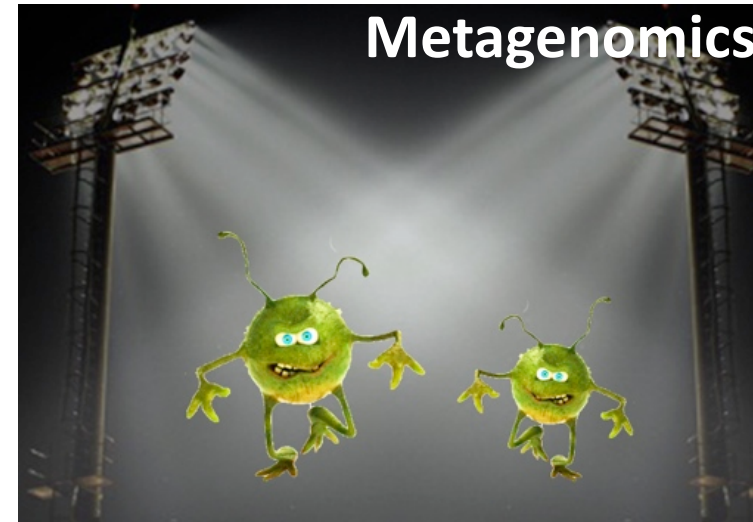
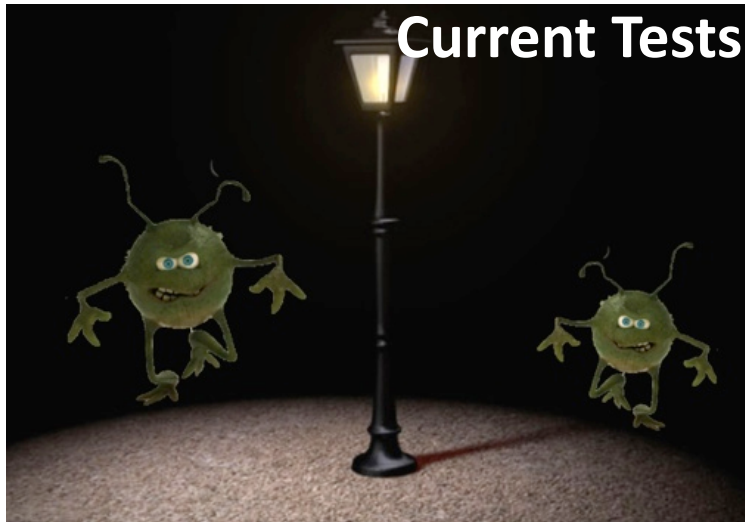


Metagenomics for Universal Pathogen Detection



Robert Schlaberg, M.D., Dr. med., M.P.H.
Assistant Professor, University of Utah
Medical Director, ARUP Laboratories

Disclosures

In accordance with ACCME guidelines, any individual in a position to influence and/or control the content of this ASCP CME activity has disclosed all relevant financial relationships within the past 12 months with commercial interests that provide products and/or services related to the content of this CME activity.

Robert Schlager, MD, MPH has disclosed the following financial relationships with commercial interests:

<u>Commercial Interest</u>	<u>What was Received</u>	<u>For What Role</u>
Roche Diagnostics	Honorarium	Advisor
Roche Diagnostics	Research Grants	PI
Hologic	Contract Research	PI
Hologic	Honorarium	Advisor
Epoch Biosciences	Contract Research	PI
Sanofi Pasteur	Contract Research	Co-PI
IDbyDNA	Stock	Co-Founder, CMO

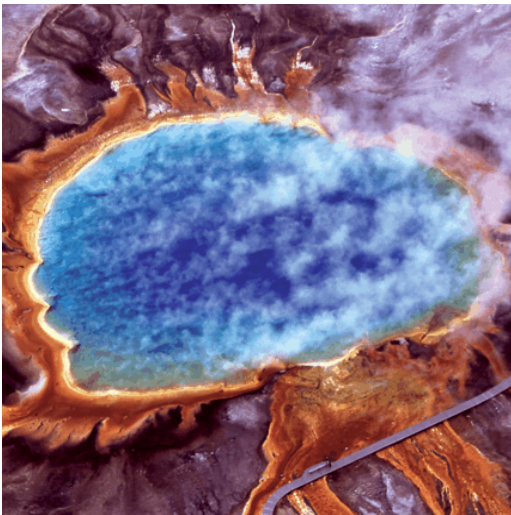
Objectives

- Discuss universal pathogen detection by metagenomics
- Summarize laboratory approaches
- Discuss challenges and solutions for data analysis
- Provide examples of applications for syndromic testing
- Review promise and challenges for diagnostic use

Applications of Metagenomics

Metagenomics: Taxonomic, functional composition of microbial communities *in toto*

Environmental



Medical

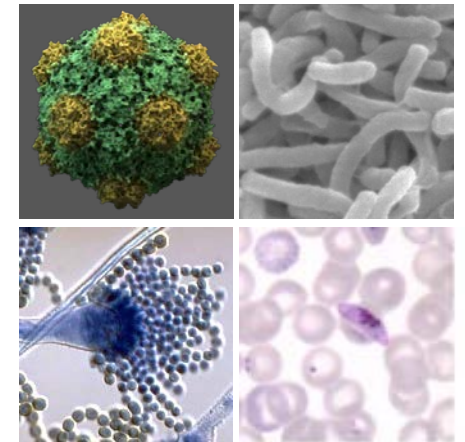
Microbiome Studies



Surveillance & Discovery



Diagnostic



Diagnostic Promise

Limitations of current tests

- *Knowledge of expected pathogens*
- *Usually targeted, specific tests*
- “Is the patient infected with X?”

Advantages of Metagenomics

- Universal pathogen detection
 - *Expected and unexpected*
 - *Common and rare*
 - *Easy to grow and fastidious*
 - *Pretreated patients*
- “What is the patient infected with?”
- *More than just detection*
 - *Molecular typing*
 - *Drug resistance*
 - *Quantification*

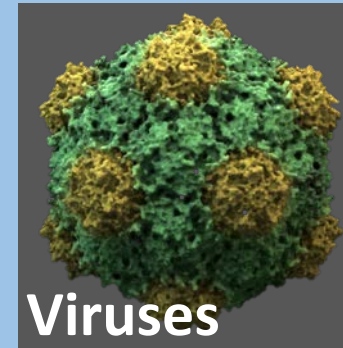
Metagenomics for Routine Diagnostics



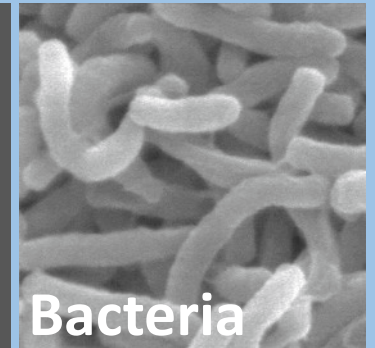
Metagenomics for Routine Diagnostics



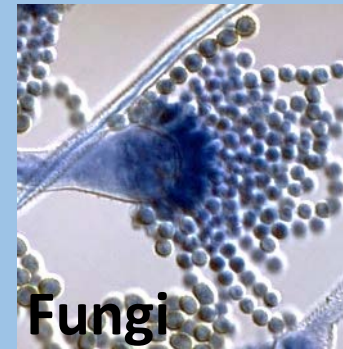
Organism Identification



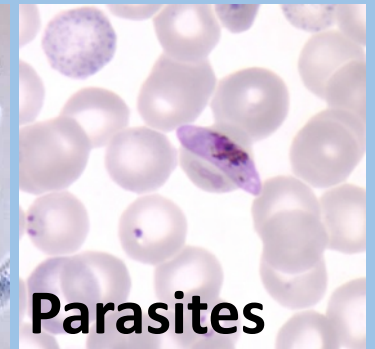
Viruses



Bacteria



Fungi



Parasites

Metagenomics for Routine Diagnostics



Goal

Rapid (24-48h)

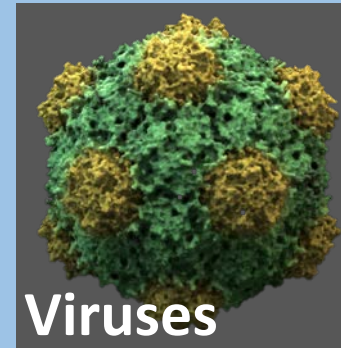
Cost-Effective

Complete & Accurate

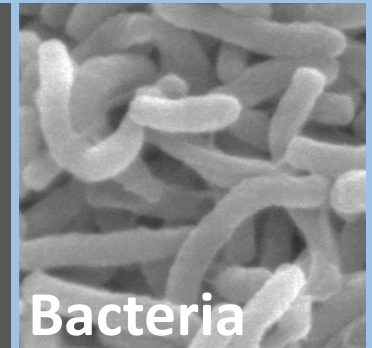
User Friendly



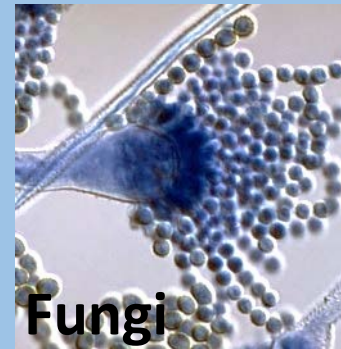
Organism Identification



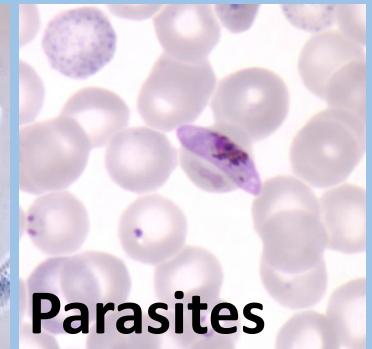
Viruses



Bacteria



Fungi



Parasites

Metagenomics for Routine Diagnostics



Goal

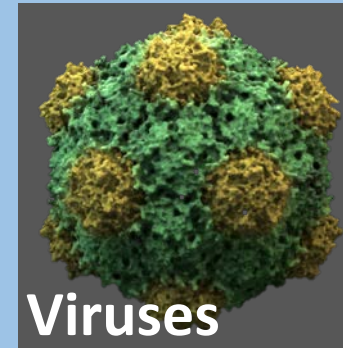
Rapid (24-48h)
Cost-Effective
Complete & Accurate
User Friendly

Challenges

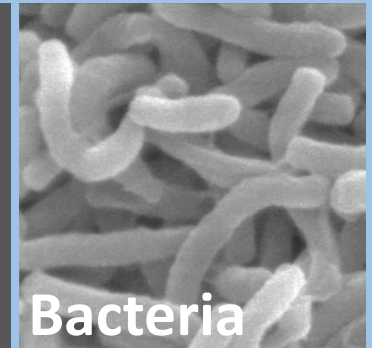
Sample Prep
Data Analysis
Logistics



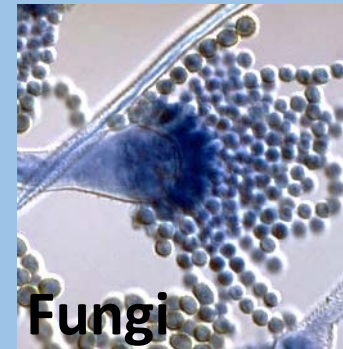
Organism Identification



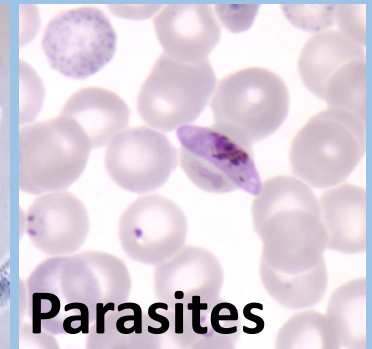
Viruses



Bacteria



Fungi



Parasites

Metagenomic Approaches

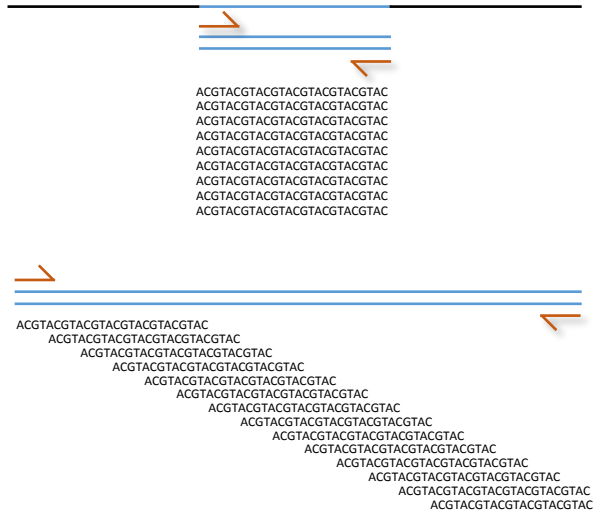
Target Enrichment

Enrichment-independent

Metagenomic Approaches

Target Enrichment

Target Amplification

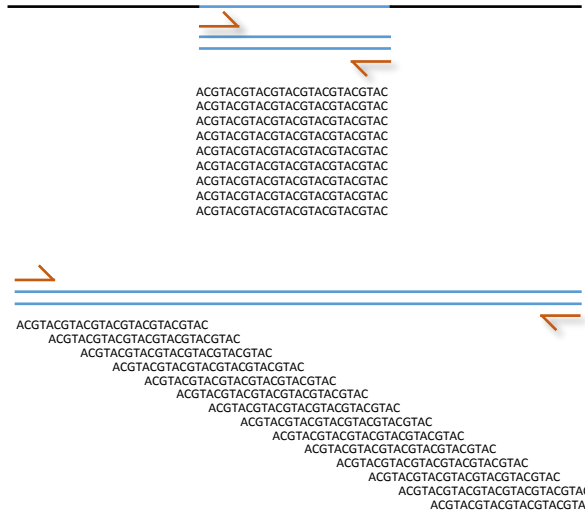


Enrichment-independent

Metagenomic Approaches

Target Enrichment

Target Amplification



Culture enrichment



Enrichment-independent

Microbial Identification
'TaxonomerDx'

Next-Generation Sequencing

Report

X Detected
Y Detected
Z Detected
...

```
X Detected
Y Detected
Z Detected
...
```

Data Analysis Approach

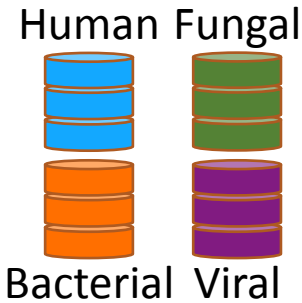
NGS Output

[illegible]

TaxonomerDx

Data Analysis Approach

NGS Output



TaxonomerDx

1st Step:
Read Binning

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

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ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Data Analysis Approach

NGS Output

TaxonomerDx

1st Step:
Read Binning

Human Reads

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Bacterial Reads

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Viral Reads

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Data Analysis Approach

NGS Output

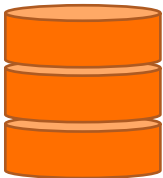
TaxonomerDx

1st Step:
Read Binning

Human Reads

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Bacterial
Databases



2nd Step:
Read Classification

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Viral Reads

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Data Analysis Approach

NGS Output

TaxonomerDx

1st Step:
Read Binning

Human Reads

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Viral Reads

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

2nd Step:
Read Classification

Streptococcus pneumoniae

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Haemophilus influenzae

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Data Analysis Approach

NGS Output

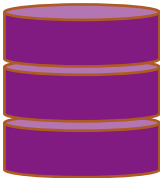
TaxonomerDx

1st Step:
Read Binning

Human Reads

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ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
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ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Viral
Databases



2nd Step:
Read Classification

Streptococcus pneumoniae

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Haemophilus influenzae

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Data Analysis Approach

NGS Output

TaxonomerDx

1st Step:
Read Binning

Human Reads

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

2nd Step:
Read Classification

Streptococcus pneumoniae

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

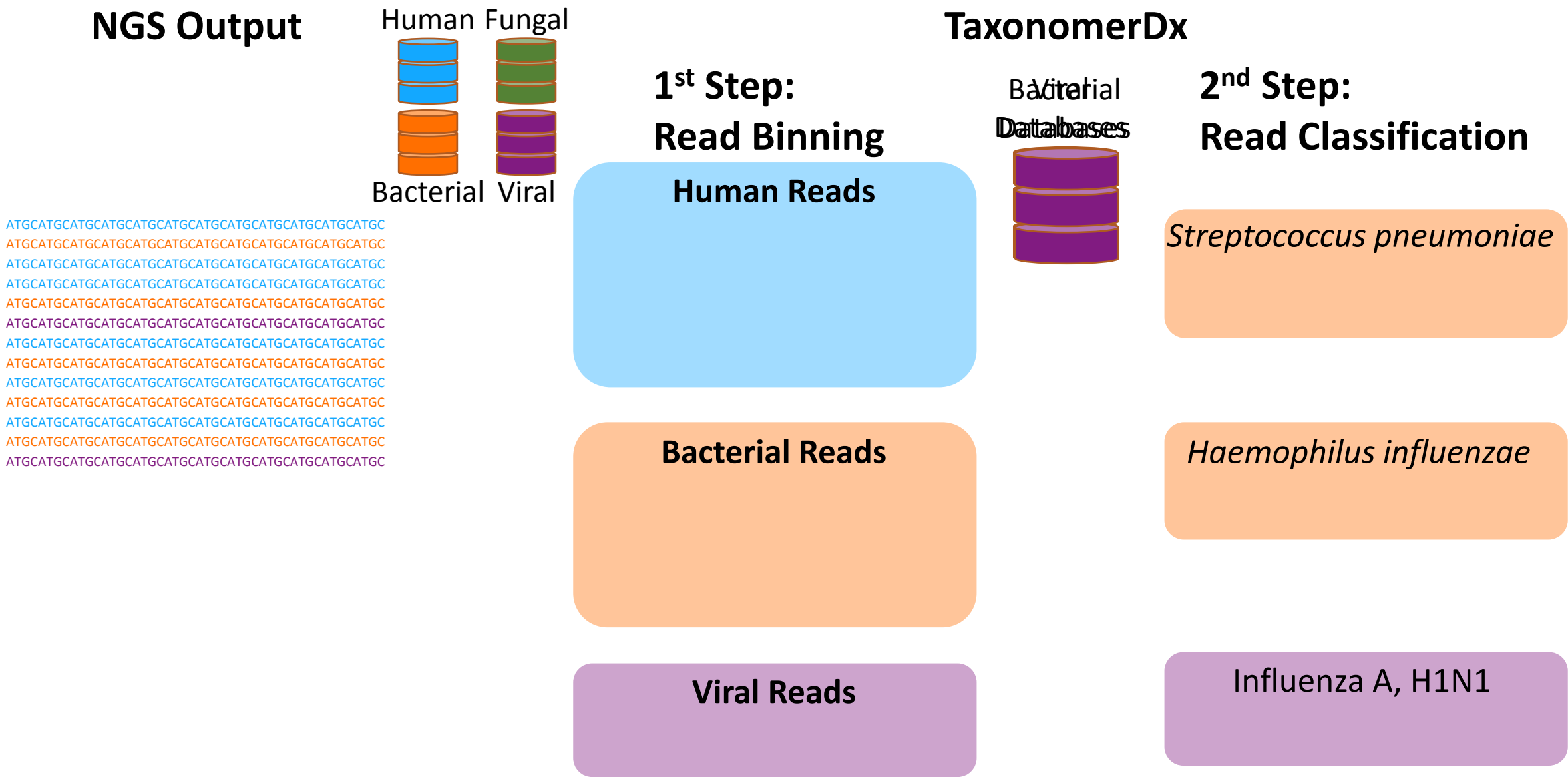
Haemophilus influenzae

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ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Influenza A, H1N1

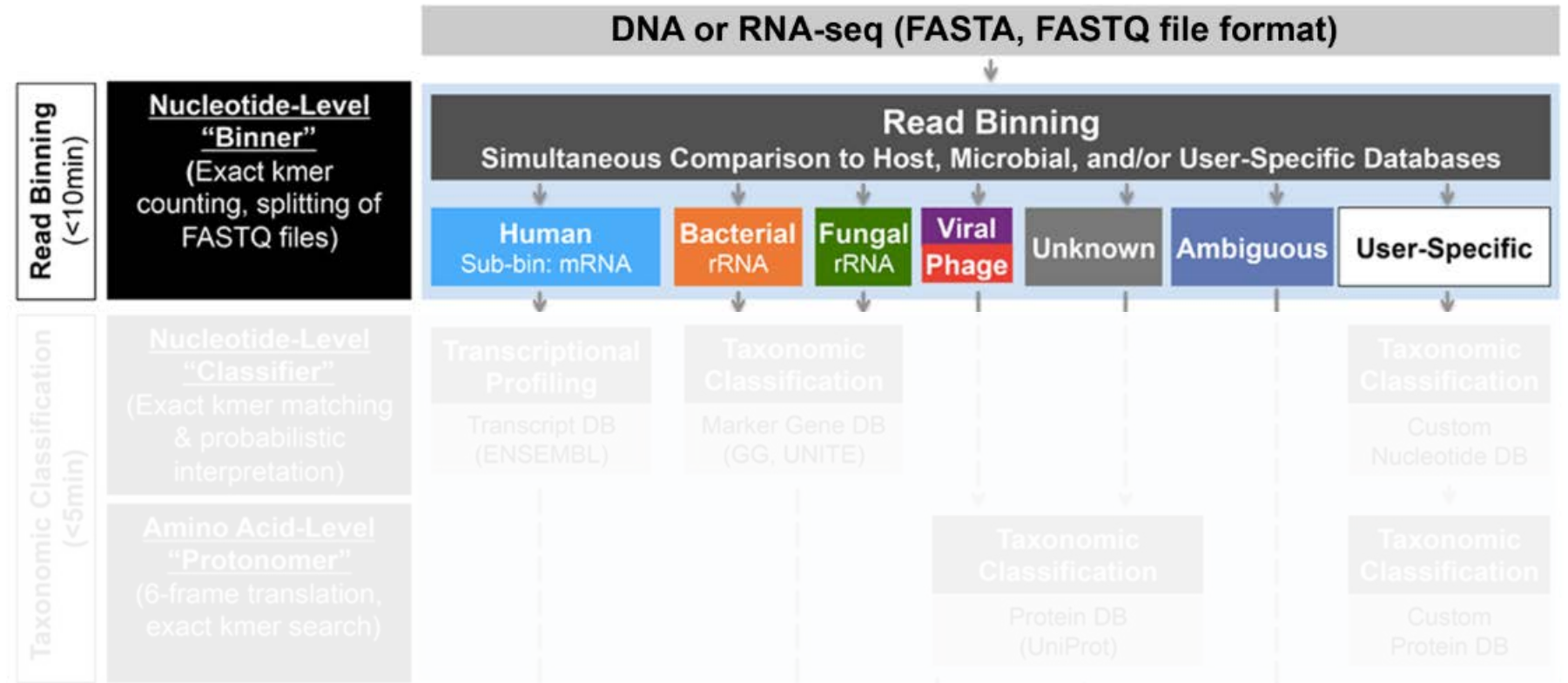
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

Data Analysis Approach





Step 1: Presort Reads ('Binning')





kmer Count-Based Binning

Sequencing Read

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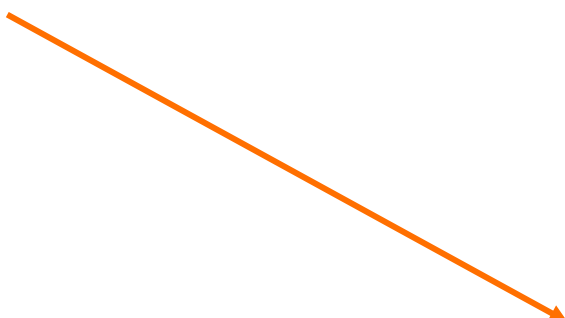


kmer Count-Based Binning

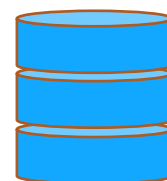
Sequencing Read

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC

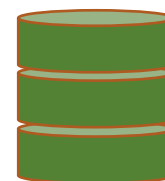
ATGCATGCATGCATGCATGCA



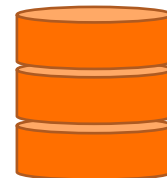
Human



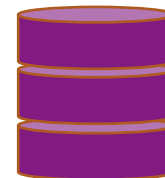
Fungal



Bacterial



Viral





kmer Count-Based Binning

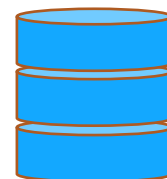
Sequencing Read

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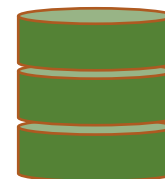
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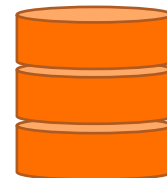
Human



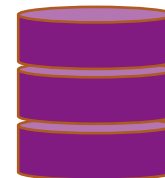
Fungal



Bacterial



Viral





kmer Count-Based Binning

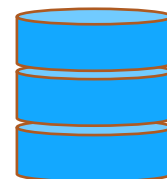
Sequencing Read

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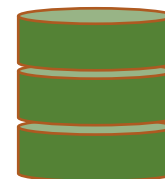
ATGCATGCATGCATGCATGCA
TGCATGCATGCATGCATGCAT
GCATGCATGCATGCATGCATG
CATGCATGCATGCATGCATGC
...
...

Database	Counts
Human	1
Viral	0
Bacterial	123
Fungal	6

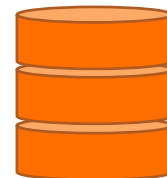
Human



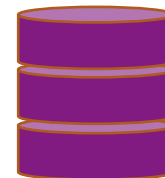
Fungal



Bacterial



Viral





kmer Count-Based Binning

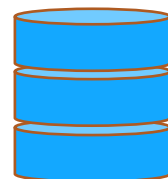
Sequencing Read

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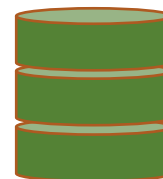
ATGCATGCATGCATGCATGCA
TGCATGCATGCATGCATGCAT
GCATGCATGCATGCATGCATG
CATGCATGCATGCATGCATGC
...

...

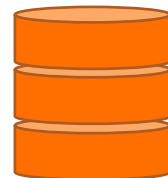
Human



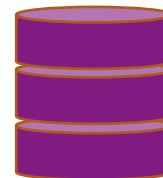
Fungal



Bacterial



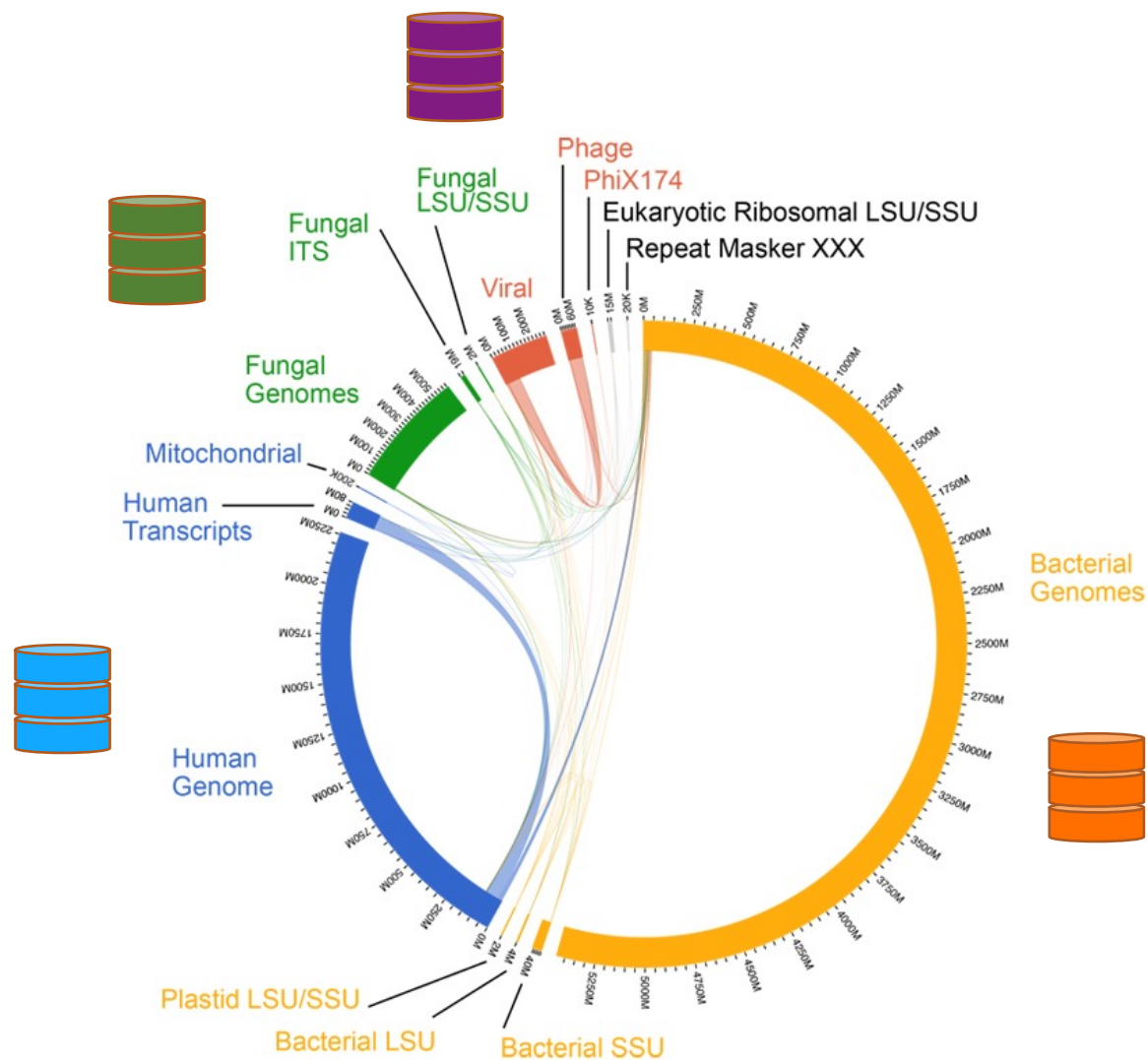
Viral



Database	Counts
Human	1
Viral	0
Bacterial	123
Fungal	6



Overlap Between kmer Databases is Minimal



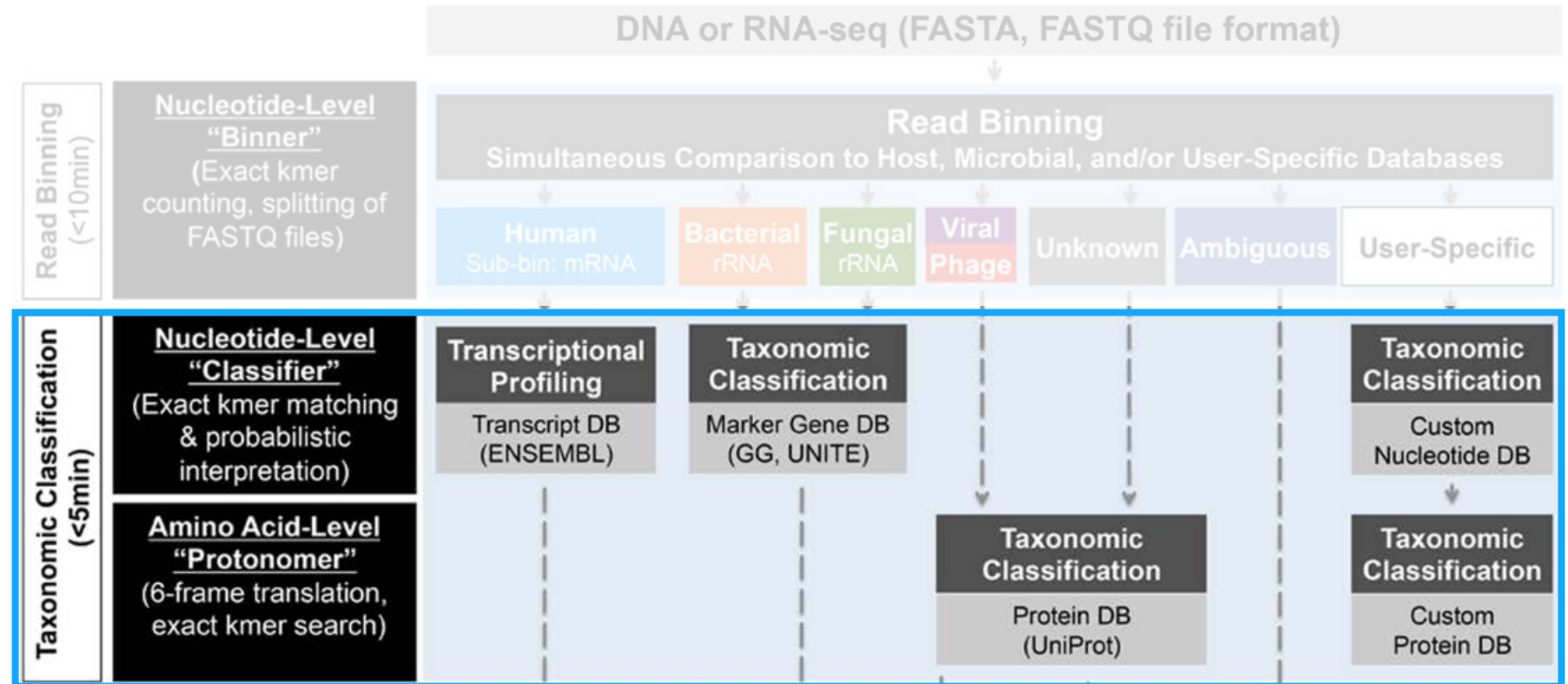


Step 2: Classify Reads

Classification vs. Match Table

Match tables require interpretive criteria for post hoc analyses

Performance depends on reads length (pitfalls)





Read-Level Classification (Nucleic Acid, Protein Level)

Sequencing Read

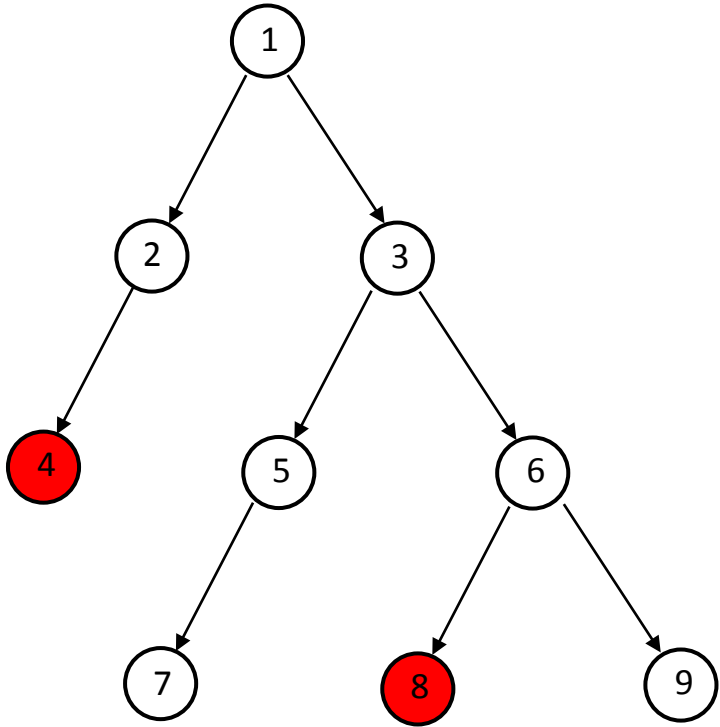
ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCA

Order

Family

Genus

Species



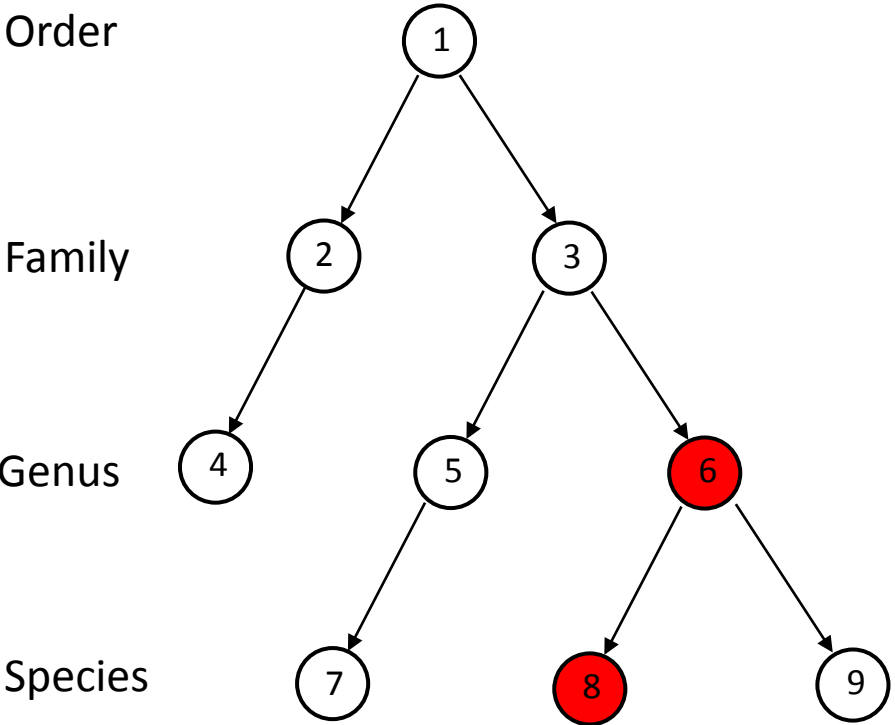
Node ID	K-mer weights
1	
2	
3	
4	2.3
5	
6	
7	
8	5.35
9	



Read-Level Classification (Nucleic Acid, Protein Level)

Sequencing Read

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCA
TGCATGCATGCATGCATGCAT



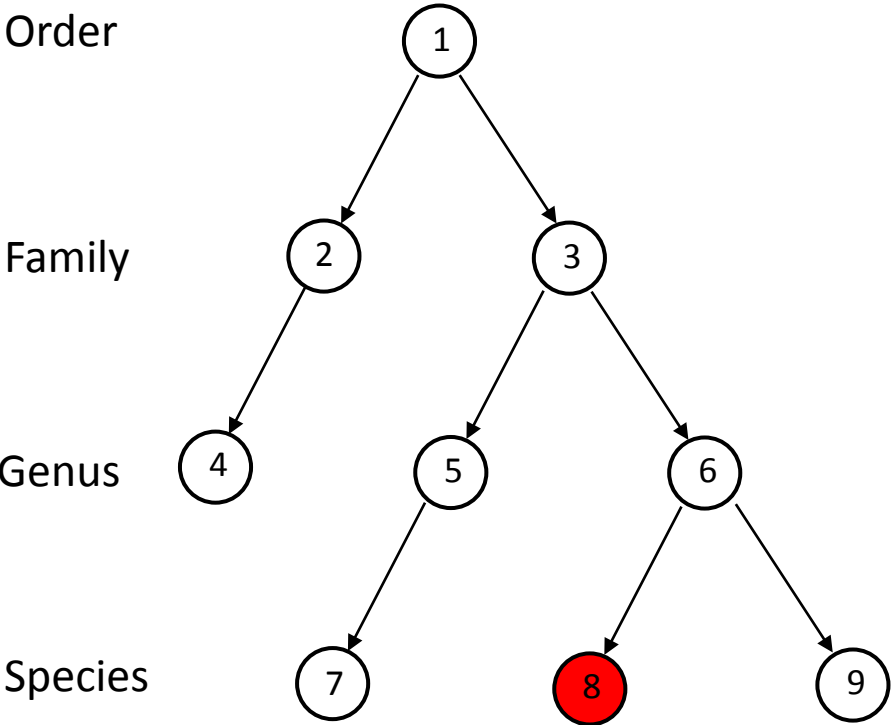
Node ID	K-mer weights
1	
2	
3	
4	2.3
5	
6	1.2
7	
8	5.35, 1.1
9	



Read-Level Classification (Nucleic Acid, Protein Level)

Sequencing Read

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCA
...



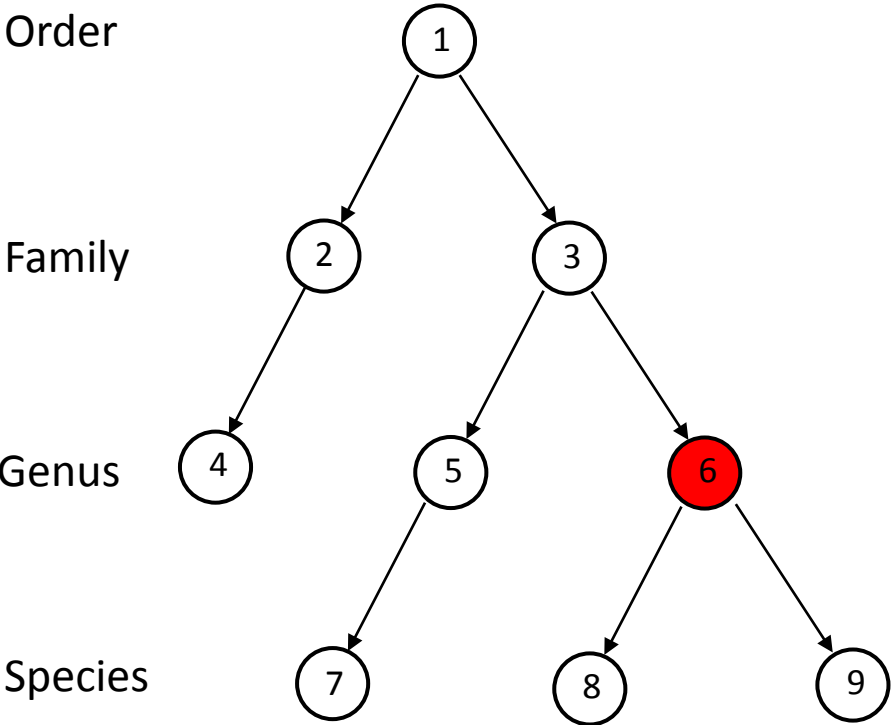
Node ID	K-mer weights	Total
1	0.5	0.5
2	3.5	3.5
3	2.6, 3.5	6.1
4	2.3, 0.5	2.8
5	1.8	1.8
6	1.2, 3.5	4.7
7	3.5	3.5
8	5.35, 1.1, 4.5	10.95
9	2.6	2.6



Read-Level Classification (Nucleic Acid, Protein Level)

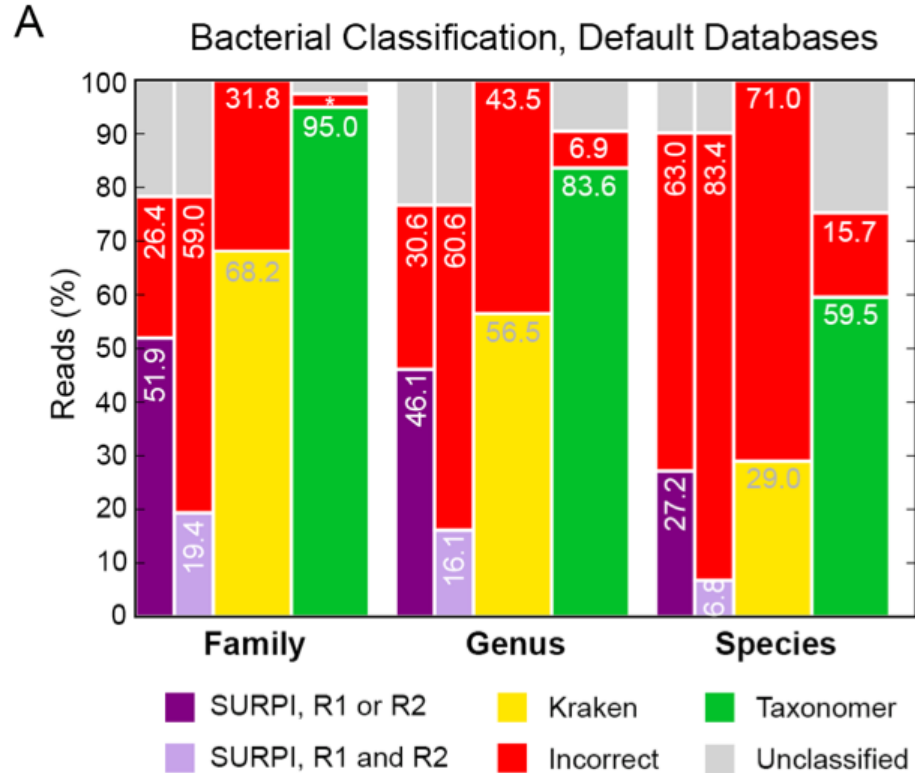
Sequencing Read

ATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGCATGC
ATGCATGCATGCATGCATGCA
...

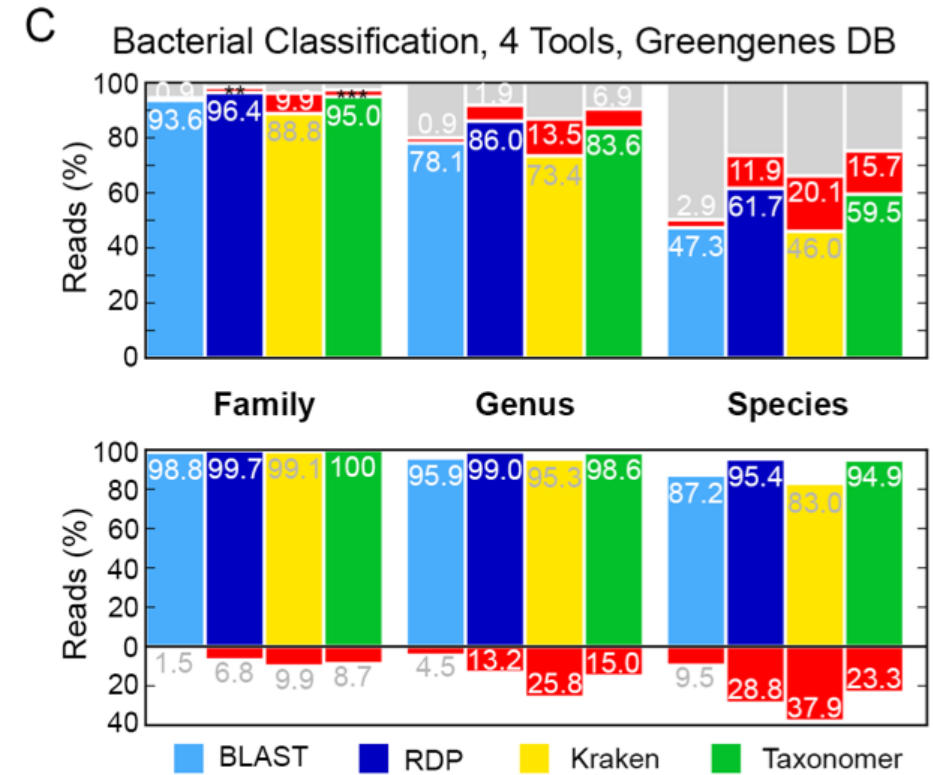
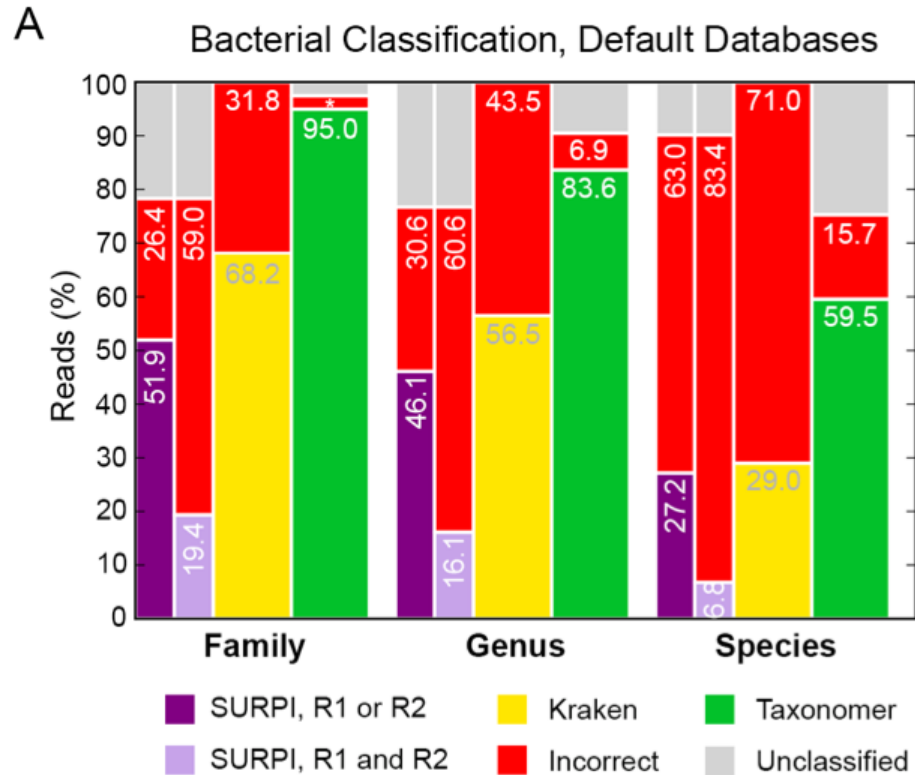


Node ID	K-mer weights	Total
1	0.5	0.5
2	3.5	3.5
3	2.6, 3.5	6.1
4	2.3, 0.5	2.8
5	1.8	1.8
6	1.2, 3.5	4.7
7	3.5	3.5
8	5.35, 1.1, 4.5	10.95
9	5.35, 1.1, 4.5	10.95

Accurate Bacterial Classification

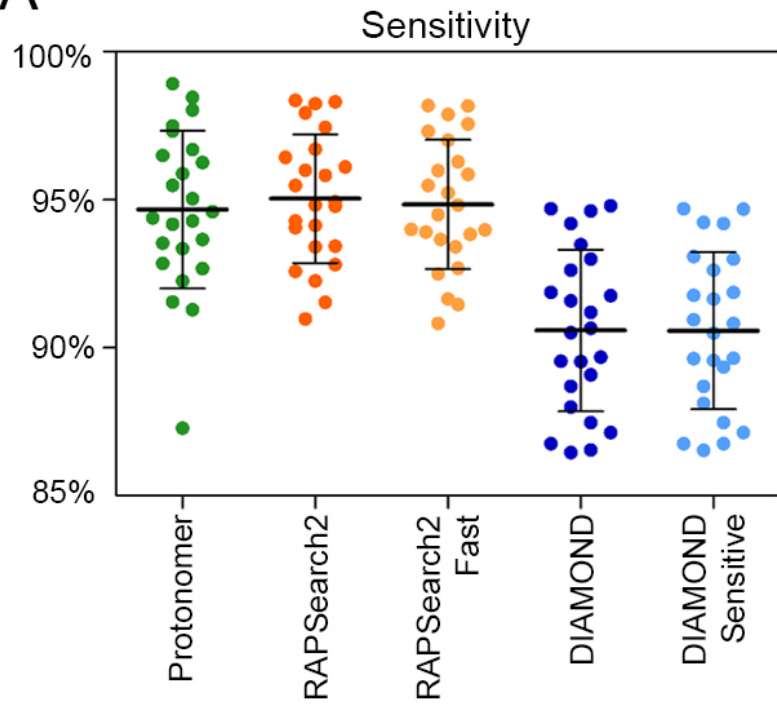


Accurate Bacterial Classification

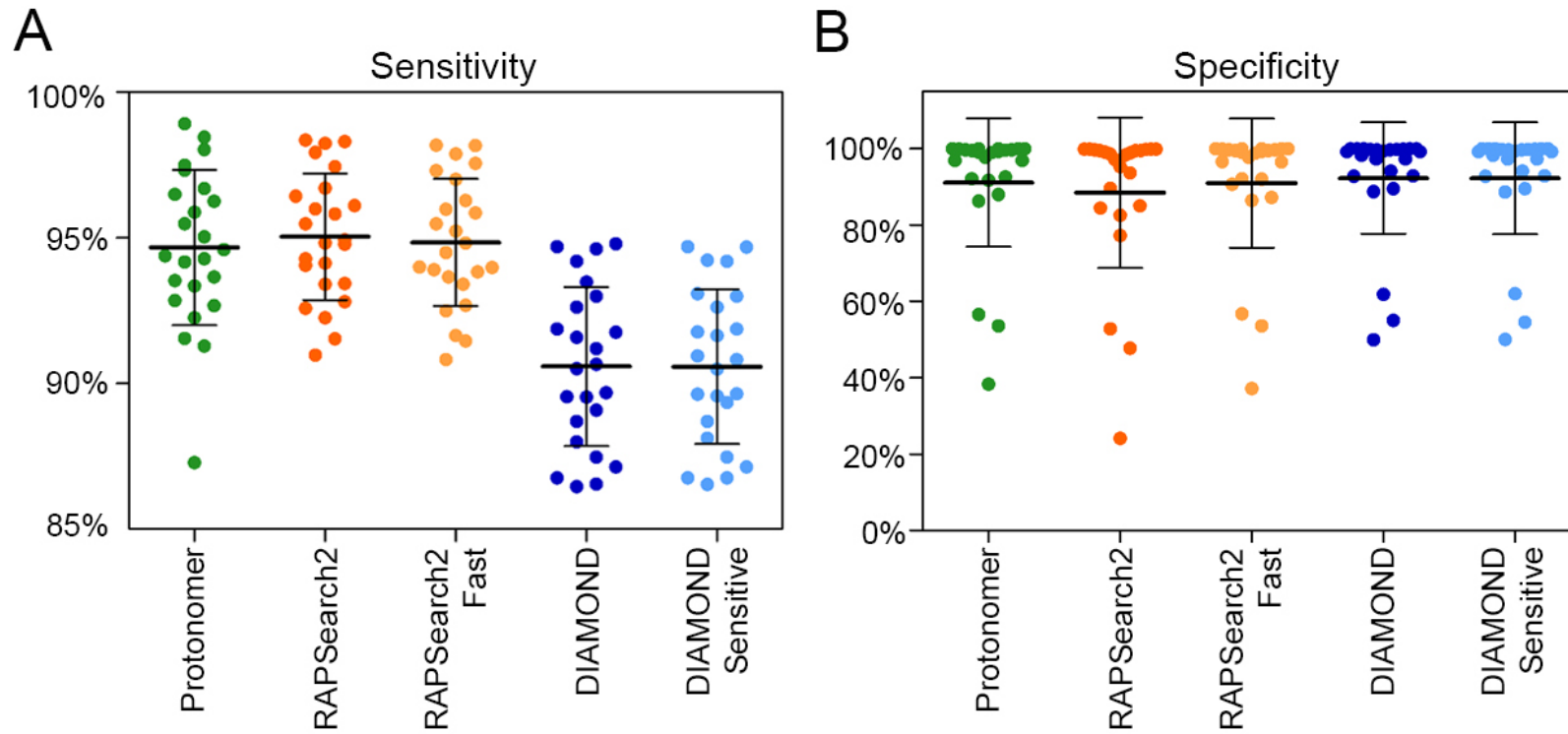


Accurate Viral Classification

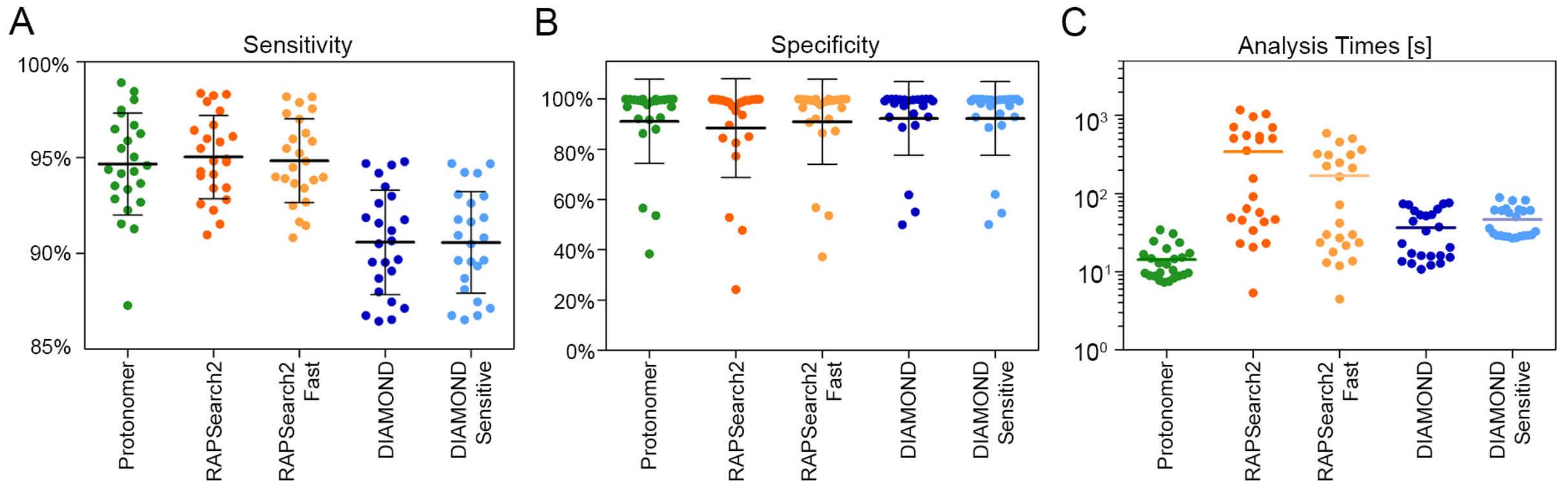
A

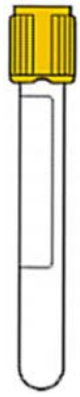


Accurate Viral Classification



Accurate Viral Classification





RNA-seq, Plasma, Patient Ebola

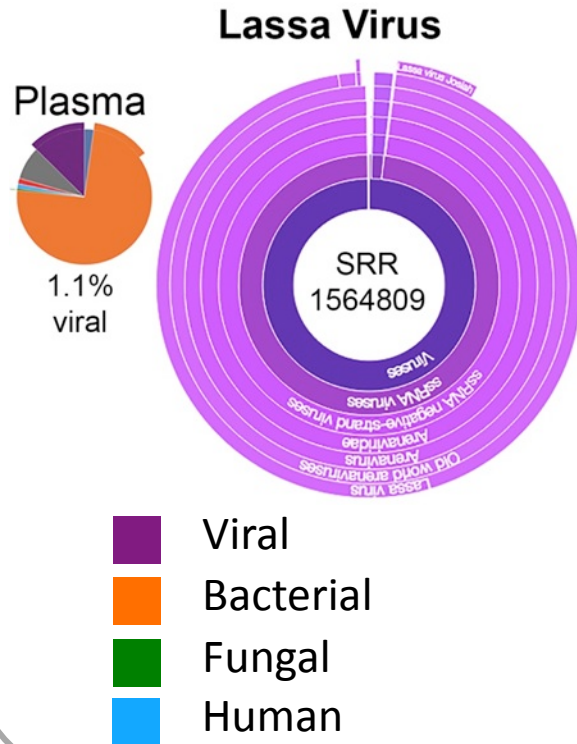


Sample applications

- Detection of previously unrecognized pathogens in published data
- Detection of pathogens in public health emergencies
- Respiratory virus detection compared to PCR
- Respiratory virus detection, children with pneumonia of unknown etiology
- Respiratory pathogen detection in BAL samples
- Host mRNA expression profiling

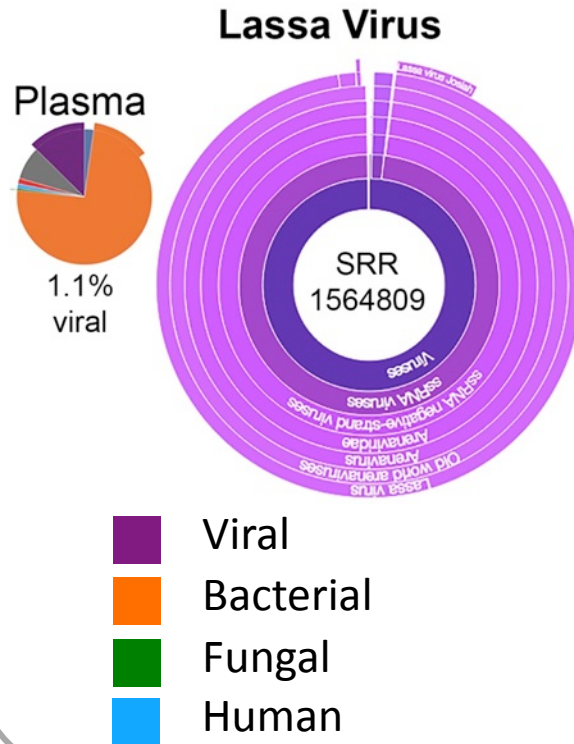
Unrecognized Pathogens, Plasma

Unexpected Viral Infection

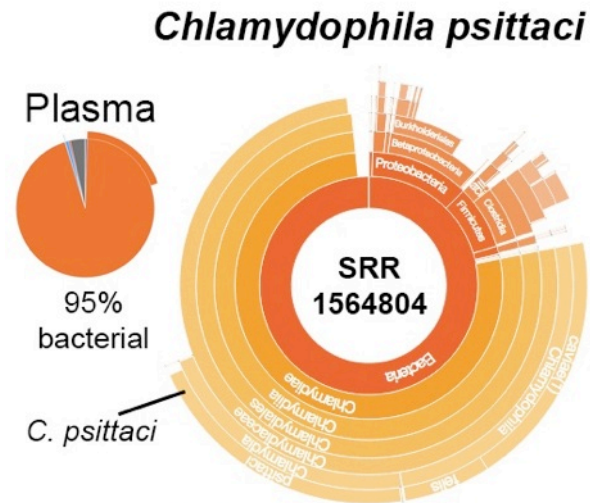


Unrecognized Pathogens, Plasma

Unexpected Viral Infection

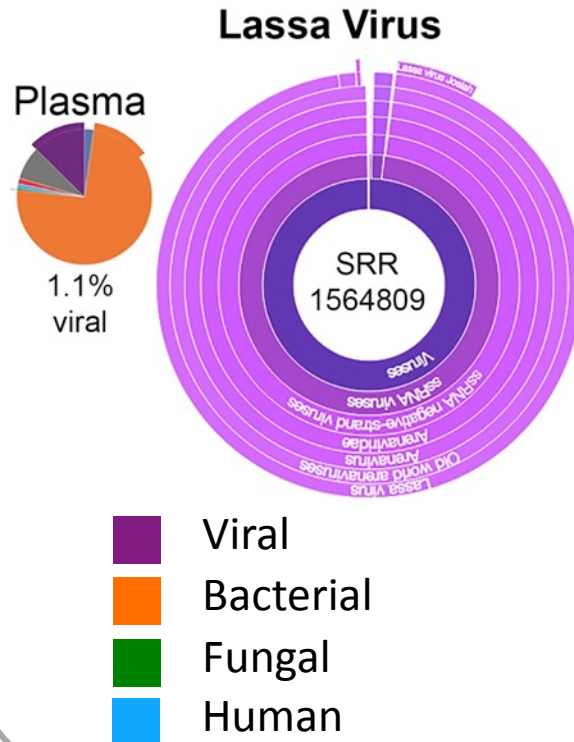


Missed Bacterial Infection I

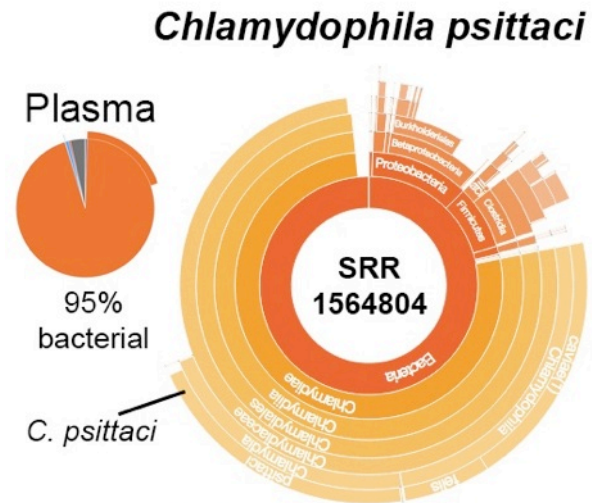


Unrecognized Pathogens, Plasma

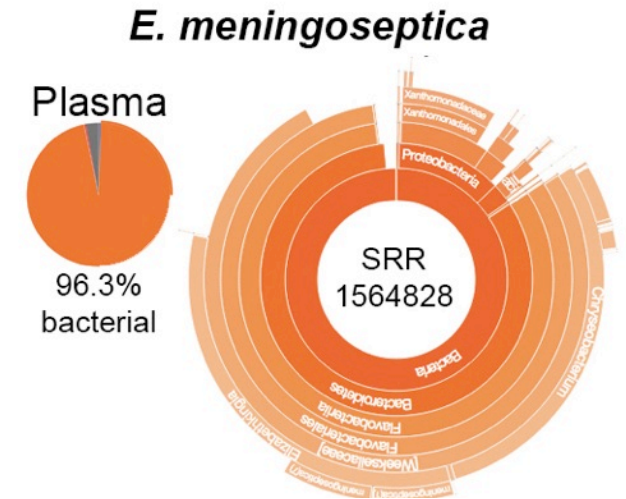
Unexpected Viral Infection



Missed Bacterial Infection I

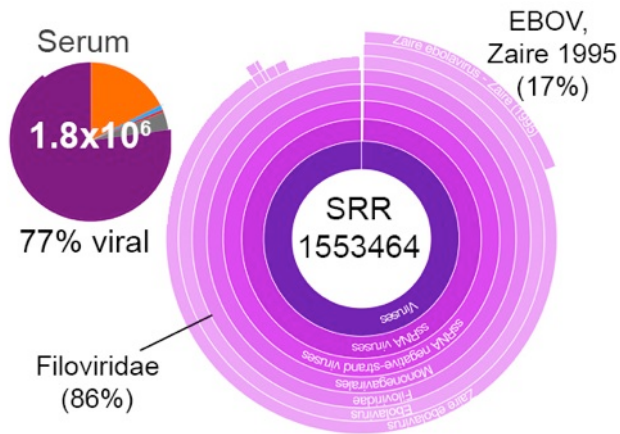


Missed Bacterial Infection II



Taxonomer For Public Health Emergencies

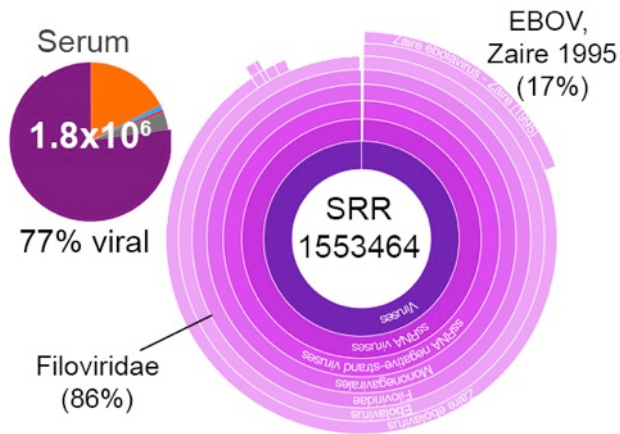
Ebola Disease EBOV Zaire Sierra Leone (2014)



Filoviridae: 86%

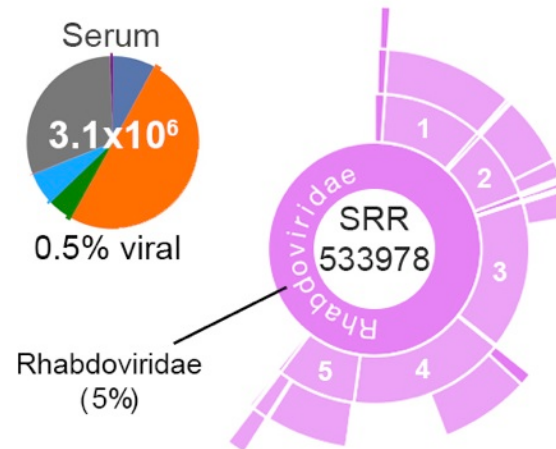
Taxonomer For Public Health Emergencies

Ebola Disease EBOV Zaire Sierra Leone (2014)



Filoviridae: 86%

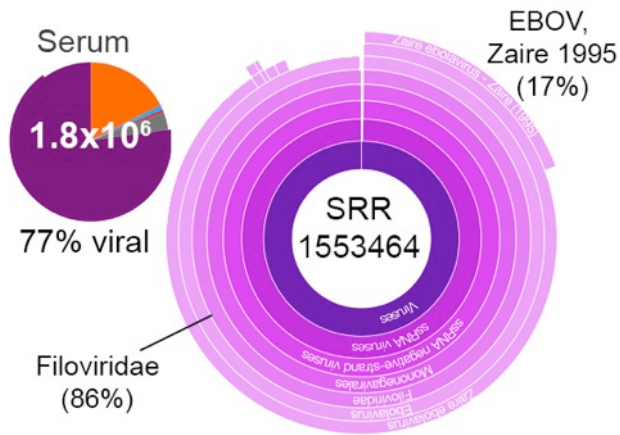
Hemorrhagic Fever Bas Congo Virus DRC (2012)



Rhabdoviridae: 5%

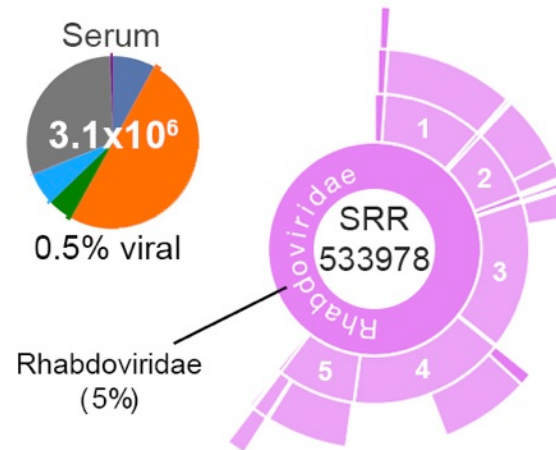
Taxonomer For Public Health Emergencies

Ebola Disease EBOV Zaire Sierra Leone (2014)



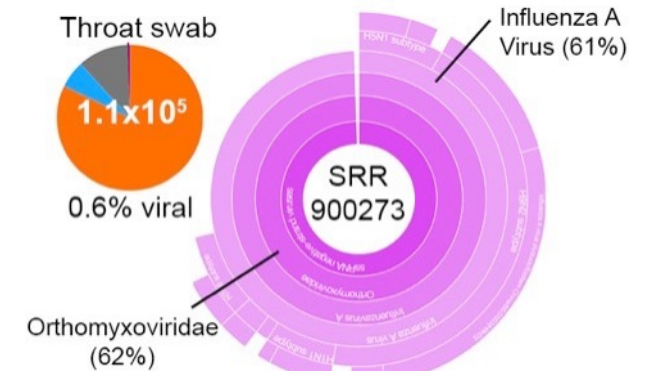
Filoviridae: 86%

Hemorrhagic Fever Bas Congo Virus DRC (2012)



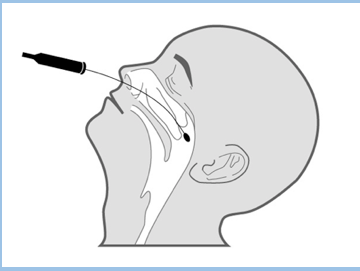
Rhabdoviridae: 5%

Avian Influenza H7N9 China (2013)



Influenza A virus: 61%

NP Swabs ($n=109$)



PCR Panel (RVP)



I. Positives ($n=42$)

II. Unselected ($n=67$)

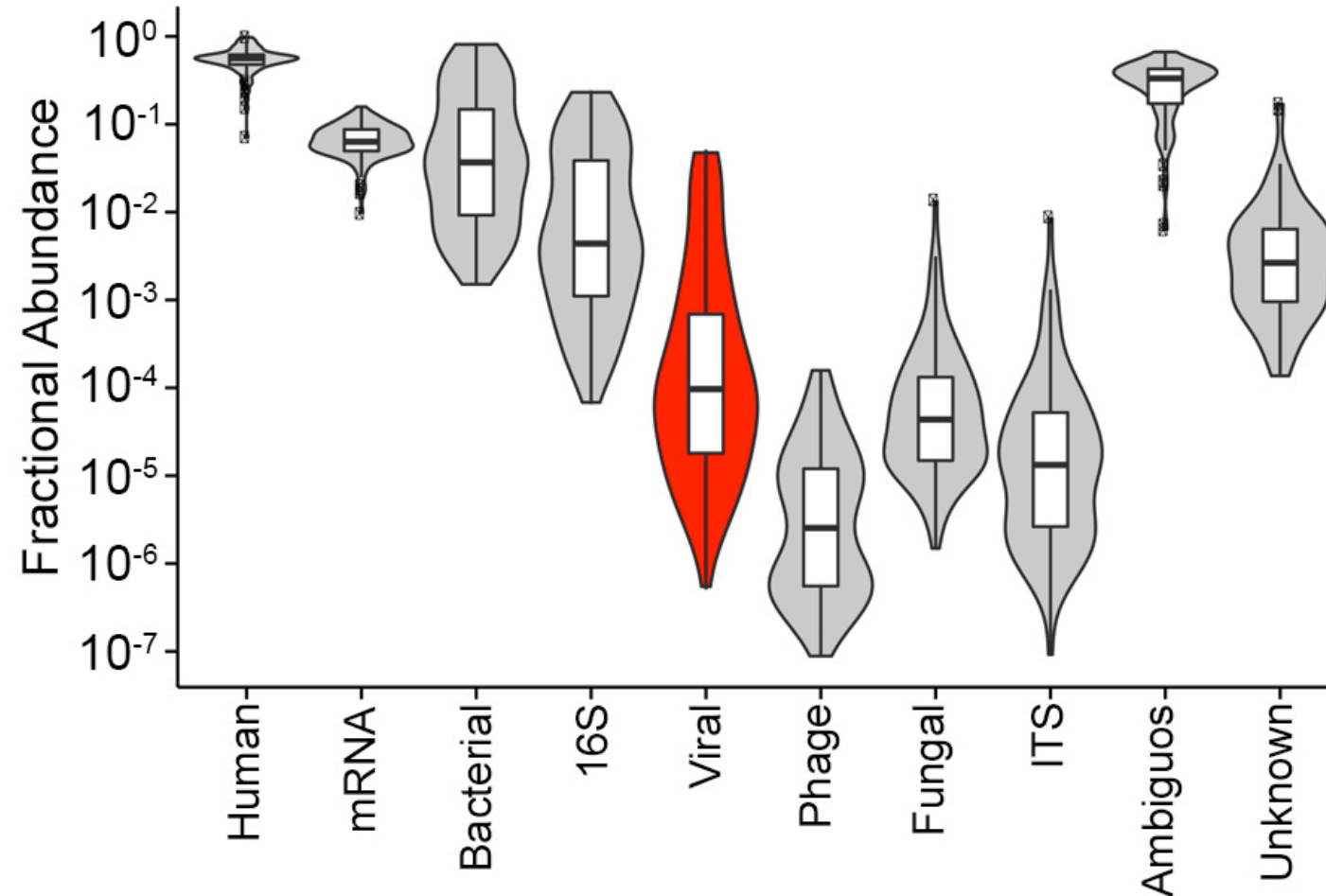
RNA-seq (HiSeq)



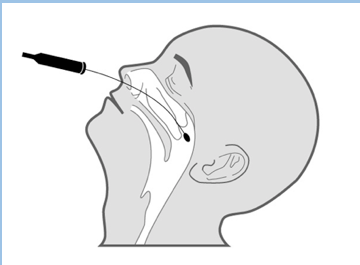
5-10 M reads/sample

Respiratory Virus Detection (NP Swabs)

RNA Composition



NP Swabs (n=109)



PCR Panel (RVP)



I. Positives (n=42)

II. Unselected (n=67)



RNA-seq (HiSeq)

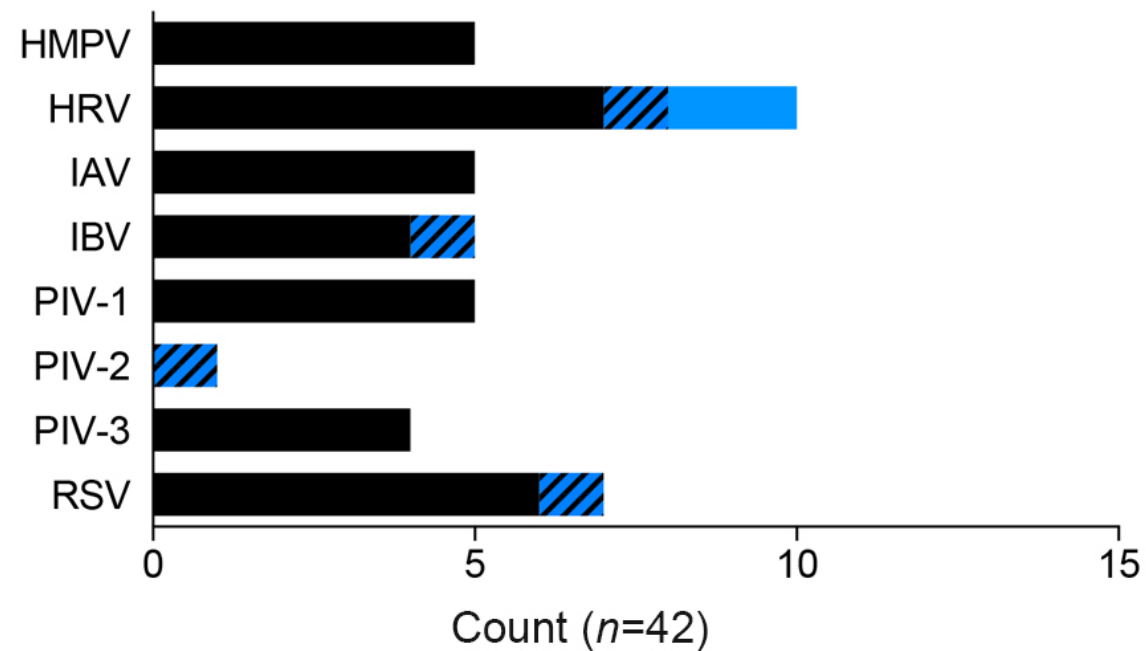


5-10 M reads/sample

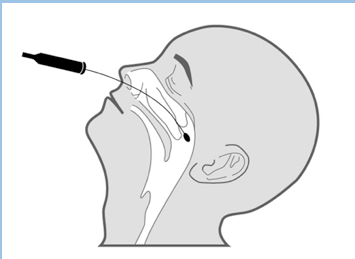
Respiratory Virus Detection (NP Swabs)

RVP-Positive Samples

- RVP+, RNA-seq/Taxonomer+
- RVP+, RNA-seq/Taxonomer-
- ▨ RVP+, RNA-seq/Taxonomer-, qPCR-



NP Swabs ($n=109$)



PCR Panel (RVP)



I. Positives ($n=42$)

II. Unselected ($n=67$)



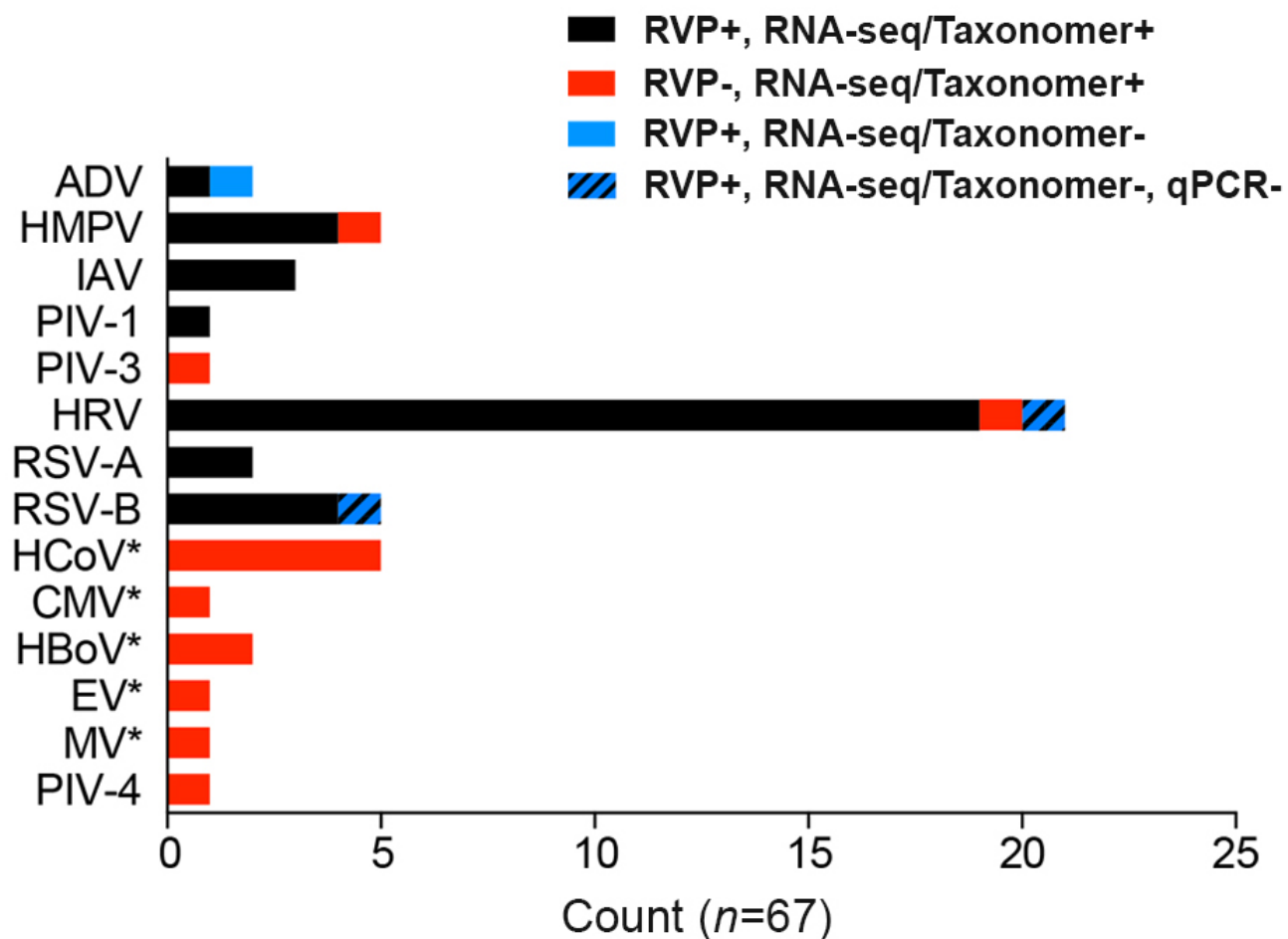
RNA-seq (HiSeq)

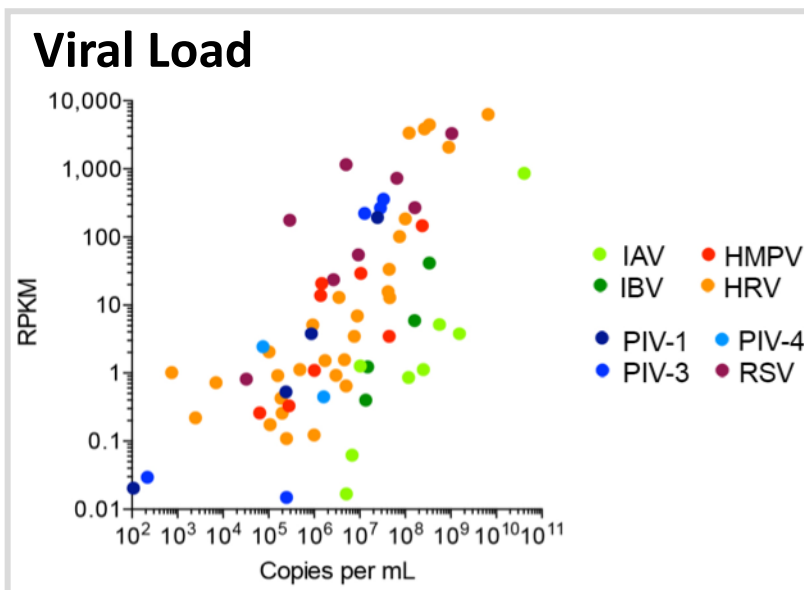
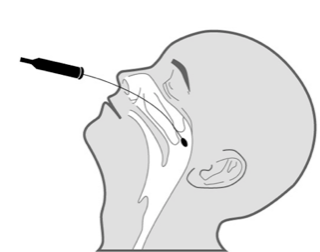


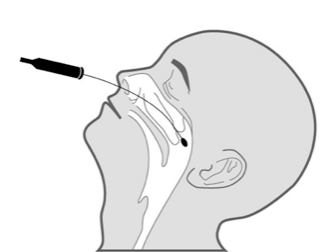
5-10 M reads/sample

Respiratory Virus Detection (NP Swabs)

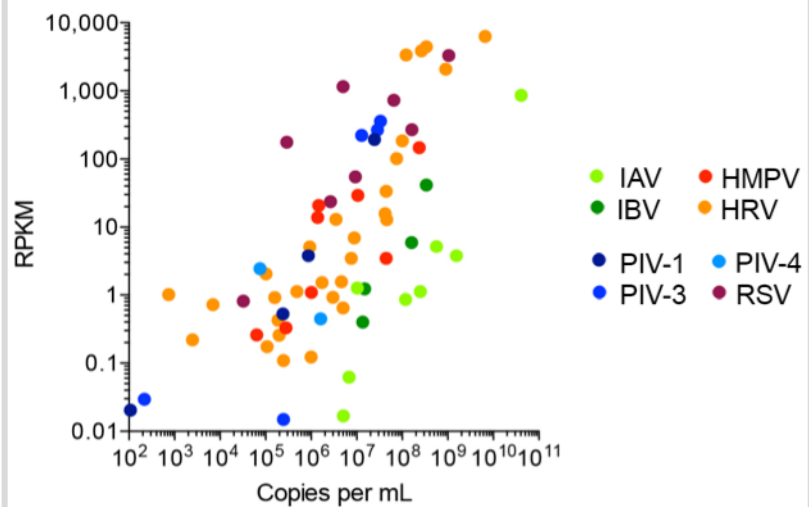
Side-by-Side



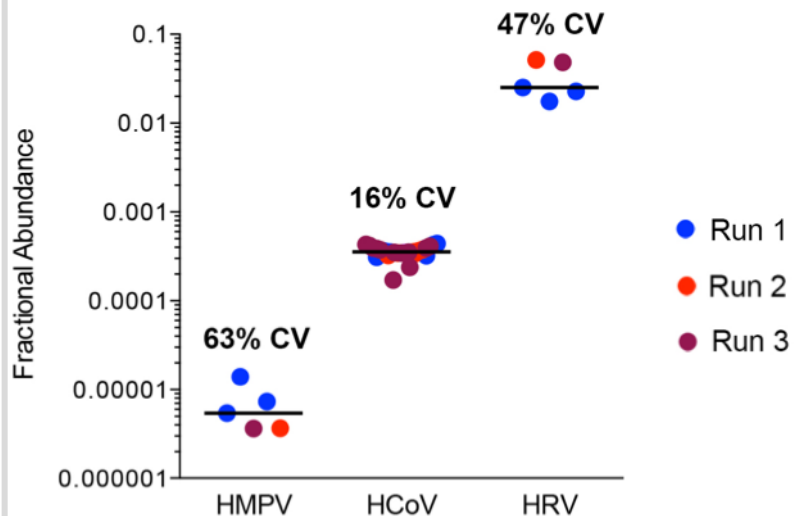


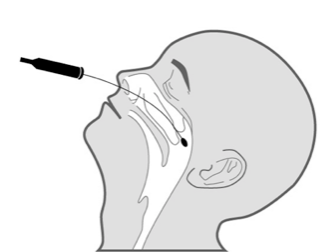


Viral Load

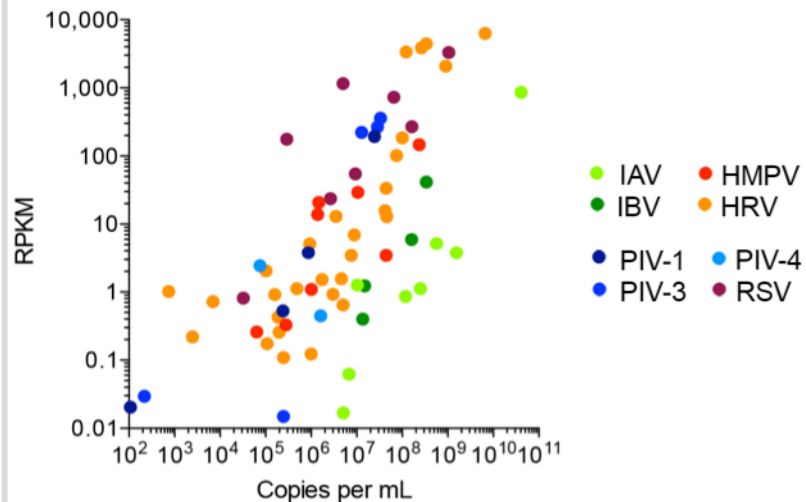


Reproducibility

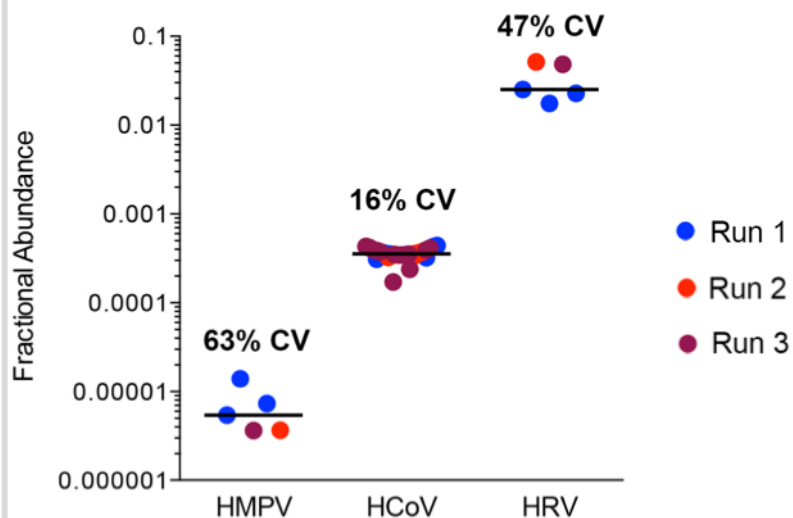




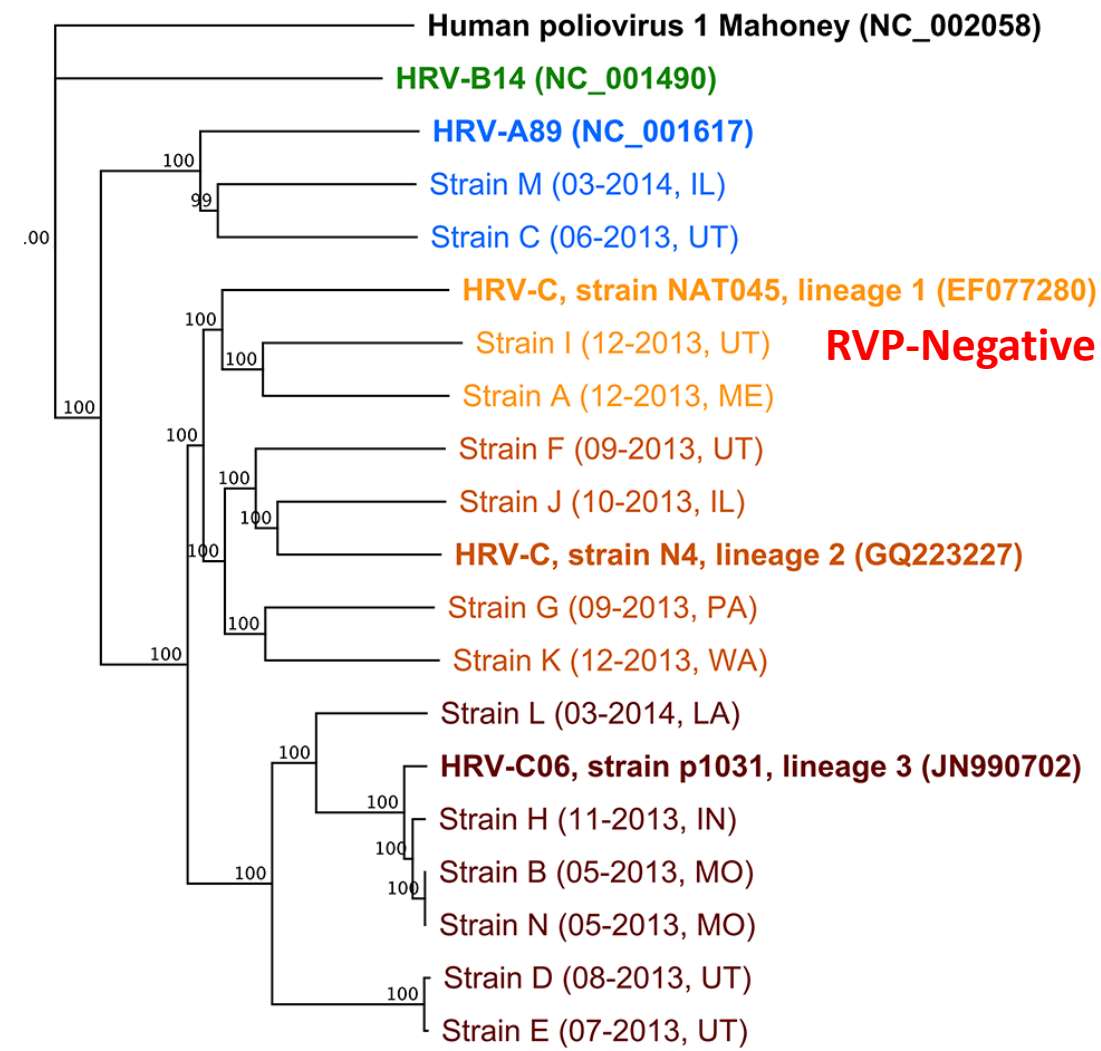
Viral Load

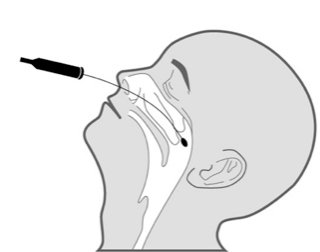


Reproducibility

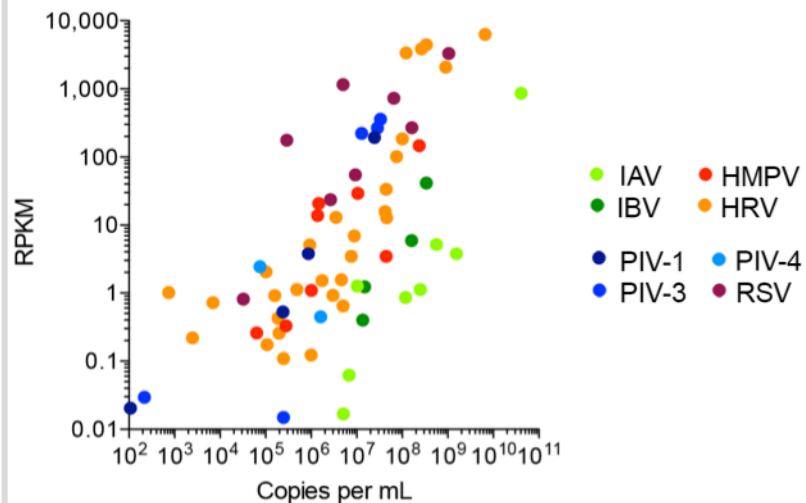


Sequence Agnostic

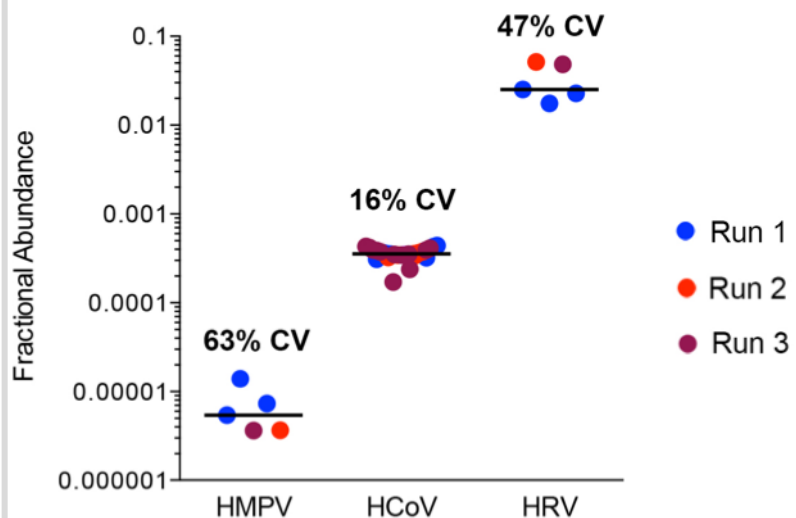




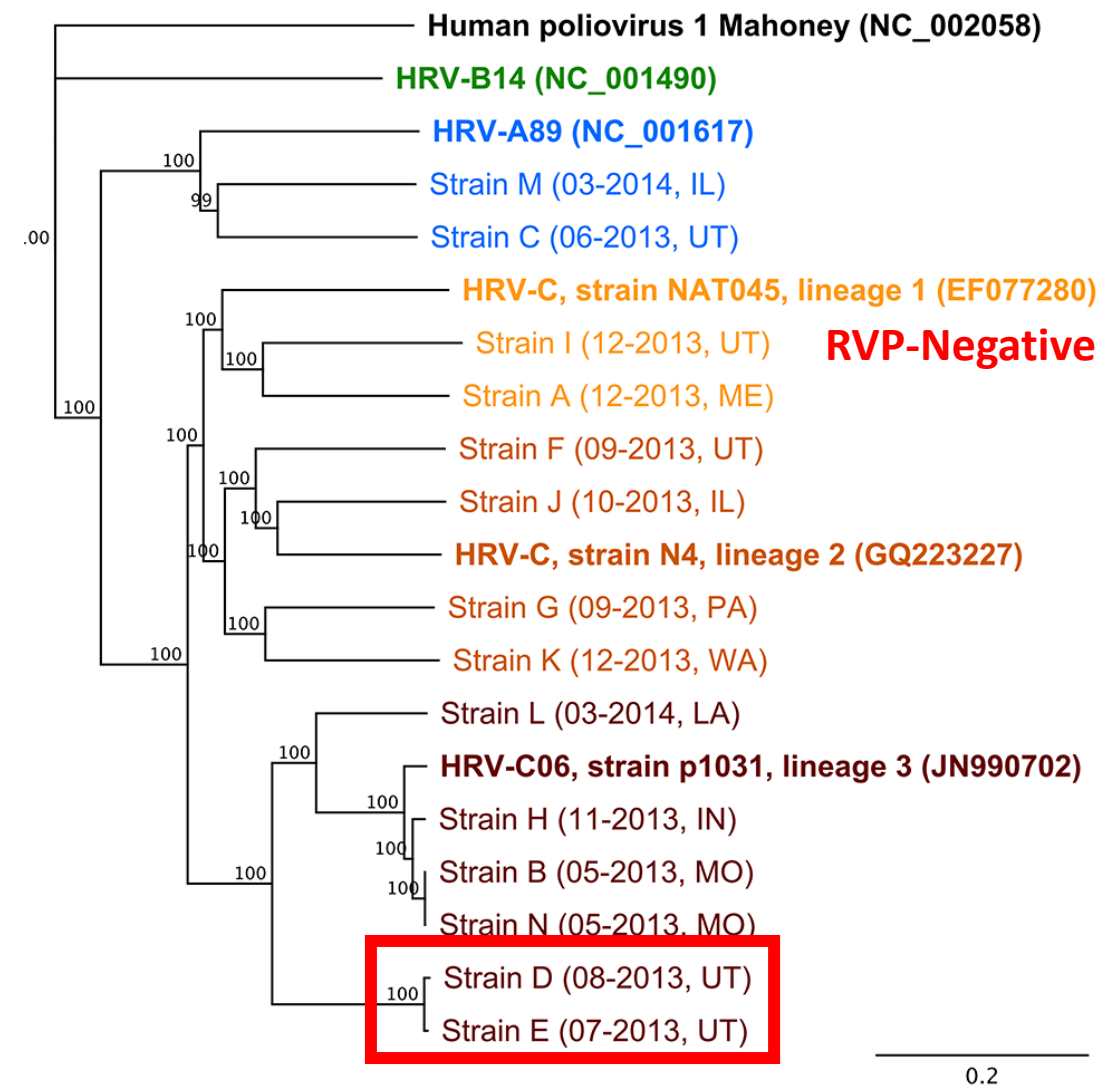
Viral Load

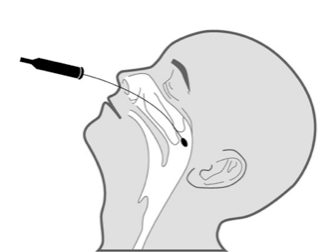


Reproducibility

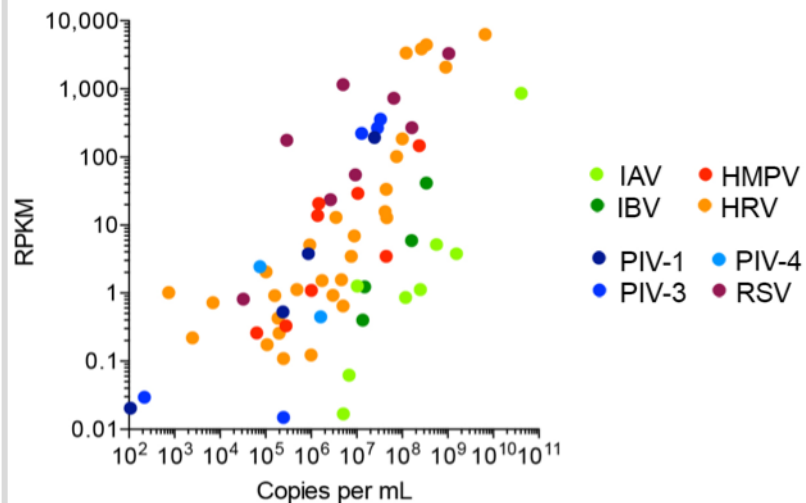


Sequence Agnostic

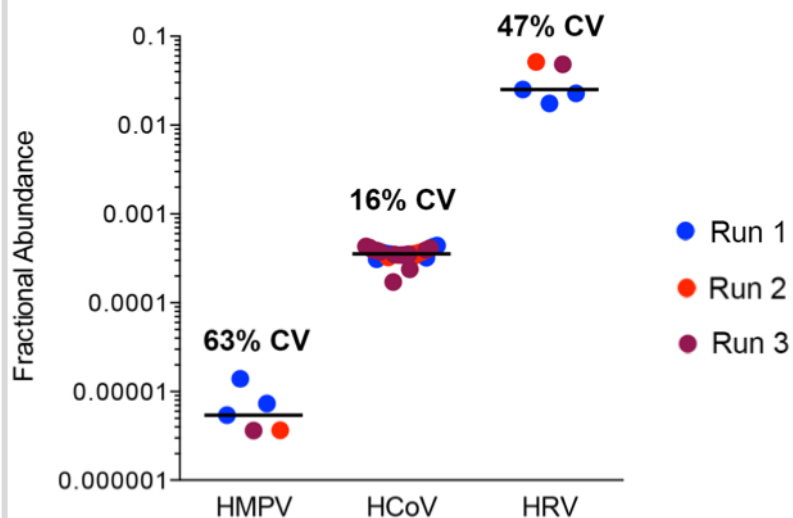




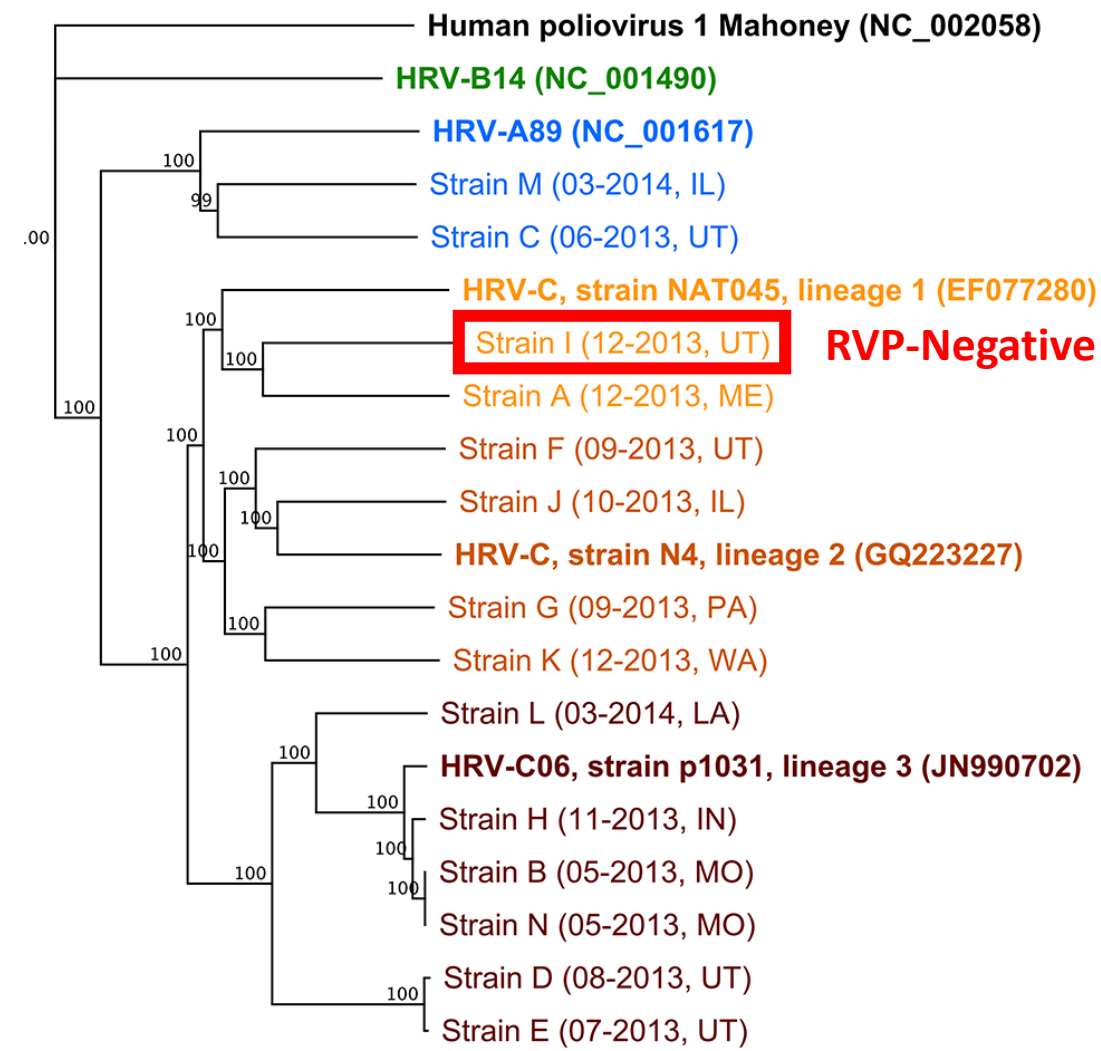
Viral Load

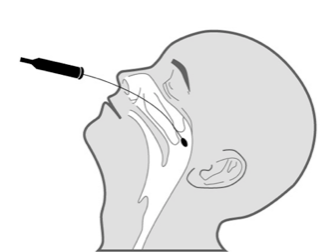


Reproducibility

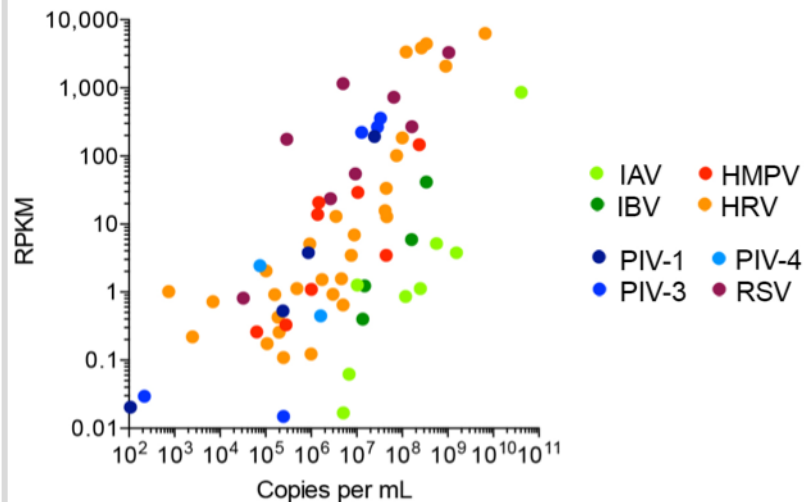


Sequence Agnostic

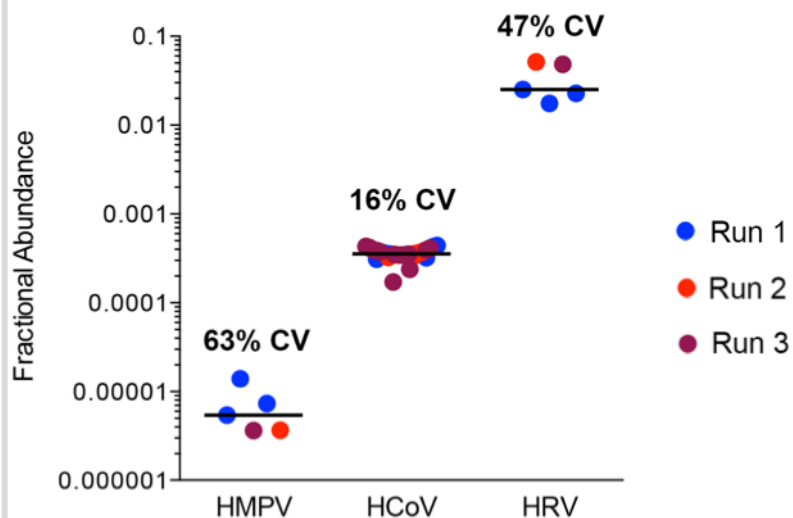




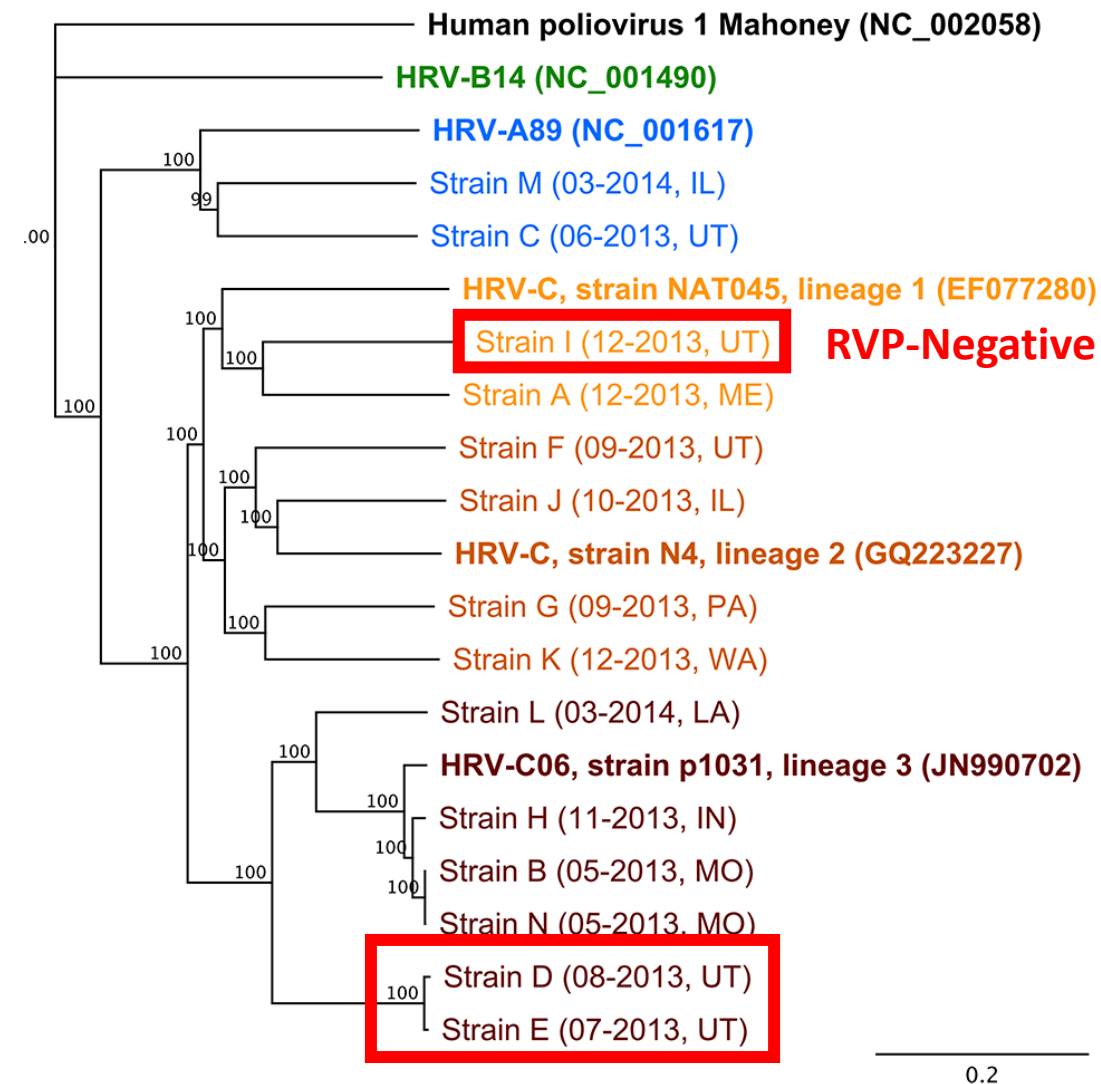
Viral Load



Reproducibility

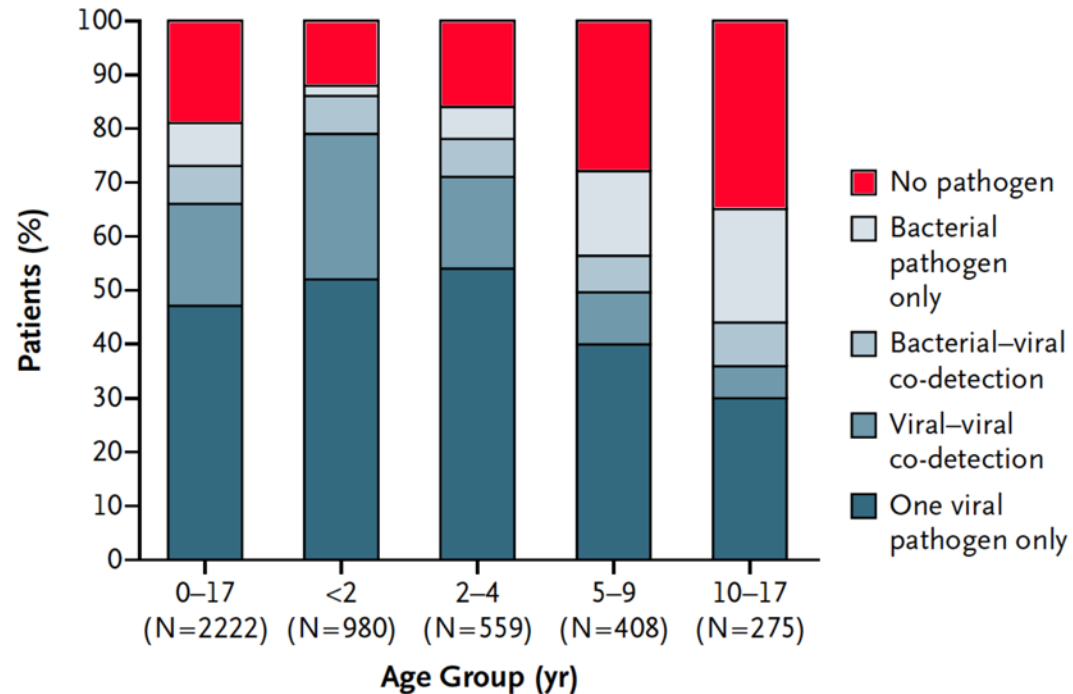


Sequence Agnostic

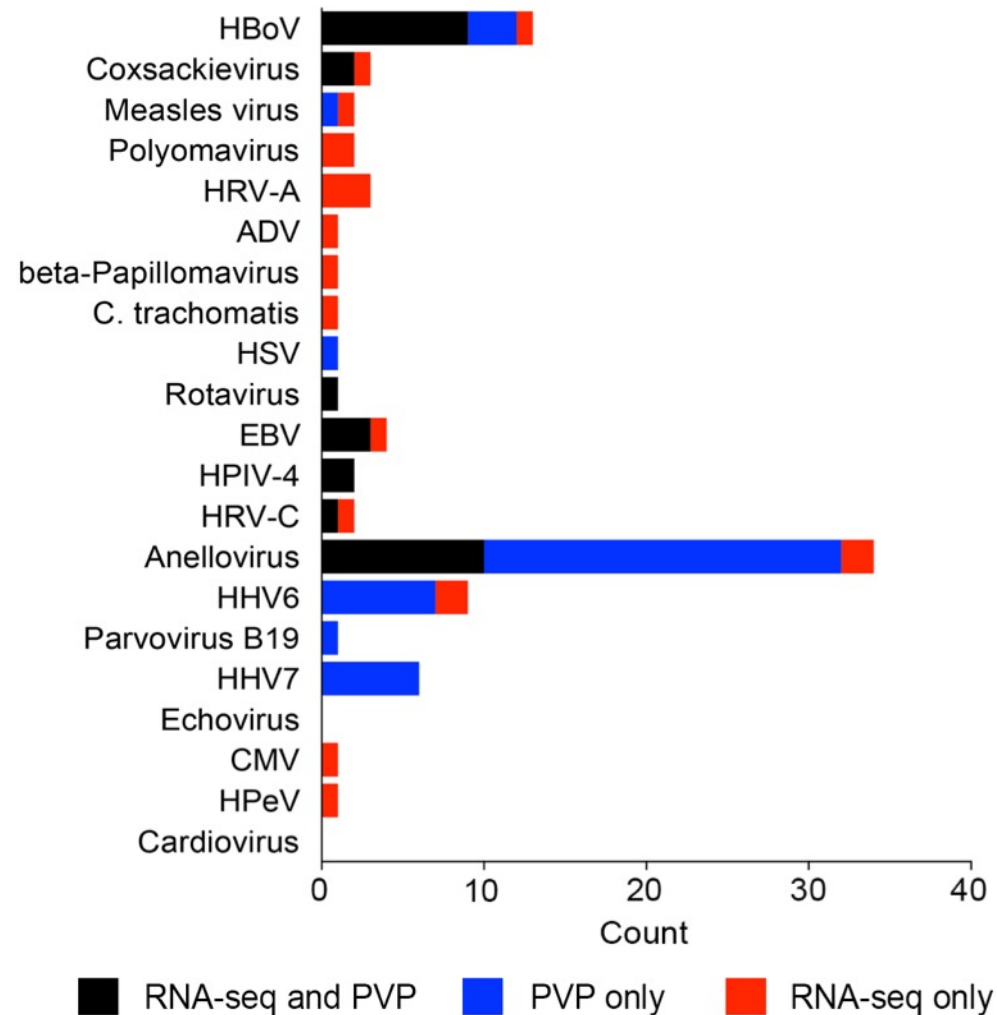


Etiology of Pneumonia often Unknown

Children

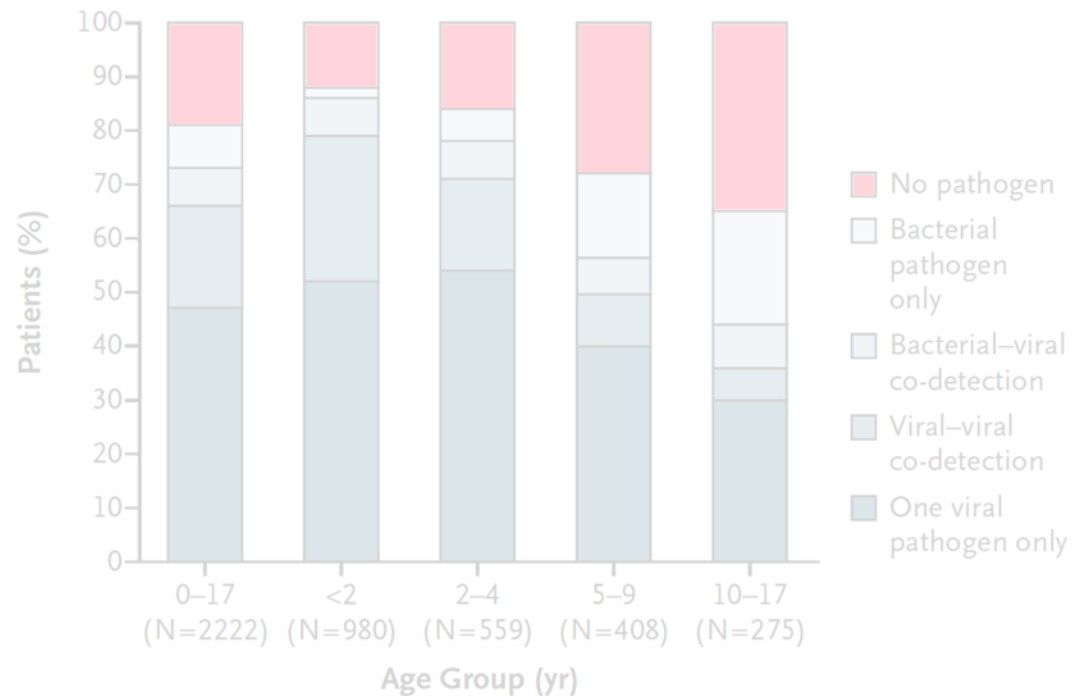


Putative Pathogens Detected in 30% of Children with Pneumonia of Previously Unknown Etiology



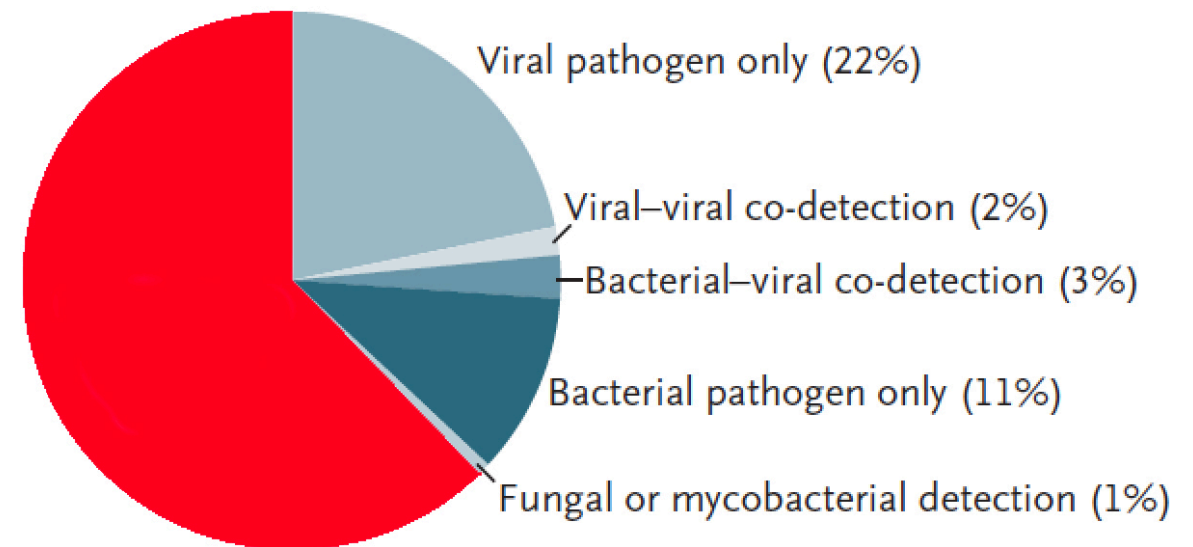
Etiology of Pneumonia often Unknown

Children



N Engl J Med 2015;372:835-45

Adults

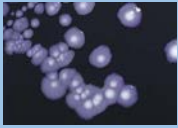


N Engl J Med. 2015;373:415-27

BAL ($n=186$)



Predicate Tests



PCR, Culture



RNA-seq (NextSeq)



~10 M reads/sample

Respiratory Pathogen Detection (BAL)

BAL ($n=186$)



Predicate Tests



PCR, Culture



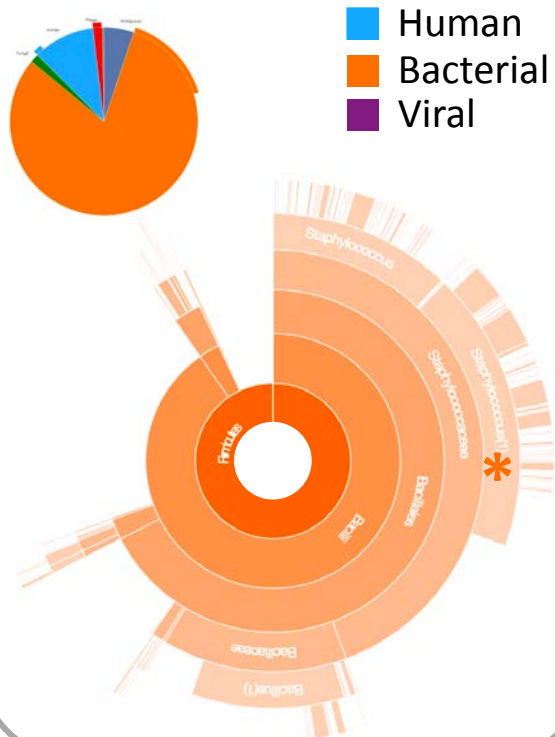
RNA-seq (NextSeq)



~10 M reads/sample

Respiratory Pathogen Detection (BAL)

Staph. aureus



BAL ($n=186$)



Predicate Tests



PCR, Culture

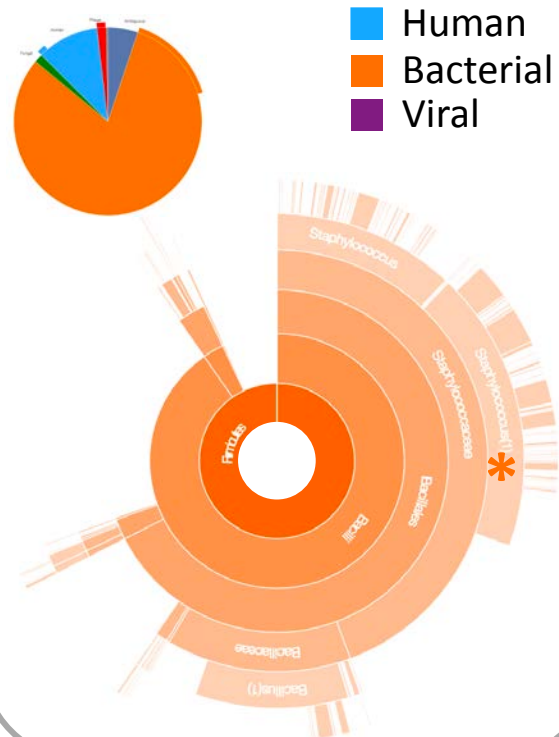
RNA-seq (NextSeq)



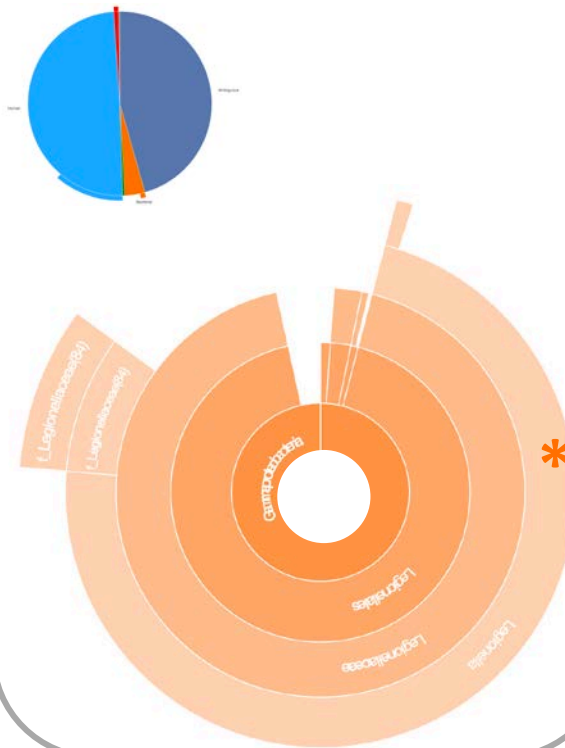
~10 M reads/sample

Respiratory Pathogen Detection (BAL)

Staph. aureus



L. pneumophila



BAL ($n=186$)



Predicate Tests



PCR, Culture

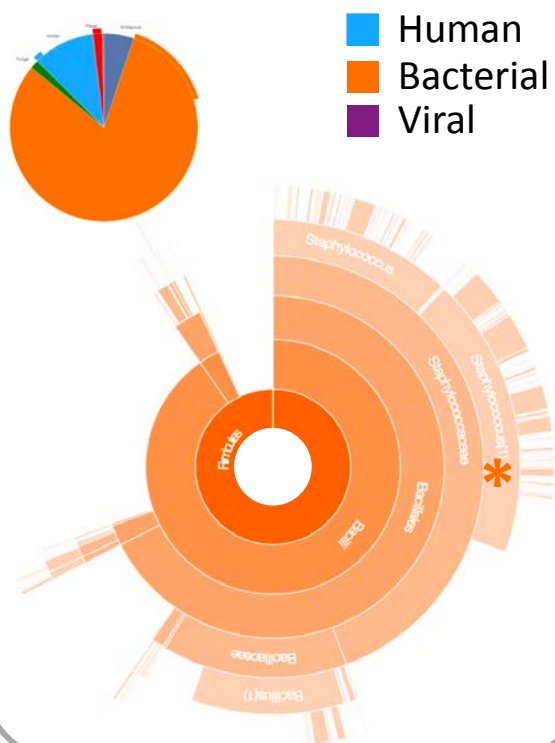
RNA-seq (NextSeq)



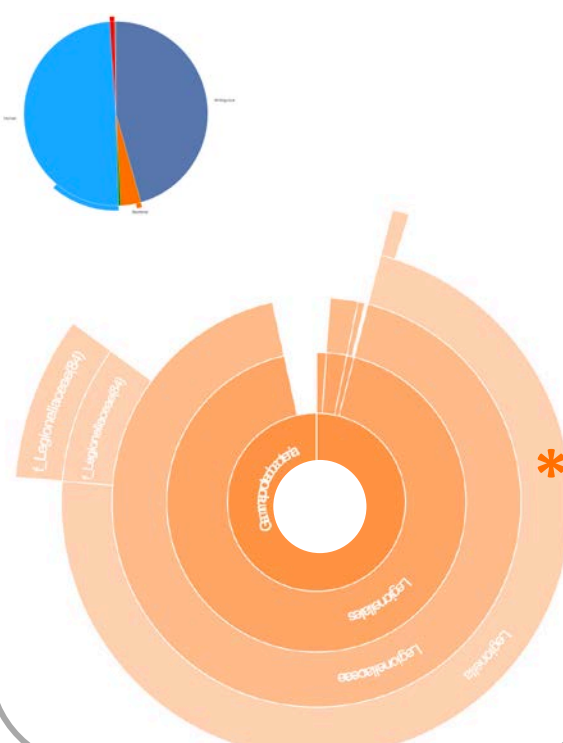
~10 M reads/sample

Respiratory Pathogen Detection (BAL)

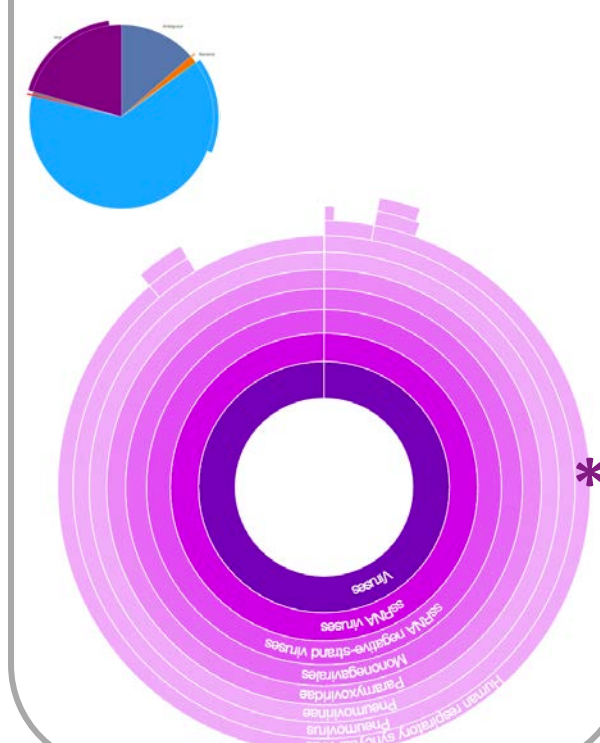
Staph. aureus



L. pneumophila



RSV



Ideally Suited for Syndromic Testing

- **Lower Respiratory Tract Infections**
 - Community-acquired pneumonia
 - Hospital-acquired pneumonia
- **Meningitis, Encephalitis**
- **Sepsis**
- **Diarrheal disease**

DNA and RNA-Seq Complementary

RNA-seq

- Metabolically active bacteria and fungi
- Replicating DNA viruses, sole target for RNA viruses

DNA-seq

- Can increase taxonomic resolution for bacteria, fungi
- Information on drug resistance genes
- DNA virus genomes

Extensive QC is Required

External positive control

- Complex process

External negative control

- Contamination from reagents/kit components, other samples

Internal controls

- Spiked into patient samples
- Monitoring of sample preparation and sequencing
- Monitoring of sample composition

Sample Composition & Analytical Sensitivity

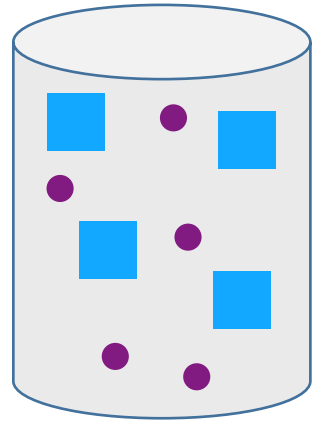
Analytical sensitivity: sequencing depth

- Number of sequencing reads
- Sensitivity proportional to abundance and genome size
- More sequencing reads = higher sensitivity

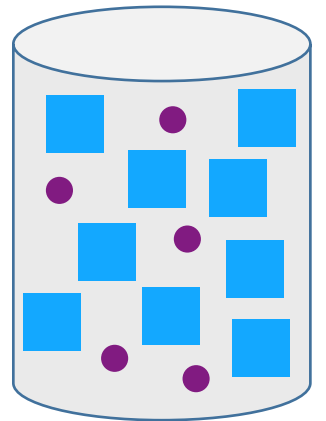
Analytical sensitivity: sample composition

- Pathogen nucleic acid competes with other nucleic acid
- Sensitivity dependent on concentration of other nucleic acids
- Read binning -> sample composition
- Internal control to identify samples with low analytical sensitivity

Higher Sensitivity



Lower Sensitivity



Universal Pathogen Detection in Pneumonia

- List of 200+ relevant viruses, bacteria, fungi
 - Fully validated
- Other potentially pathogens
 - Reported as incidental findings after review
- 24-48 hour in lab turn-around time
- Enhanced report
 - Sample composition
 - Qualitative results
 - Quantification of relevant pathogens
 - Select antimicrobial resistance genes
 - References for unusual pathogens

Test Code	Target
2010775	<i>M. tuberculosis</i> PCR
0060122	Bacterial culture
0060093	Nocardia culture
0060149	Fungal culture
2004589	Fungal stain
0065005	HSV by culture
2007805	Resp. viruses by PCR
0060040	CMV by PCR
2006254	<i>P. jiroveci</i> by PCR
0060715	<i>C. pneumoniae</i> by PCR
0060256	<i>M. pneumoniae</i> by PCR
2003150	<i>Aspergillus</i> antigen detection

Summary

- *Data analysis is complex, solutions exist*
- *Universal pathogen detection by NGS now feasible*
- *Universal pathogen detection detects previously missed pathogens*
- *Genomic characterization of pathogens provides valuable information*
- *Analytical sensitivity is sample dependent*
- *Promising for syndromic testing in vulnerable patients*
 - *Seriously ill*
 - *Immunocompromised*
 - *Elderly, young infants*

Pediatric Infectious Diseases

Chris Stockmann
Carrie Byington
Anne Blaschke
Krow Ampofo
Andy Pavia

Human Genetics

Steven Flygare
Brett Kennedy
Mark Yandell

CDC

Seema Jain
Sue Tong
Krista Queen
Dean Erdman

Biomedical Informatics

Keith Simmon
Karen Eilbeck

Pathology, ARUP

Keith Tardif
Erin Graf
Karl Voelkerding

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UNIVERSITY OF UTAH
SCHOOL OF MEDICINE

Center for Clinical & Translational Science