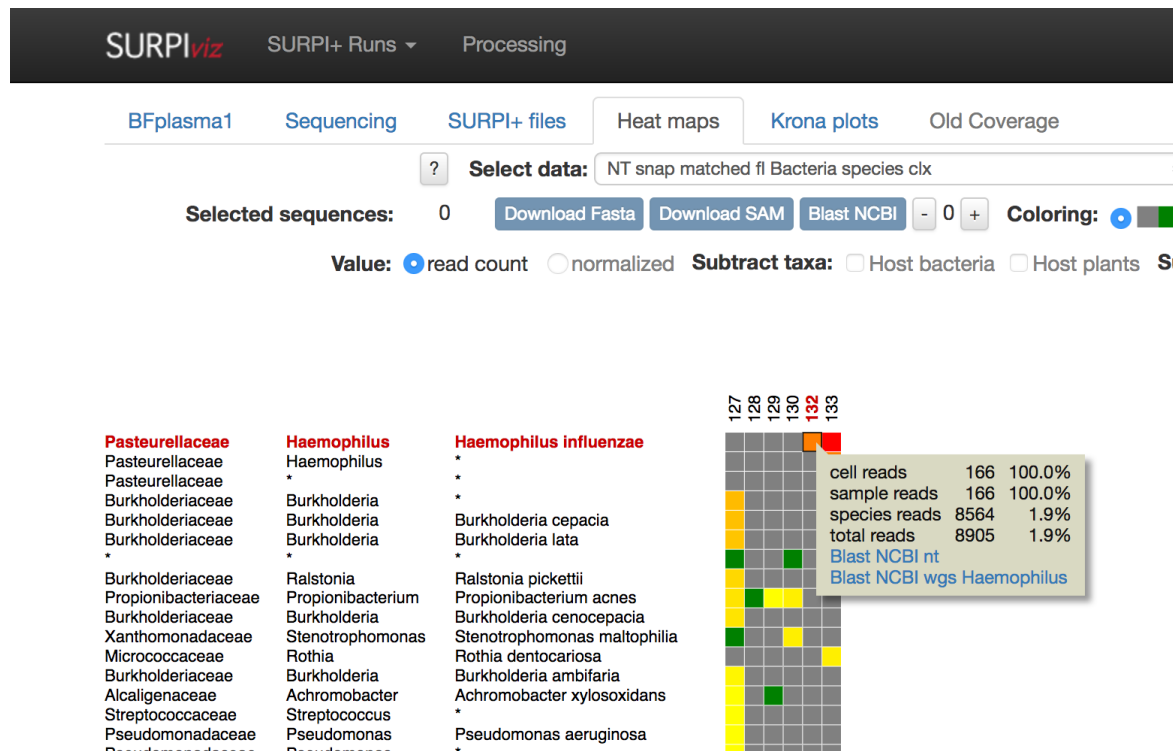
- Training set: 25 bacterial positive cases, 48 viral positive cases
- Test set: 6 bacterial positive cases, 9 viral positive cases

	CV	RSME	Score	CV	RSME	STD	CV	Accuracy
Linear SVM		0.221034		0.226150			0.900000	
Logistic Regression		0.250920		0.265278			0.866667	
Polynomial SVM		0.323491		0.220651			0.846667	
Stochastic Gradient Descent		0.241841		0.248018			0.840000	
AdaBoost		0.274579		0.290871			0.806667	



Tony Li, BS

Identification of *Haemophilus influenzae* Pneumonia / Sepsis in a Leukemic Patient



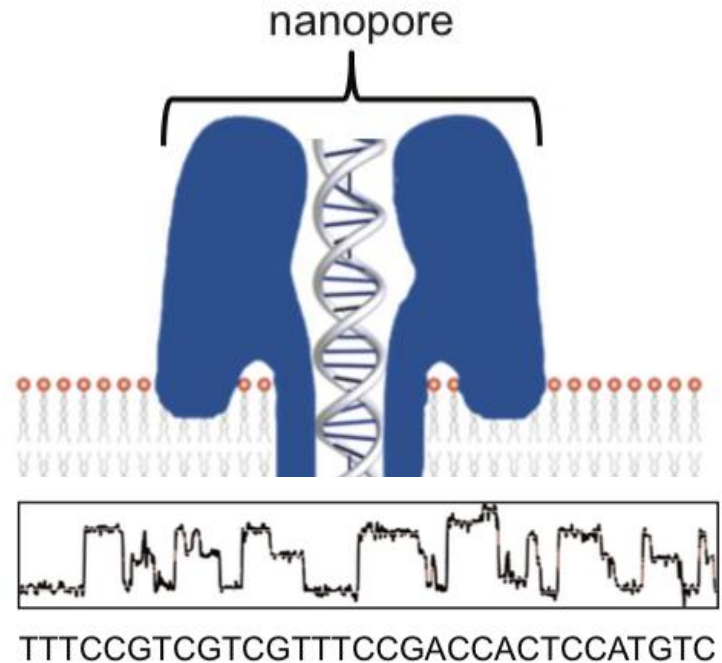
Wei Gu, MD, PhD

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

BACTERIAL

- Rickettsioses
- Bacillary Dysentery
- Plague
- Meningococemia
- Typhoid fever
- Other bacterial septicemia
- Leptospirosis
- Ehrlichiosis
- Tuberculosis
- Bartonellosis
- Brucellosis

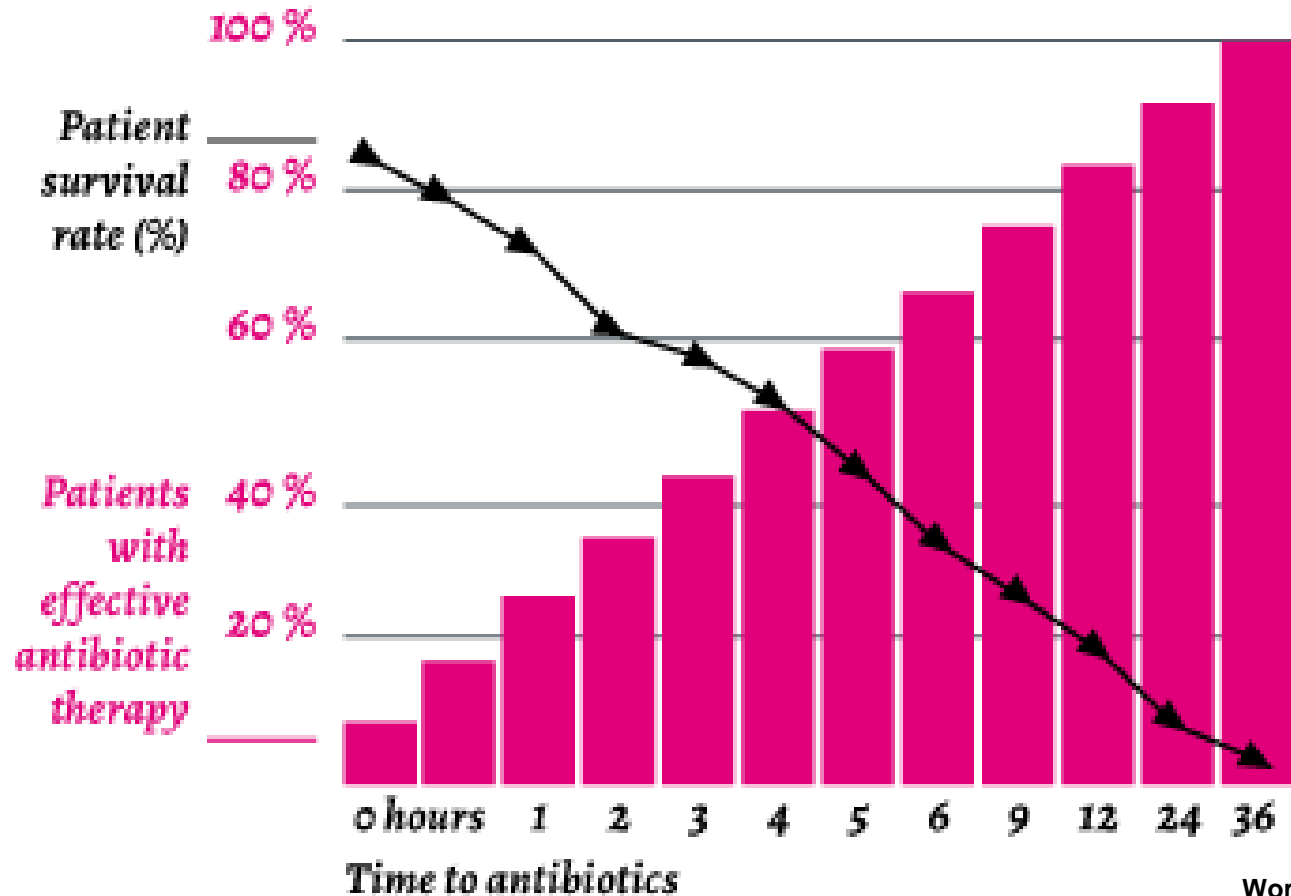
VIRAL

- Arboviral infections
- Viral hepatitis
- Enterovirus
- Measles
- Rubella
- Acute Retroviral Syndrome (HIV)
- Epstein-Barr virus
- Parvovirus
- Roseola virus
- Filovirus infection (Ebola, Marburg)
- Lassa virus
- bunyaviruses

OTHER

- Malaria / Babesiosis
- Amebiasis
- Visceral leishmaniasis
- Acute schistosomiasis
- Filarial fever
- Trypanosomiasis

Assay Turnaround Time is Critical for Sepsis



Nanopore Sequencing

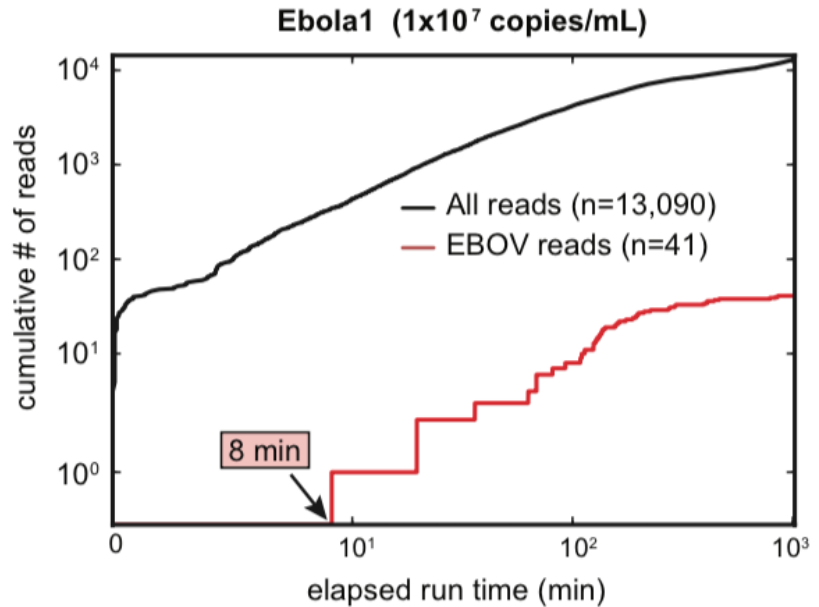
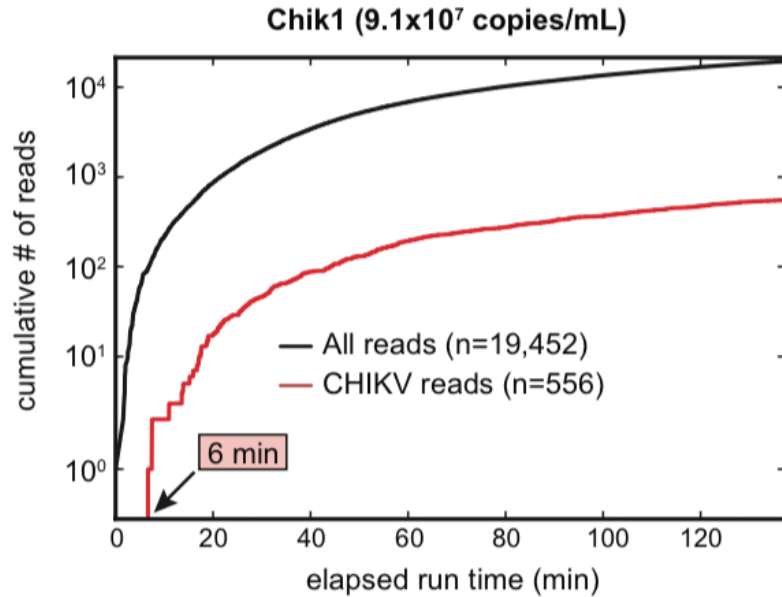
- ***Advantages***

- 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***

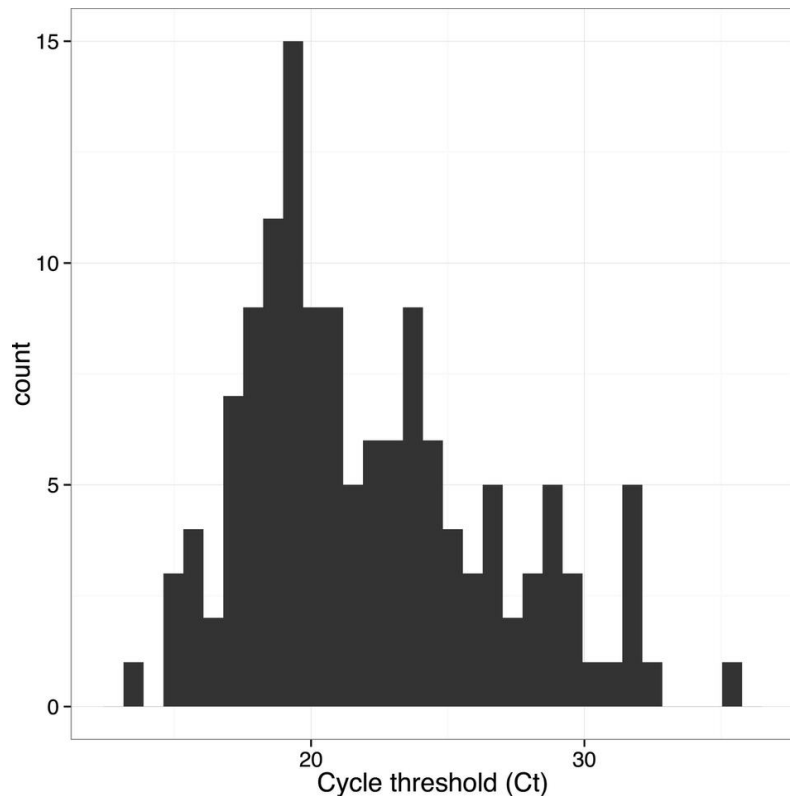
- Cost of sequencing (\$500 per flow cell)
- Error rates still 8-12%
- Oxford Nanopore Technologies is a startup company (? reliable source); quality of flow cells can be variable

Viral Reads Detected <8 Min into Sequencing Run



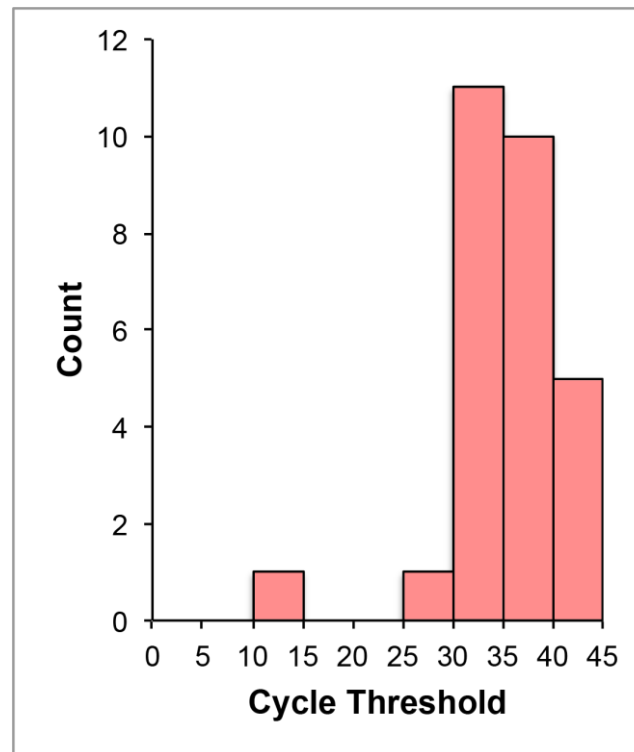
Low Serum Titers in Acutely Infected ZIKV Patients

EBOV



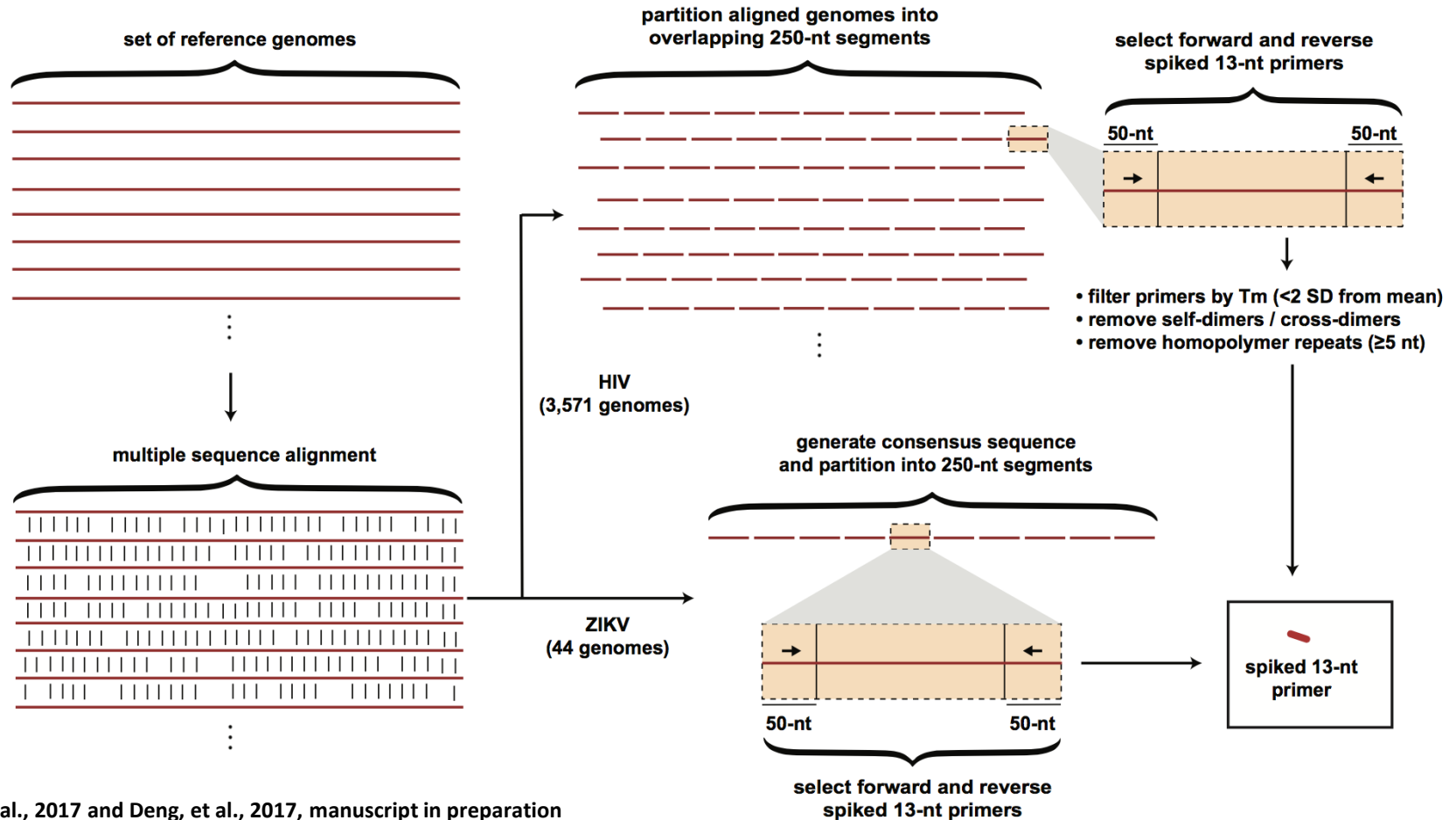
(Quick, et al., 2016, *Nature* 530:228-232)

ZIKV

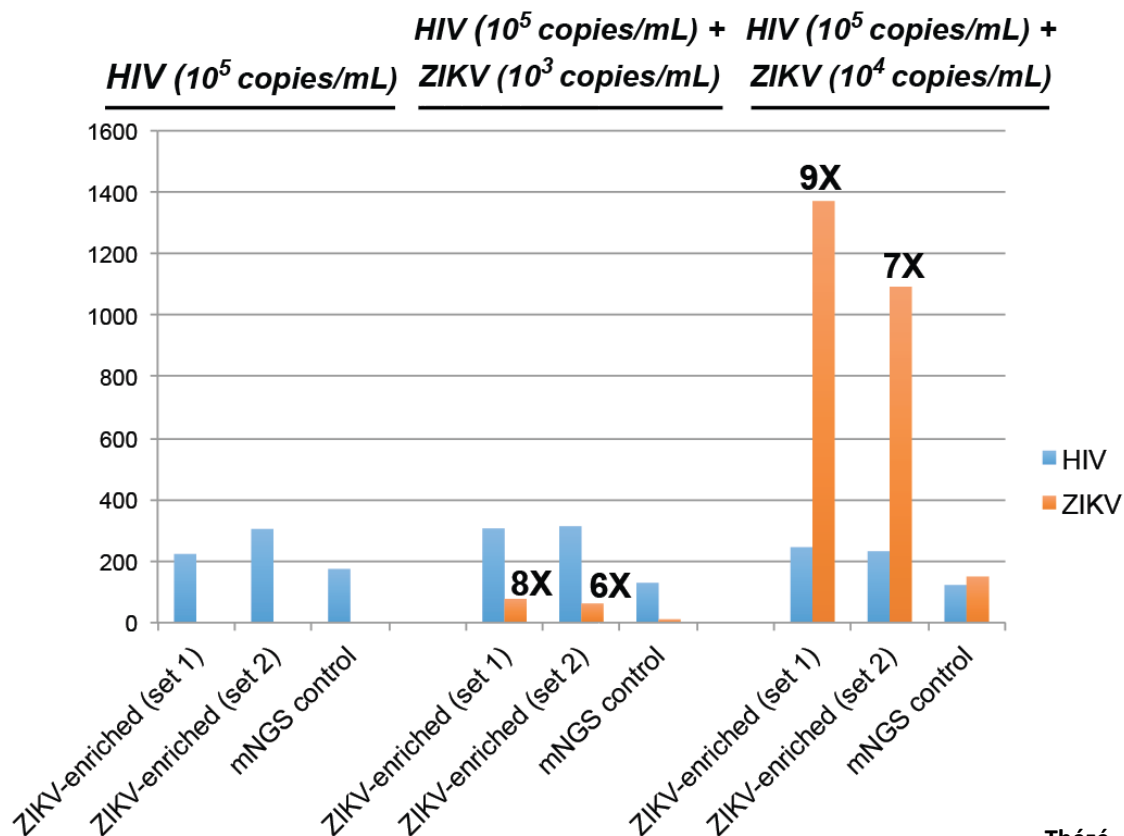


(Naccache, Thézé, et al., 2016, *EID*, 22:10)

Spiked Primer Strategy for Metagenomic Target Enrichment



Targeted Primers Increase Sensitivity But Do Not Impact Off-Target Metagenomic Detection



Protocol Optimization on the MinION Nanopore Sequencer



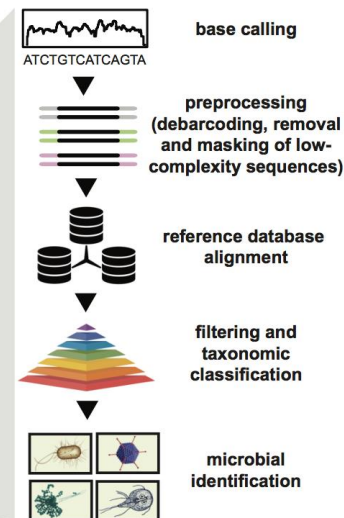
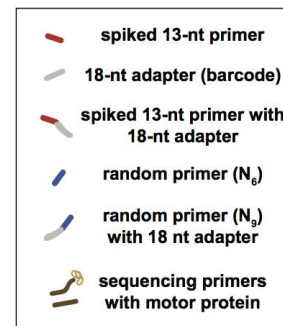
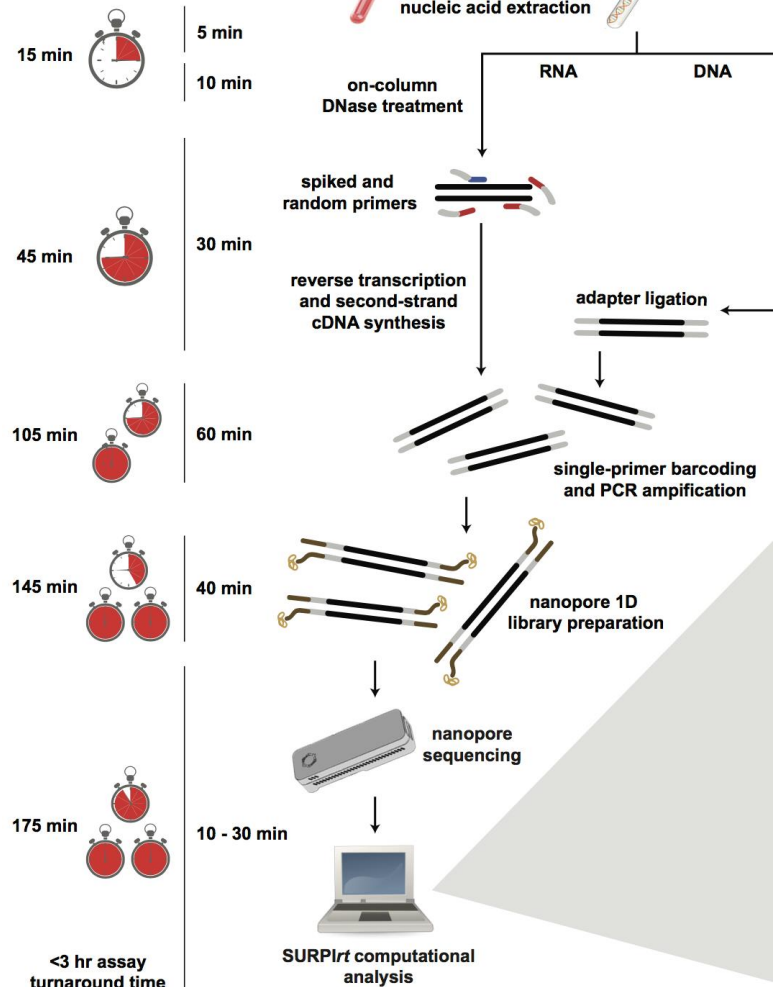
Wayne Deng,
PhD

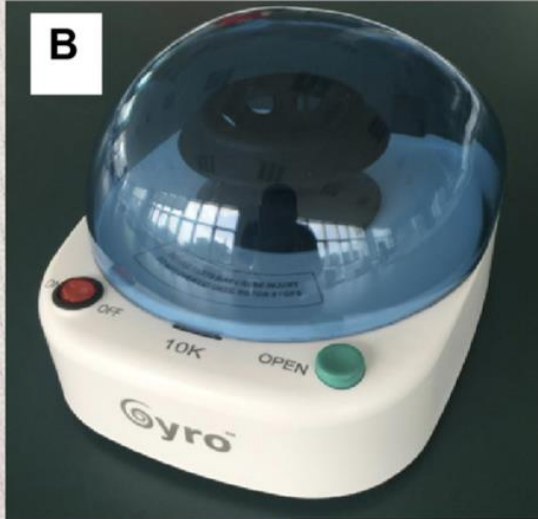
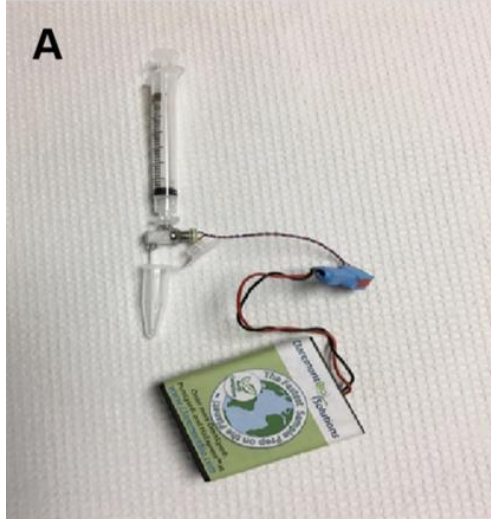


Dianna Ng,
MD

Deng, et al., 2017, manuscript in preparation

CUMULATIVE ELAPSED TIME





A Field-Ready, Portable Nanopore Sequencing Assay

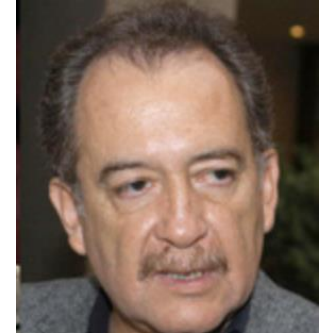


Instituto de Biotecnología, UNAM

Susana López /Carlos Arias Laboratories, Cuernavaca, Mexico



**Carlos Arias,
PhD**

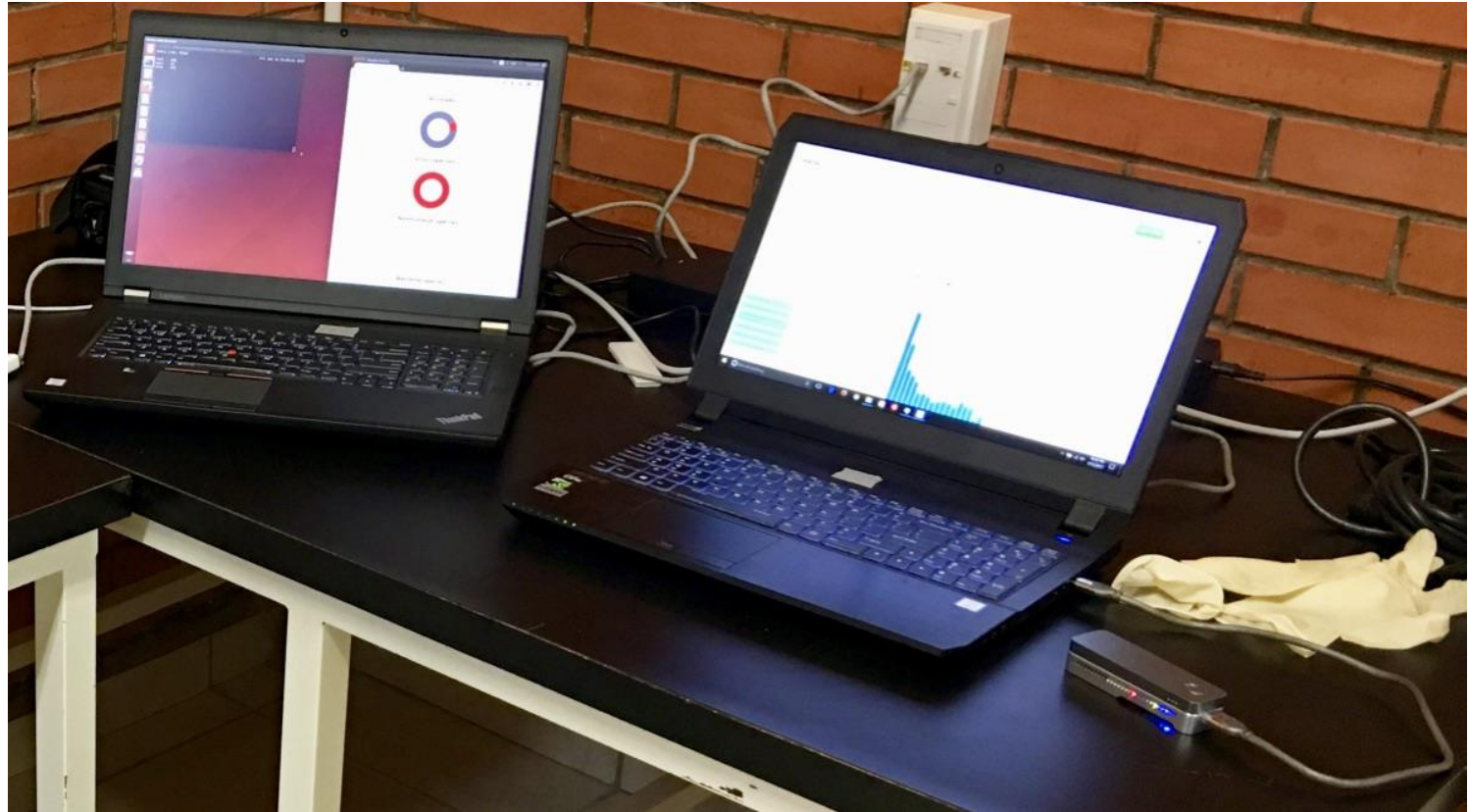


**Susana
López, PhD**



SURPIrt Setup

(offline use)

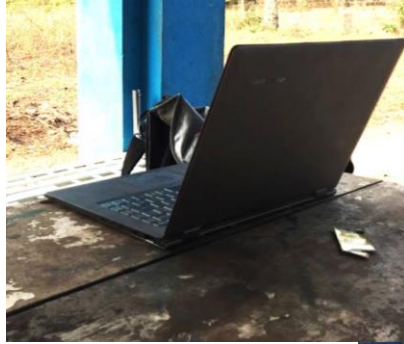


INRB (Institut National de Recherche Biomedicale)

Anne Rimoin and UCLA-DRC Team



**Anne Rimoin,
PhD**



**Matt Bramble,
PhD**



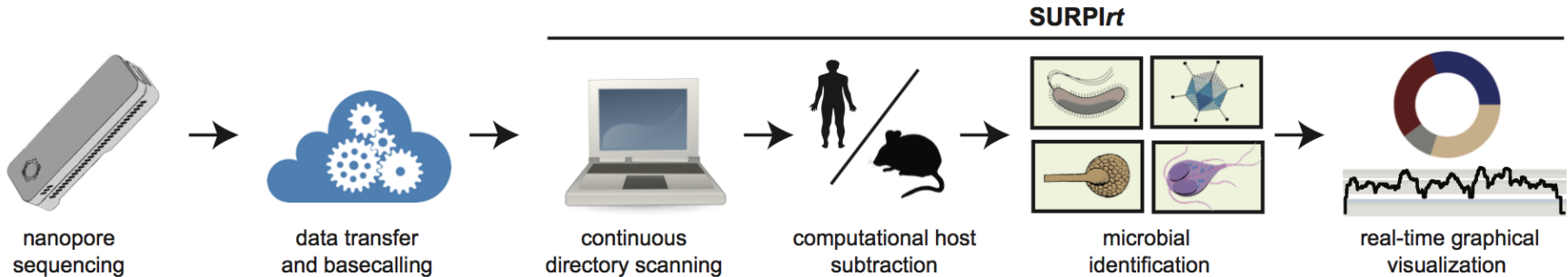
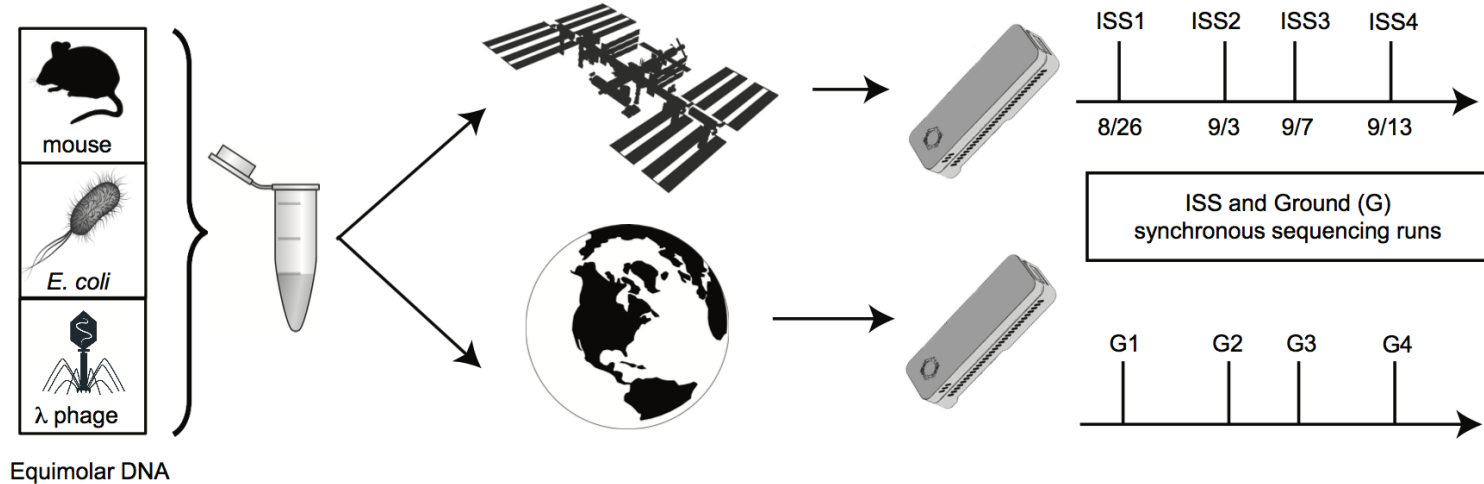
**Russell
Williams, PhD**

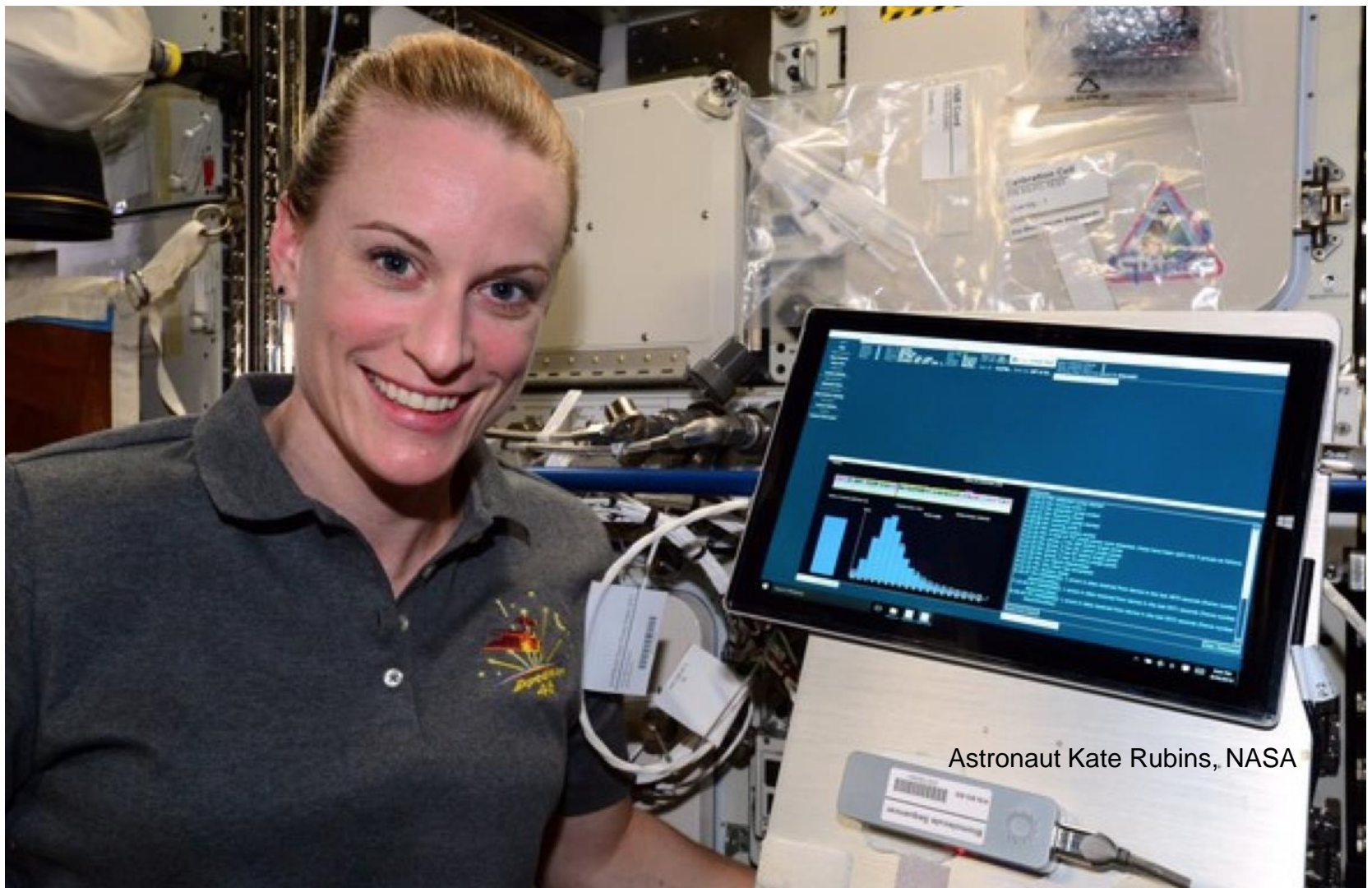


Nanopore Sequencing of Clinical Samples

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

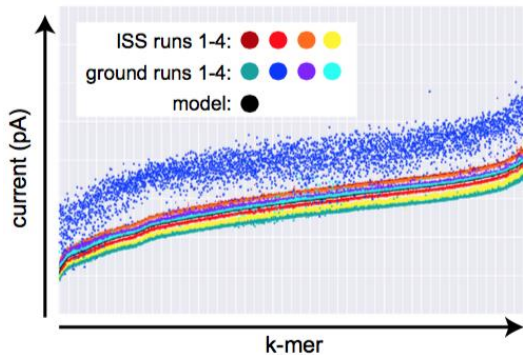
Nanopore Sequencing in Space





Astronaut Kate Rubins, NASA

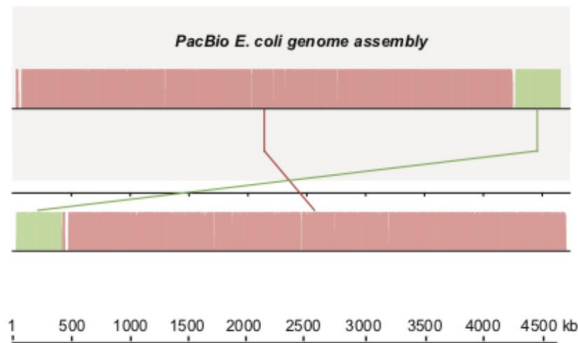
Analysis of Nanopore Data Collected on the ISS



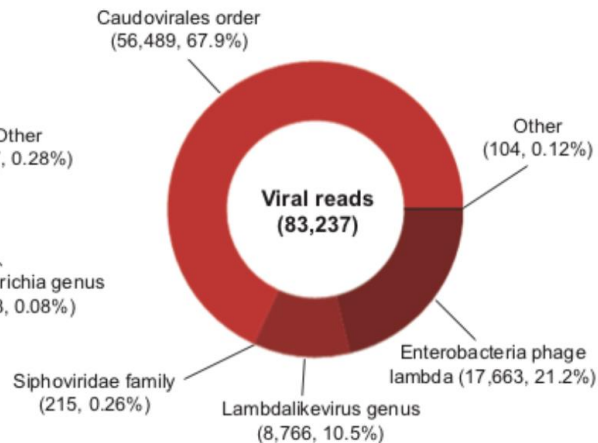
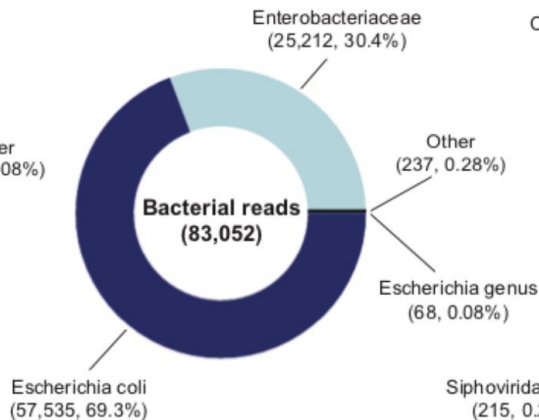
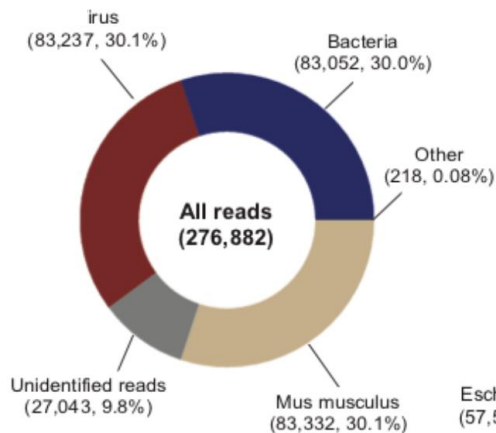
E. coli de novo assembly
(ISS runs #1-8, Canu)

raw 2D reads (n=192,042)

(1 mapped contig, 99.9% complete, 98.6% pairwise identity)



ISS runs #1-8 (pooled SURPIrt analysis)



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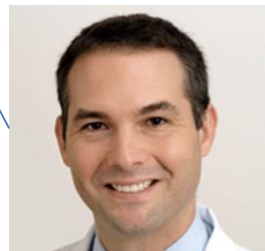
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