Harnessing the Host Response for Real Time Clinical Decision Making in Infectious Diseases

Christopher Woods MD, MPH
Professor of Medicine, Pathology, and Global Health
Duke University

Duke Center for Applied Genomics & Precision Medicine
Duke Global Health Institute
Duke-NUS Emerging Infections Program
Durham VA Medical Center
Disclosures

• Predigen: Co-Founder

Patents

*US 8821876. Methods of identifying infectious disease and assays for identifying infectious disease.*

• Abbott Molecular/Ibis Diagnostics R
• Biofire/bioMerieux A,R
• Becton Dickinson A,R
• BioMeme R
• Cepheid R
• Elitech R
• GenMark R
• Giner R
• GSK R
• IDbyDNA A
• Luminex/Nanosphere A
• Merck R
• OnSiteGene R
• Qiagen R
• Qvella R
• Roche Molecular R
• Sanofi R

A=Advisory, R=Research Contract/Grant

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### Program Leadership & Administration
- Geoffrey S. Ginsburg, MD, PhD
- Donna Crenshaw, PhD
- Lori Orlando, MD
- Tim Veldman, PhD
- Pamela Smith
- Ytina Mangum, MS
- Cherre Bethea

### Data and Statistical Analysis
- Ricardo Henao, PhD
- Joseph Lucas, PhD
- Lawrence Carin, PhD
- Alfred Hero, PhD
- Ashlee Valente, PhD
- Larry Park, PhD
- Rachel Myers, PhD
- Sunil Suchindran, PhD
- Chuan Gao, PhD
- Marshall Nichols, MS
- Ram Chakraborty, BS
- Vaishnavi Venkat, MS

### Antibacterial Resistance Leadership Group
- Durham VA Medical Center
- Henry Ford Hospital
- University of Michigan
- DoD (DARPA, DTRA, USAMRIID)
- Gates Foundation
- Brigham and Women’s Hospital

### Laboratory and Sample Management
- Tom Burke, PhD
- Brad Nicholson, PhD
- Anna Mazur
- Olga Better
- Carlos Ramirez
- Mert Aydin
- Pam Isner

### Federal Partners
- NIH/NIAID
- CDC
- BioFire Diagnostics
- Ibis Diagnostics
- Durham VA Medical Center
- UNC-Chapel Hill
- Qvella

### Other Partners
- National Center for Genome Resources
- ACESO/Henry M. Jackson Foundation
- Coulter Foundation
- University of Utah
- Applied Genomics – ID
- hVivo/Retroscreen
- Imperial College
- BioFire Diagnostics
- Ibis Diagnostics
- Qvella
- CDC
- NIH/NIAID
- Durham VA Medical Center
- UNC-Chapel Hill
Is It Just a Cold? The Flu? Or More?

- 17-year-old college student
- Develops fevers, mild headache
- Seen at student health, discharged “viral syndrome”
- Becomes confused, roommates take to ED
- T = 38.9, BP 90/70, HR 110

Emergence of Antimicrobial Resistance

- As much as 50% of the time, antibiotics are prescribed when NOT NEEDED
- Antibiotics are frequently misused for upper respiratory tract infections, most of which are caused by viruses
  - Need for clinical diagnostic support for providers

Antibiotic resistance threats in the United States, 2013
http://www.cdc.gov/drugresistance/threat-report-2013/
Etiology of Pneumonia in the Community (EPIC)

Adults

- No pathogen detected (62%)
- Viral pathogen only (22%)
- Bacterial–viral co-detection (3%)
- Bacterial pathogen only (11%)
- Fungal or mycobacterial detection (1%)

Children

Detection of Bacterial and Viral Pathogens

The Human Experimental Model: Host Response to Exposures

Multi-dimensional Models of Health and Disease

- Gene Expression
- Protein Expression
- Metabolite Expression
- Phenotypic Data
RNA Classifiers in Medical Practice Today

Cancer Diagnosis and Prognosis

- **Oncotype DX®**: 21 gene RNA signature from breast tumor; 12 gene RNA signature from colon tumor
- **MammaPrint®**: 70 gene RNA signature from breast tumor (FDA approved)
- **BluePrint™**: 80 gene RNA signature that distinguishes basal, luminal and ERBB2 subgroups of breast cancer
- **Pathwork® Tissue of Origin Test**: 2,000 RNAs to classify cancer of unknown primary (FDA approved)

Cardiovascular Disease Diagnosis and Prognosis

- **AlloMap®**: 11 blood gene RNA signature for rejection following cardiac transplant (FDA approved)
- **Corus™ CAD**: 23 gene blood RNA signature for coronary artery disease
- **Triage® Cardiac Panel**: 5 blood protein signature for assessment of chest pain and shortness of breath
Targeting the Host Response

Adapted from Ramilo and Mejias, Cell Host Microbe, 2009. 6(3): p. 199-200.
Science of Host Response

Sample acquisition
Examples: serum, plasma, saliva, nasal wash, urine

Measurements
Epigenomics
Transcriptomics
Genomics
Metagenomics
Microbiomics
Metabolomics
Proteomics
Lipidomics

Dimension Reduction and Statistical Analysis

Classifier and Signature for susceptibility, diagnosis, or prognosis

Validation

>40 Publications
Viral Infection
Pre-Symptomatic Viral Infection
Bacterial vs. Viral Infection
Fungal Infection
Sepsis Diagnosis
Sepsis Prognosis
Aspirin Responsiveness
Cardiovascular Risk Prediction
Febrile Illness: Nepal

• Active surveillance for consecutive cases of febrile illness in adult non-surgical patients
  – Axillary temp ≥38.0°C
  – ≥14 years
  – Informed consent
• Wet season: July - August

• Patan Hospital, Kathmandu
  – 251 beds
  – 250,000 outpatients
  – 30,000 ER visits
Nepal: Microbiological Diagnoses and Host Response

- Single-agent, well-established Dx, on arrays: n=76
- Also 7 healthy local donors

<table>
<thead>
<tr>
<th>Etiologic Agent</th>
<th>n</th>
<th>Age (Median)</th>
<th>Temp (F) (Median)</th>
<th>WBC (Median)</th>
<th>Sxs (days) (Median)</th>
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<td>4</td>
<td>30</td>
<td>101.9</td>
<td>12.15</td>
<td>2.5</td>
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<tr>
<td>Leptospira</td>
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<td>26</td>
<td>100.9</td>
<td>6.5</td>
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<td><em>O. tsutsugamushi</em></td>
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<td>101.4</td>
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<td>102</td>
<td>6</td>
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</table>

* typhi (22), paratyphi (18)

Murdoch et al; AJTMH 70(6): 670-675  2004
DARPA: Predicting Health and Disease

Develop a predictor of incipient respiratory viral infection following exposure

Healthy Volunteers → Standard Viral Challenge → 5 Day Observation

Samples:
- Transcriptome
- Proteome
- Clinical Predictors
- Metabolome

Candidate Biomarkers

APPLIED GENOMICS & PRECISION MEDICINE
Host Gene Expression Classifier for Acute Respiratory Infection

97% accuracy for viral vs no viral infection

Zaas et al, Cell Host and Microbe, 2009
Woods et al PLoS ONE 2013
Ramilo et al Blood 2007
How early does the viral classifier identify those who will become sick?
Pre-Symptomatic detection in naturally-acquired infection?

- Study design aiming to capture pre-symptomatic upper respiratory infection in a native infection environment.
- Living groups loosely defined as the same floor of the same dorm, or subject-identified contacts.
- Online surveys include collection of modified Jackson Symptom Score for upper respiratory infection.
- Symptomatic individuals defined as those with an increase of 6 or greater in symptom score over a 5 day window.
- Blood samples collected for host transcriptomics, Nasal lavage samples collected for viral etiology testing.
- Not all Close Contacts become symptomatic.
- Not all Close Contacts becoming symptomatic do so at the same time.
Viral etiologies of URI in the Student Cohort

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<td>18</td>
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<td>4</td>
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<td>Parainfluenza</td>
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<td>0</td>
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<td>Rhinovirus</td>
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<td>25</td>
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<td>6</td>
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<td>Coronavirus</td>
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<td>19</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>61</td>
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<tr>
<td>Coxsackie/Echovirus</td>
<td>24</td>
<td>23</td>
<td>10</td>
<td>ND</td>
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<td>Adenovirus</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Metapneumovirus</td>
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<td>0</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>17</td>
</tr>
</tbody>
</table>

On Average: 54% of Index Cases have + Viral Etiology
17% have multiple viruses

15% of Close Contacts have + Viral Etiology
57% of these match their Index Case
Performance accuracy of a gene signature of viral infection across time
Early Detection, Early Cure:
Early Oseltamivir Reduces Symptom and Classifier Intensity

McClain et al, Open Forum of Infectious Diseases, 2016
Resisting antibiotics
Pathogen-specific changes in host gene expression stem emerging drug resistance

Host gene expression classifiers diagnose acute respiratory illness etiology

Deriving a Host Response ARI Classifier
Deriving a host response ARI Classifier

• Training cohort of host gene expression measured by microarray

• Generate binary classifiers
  – Bacterial vs. Non-Bacterial (71 genes)
  – Viral vs. Non-Viral (33 genes)
  – Non-Infection vs. Infection (26 genes)

• Apply all three classifiers to each individual

• Generate three discrete probabilities for each condition

• Highest probability wins
Viral ARI Classification

104/115 correctly identified (90%)
145/158 correctly excluded (92%)
Viral ARI Classification

16 year old adolescent with fever, cough, sore throat, myalgias.

PCR+ for Influenza 2009 H1N1.

p(Viral ARI) = 98.7%

p(SIRS) = 1.4%

p(Bacterial ARI) = 0.09%
Bacterial ARI Classification

58/70 correctly identified (83%)
179/191 correctly excluded (94%)
Bacterial ARI Classification

60 year old man with liver transplant developed pleuritic chest pain, fever.

CT showed consolidative opacities.

Found to have *S. aureus* bacteremia.
Non-Infectious SIRS Classification

Infection excluded in 76/88 cases (86%)
SIRS Classification

62 year old woman with non-small cell lung cancer developed dyspnea, hemoptysis, and hypoxia. CT showed increased size of mass-like opacity.

Probability Bacterial ARI: 0.14%
Probability Viral ARI: 2.5%
Probability Non-Infectious: 97.9%
External Validation Studies

- AUC 0.95
- AUC 0.90
- AUC 0.93
- AUC 0.99

Includes adults and children; mild infection and severe infection; inpatients and outpatients; US and international
Migration of Microarray Results to RT-PCR

- RT-PCR
  - 29 genes in the “Pan-Viral” Factor
  - Interferon pathway
  - Oligo adenylate synthase pathway
  - MX1
  - RSAD2
  - Control genes
Antimicrobial Resistance Rapid, Point-of-Need Diagnostic Test’ Challenge

Overview | Participation Requirements | View FAQ's | Resources | Forum | Letter of Intent | Submission Form | Executive Summary

Notice

Antimicrobial Resistance Diagnostic Challenge selects 10 semifinalists in first phase of competition

Each will receive $50,000 to develop prototypes of diagnostics to improve detection of drug resistant bacteria

Ten semifinalists have been selected in the first phase of the Antimicrobial Resistance Diagnostic Challenge, a federal prize competition that will award up to a total of $20 million in prizes, subject to the availability of funds, for innovative rapid, point-of-need diagnostic tests to combat the emergence and spread of drug resistant bacteria. The semifinalists were selected for their concepts for a diagnostic based on a technical and programmatic evaluation from among 74 submissions. While semifinalists will each receive $50,000 to develop their concepts into prototypes, anyone can submit a prototype to compete in the second phase of the challenge to win up to $100,000.

Read the Full Press Release
Antibacterial Resistance Leadership Group

**Four Priority Areas**
- Gram-negative bacteria
- Gram-positive bacteria
- Infection Control/Stewardship
- Diagnostics
Rapid Diagnostics in Categorizing Acute Lung Infections (RADICAL)

**RADICAL**

**GOAL:** Validate bacterial/viral/non-infectious illness signatures

**RADICAL-2**

**GOAL:** FDA clearance for 510(k)

**RADICAL-3**

**GOAL:** Clinical utility study
Developing a Host Gene Expression Test

- Rapid
  - <5 minutes Field/Home
  - <20 minutes Outpatient
  - <1hr ER
  - <4 hours hospital
- Low complexity
- Inexpensive
- Non-invasive/Minimally invasive
- High degree of multiplexing
- Integrated sample processing
Qvella

68 Whole blood samples
24 healthy controls
19 viral infections
15 bacterial infections
10 SIRS (non-infectious)

Data Analysis

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<table>
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<tr>
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<tr>
<td>True positive rate</td>
<td>19/19</td>
<td>100%</td>
</tr>
<tr>
<td>(sensitivity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True negative rate</td>
<td>48/49</td>
<td>98%</td>
</tr>
<tr>
<td>(specificity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>67/68</td>
<td>98.5%</td>
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</table>
BioFire Pilot Data
50 subjects, 88% overall accuracy

Proportions

<table>
<thead>
<tr>
<th>True vs. Pred</th>
<th>Bacterial</th>
<th>Viral</th>
<th>SIRS</th>
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<tbody>
<tr>
<td>Bacterial</td>
<td>0.937</td>
<td>0.062</td>
<td>0.000</td>
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<tr>
<td>Viral</td>
<td>0.058</td>
<td>0.764</td>
<td>0.176</td>
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<tr>
<td>SIRS</td>
<td>0.000</td>
<td>0.058</td>
<td>0.941</td>
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<tr>
<th>Classifier</th>
<th>AUC</th>
<th>TPR</th>
<th>TNR</th>
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<tbody>
<tr>
<td>Bacterial</td>
<td>0.936</td>
<td>0.938</td>
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<td>Viral</td>
<td>0.923</td>
<td>0.882</td>
<td>0.909</td>
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<tr>
<td>SIRS</td>
<td>0.984</td>
<td>1.000</td>
<td>0.909</td>
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</tbody>
</table>
BioFire – Host Response B/V Test

• FilmArray pouch with host response targets for viral infection and bacterial infection
• Can identify viral infection, bacterial infection, co-infection, or non-infectious illness
• 325 subjects tested
  – 117 Bacterial
  – 165 Viral
  – 103 Non-infectious illness
BioFire – Host Response B/V Test

Clinical Adjudication
- Bacterial
- Viral
- Non-Infectious Illness

Area under the curve (AUC)
- Bacterial – 0.92
- Viral – 0.92
- Non-Infectious Illness – 0.89
Probability of viral infection vs. probability of bacterial infection. The vertical dashed line is the threshold (.263) which maximizes the bacterial test AWA (87%). The horizontal line is the threshold (.361) which maximizes the viral test AWA (85%). Blue = adjudicated bacterial infection; red = viral infection; gold = non-infectious illness. Each circle represents one subject.

Average Weight Accuracy

Bacterial – 87%
Viral – 85%
Co-Infection
Modeling the impact of signature size on predicted accuracy as measured by leave one out cross validated (LOOCV) area under the curve (AUC).

Achieving Sparsity
ANNOUNCEMENTS
December 3, 2018
Antimicrobial Resistance Diagnostic Challenge names five finalists

Host gene expression to classify viral and bacterial infection using multiplex PCR
Ephraim Tsalik, Duke University, Durham, North Carolina
Rapid Diagnostics in Categorizing Acute Lung Infections (RADICAL)

**RADICAL**
- **GOAL:** Validate bacterial/viral/non-infectious illness signatures

**RADICAL-2 Analytical & Clinical Validation**
- **GOAL:** FDA clearance for 510(k)

**RADICAL-3 Clinical Utility**
- **GOAL:** Clinical utility study
RADICAL-2

• 1200 subject validation
• Enrollment 2017 – 2019
• Results will be used to validate available platforms (e.g., BioFire)
• Support FDA application
RADICAL 3 Design (~2020)

ED Patient with ARI

Enroll & Collect Blood Sample

RADICAL Test

Randomize Patient

Result-Guided Rx

Results Blinded, Standard of Care
How do host response-based diagnostics perform in hosts with altered immune responsiveness?

1. Host biomarker signatures for diagnosis of acute respiratory syndromes in CF patients following lung transplant. Cystic Fibrosis Foundation
   - Biobanked samples of viral and bacterial infection in normal hosts as comparators
   - Banking of CF / Lung transplant samples for future applications

2. Performance of biomarker diagnostics in an aging population (VA)
   - Biobanked samples of younger adults as comparator arm.

3. Resilience in Older Adults (UH2/UH3, NIA - Whitson, Colon-Emeric)
   - Biobanked samples of older adults with respiratory infections – biomarker discovery for resilience to infection
Diagnostics– in vitro PBMC Modeling

- Bonferroni correction
- 174 significant with threshold 0.01

- Sparse linear classifier
- Leave-one-out cross-validation

Candida and Crypto

max AUC 0.9856
threshold: 0.1308
TPR: 0.9444
TNR: 0.9848
probes: 25
Diagnostic host genomic signatures can be stable across multiple forms of host immunosuppression

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Classifier-Predicted Condition</th>
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<tr>
<td></td>
<td>Aspergillus</td>
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<tr>
<td>Aspergillus</td>
<td>11</td>
</tr>
<tr>
<td>Aspergillus + prednisone</td>
<td>0</td>
</tr>
<tr>
<td>Aspergillus + cyclophosphamide</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>2</td>
</tr>
<tr>
<td>Control + prednisone</td>
<td>0</td>
</tr>
<tr>
<td>Control + cyclophosphamide</td>
<td>0</td>
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</tbody>
</table>

Murine aspergillus infection model. Numbers in the diagonal dark blue cells indicate correct classifications.
Host-derived genomic signature of human candidemia
NIAID R21
Elderly vs Young Veterans with viral URI: Differentially expressed genes
Global Febrile Illness

- **Durham, NC**
  - Enterobacteria
  - Influenza A & B
  - RSV
  - Staph
  - Strep
  - Noninfectious

- **Kenya**
  - Flu A/B
  - RSV

- **Tanzania**
  - *Brucella*
  - Leptospirosis
  - Spotted Fever

- **Sri Lanka**
  - Dengue
  - Influenza A & B
  - Leptospirosis
  - RSV
  - Scrub typhus
  - Noninfectious

- **Nepal**
  - Enterobacteria
  - Leptospirosis
  - Scrub
  - *S. paratyphi*
  - *S. typhi*
# Global Fever mRNA classifiers: Discovery

<table>
<thead>
<tr>
<th>Class: 338</th>
<th>Pathogen</th>
<th>Duke</th>
<th>Sri Lanka</th>
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<td><strong>Bacterial: 128</strong></td>
<td><em>Staphylococcus</em> spp.</td>
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<td></td>
<td><em>Streptococcus</em> spp.</td>
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<tr>
<td></td>
<td>Gram Negative Rods (<em>E.coli</em> &amp; <em>K. pneumoniae</em>)</td>
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<td><em>Leptospira</em> spp.</td>
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<td></td>
<td><em>Coxiella burnetii</em></td>
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<tr>
<td></td>
<td>Scrub Typhus</td>
<td>22</td>
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<td></td>
<td>Spotted Fever Group</td>
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<td><strong>Viruses: 138</strong></td>
<td>Respiratory viruses: Flu A/B</td>
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<td>RSV</td>
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<tr>
<td></td>
<td>Dengue</td>
<td></td>
<td>40</td>
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<td></td>
<td><strong>NI-SIRS: 72</strong></td>
<td><strong>NI-SIRS</strong></td>
<td>69</td>
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</table>
Global Fever mRNA classifier: Validation and Exploratory

Bacterial/Viral Co-Infection: Duke/Sri Lanka (7)
QC checks (possible mismatch): Duke/Sri Lanka (7)
Updated etiology: Duke/Sri Lanka (21)
Bacterial/Parasitic Co-Infection: Tanzania (2)

Confounded Sites:

<table>
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<tr>
<th></th>
<th>Tanzania</th>
<th>Nepal</th>
<th>Emory</th>
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<tbody>
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<td><em>Zika</em></td>
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<tr>
<td><em>Dengue</em></td>
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</tbody>
</table>
Performance characteristics for predicting bacterial infection (n=338):
Sensitivity: 0.90; Specificity: 0.88
Transcriptomic Signatures Classify Ebola Deaths vs. Survivors

Liu et al. Transcriptomic Signatures Differentiate Survival from Fatal Outcomes in Humans Infected with Ebola Virus. Genome Biology August 2017
Nasal Lavage Proteomics: Peptides Detect Viral Response in Human Challenge Model

Classifier Based on 8 Targeted Peptides (leave one out cross-validation, p-value 2e-5)

Burke et al, EmBio 2017
Current and Future Directions

• Developing a model for the ‘healthy state’
• Biomarkers for
  – Durable vaccine response
  – Hospital-Acquired Infections
  – Prosthetic joint infections
  – Rickettsial infections
  – Bacterial and viral gastroenteritis
  – Pathogens of global importance (e.g., Dengue, Malaria)
• Translate biomarkers into useable diagnostic platforms
• Utility in aged, and immunosuppressed populations
• Statistical methods for complex temporal data analyses
Ongoing Programs

- NIH/NIAID/ARLG RADICAL
- DARPA Sigma Plus
- DARPA Prometheus
- DARPA Biochronicity
- DTRA Global Fever
- VA Tick Borne Illness
- VA/NIA Resilience in the Elderly
- NIH/VTEU Valley Fever Program
- NIH Candidemia
- Biomarkers in Cystic Fibrosis
- DARPA ECHO