Acute Respiratory Illness from the Host Perspective

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Clinical Conundrum

- 31 yo man with Cystic Fibrosis, colonized with *Pseudomonas aeruginosa*
- Discharged 1 week ago for flare where he received limited course of anti-Pseudomonal antibiotics
- Then develops dyspnea, abdominal cramping, diarrhea. Reports close contact to someone with a “stomach virus”.
- Sputum culture reveals *Pseudomonas aeruginosa*
- He is treated with a prolonged course of anti-Pseudomonal antibiotics for another CF flare

Trial Conundrum:
To enroll or not to enroll?

- Phase 3 trial of Drug X to treat CABP identifies an 87 year old man with congestive heart failure and multiple myeloma
- 1 week of weakness and cough
- ER evaluation: Febrile, infiltrate on chest x-ray consistent with edema or atypical infection
- Troponin and BNP elevated indicating myocardial infarction and decompensated CHF
- All microbiology is negative

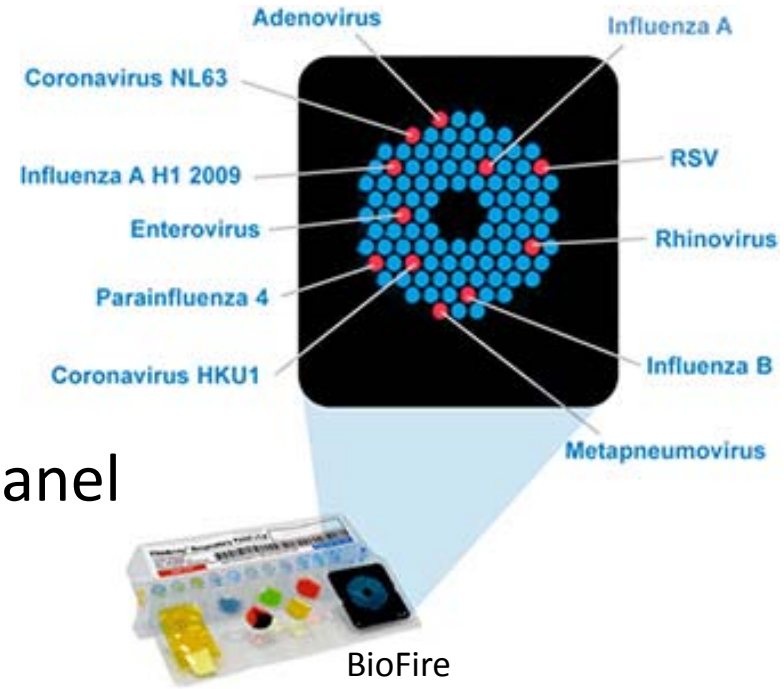
How do we ‘know’ what is happening with such patients?

Pathogen Detection

- Culture
  - Insensitive
  - Not timely

Pathogen Detection

- Culture
  - Insensitive
  - Not timely
- Multiplex PCR
  - Primarily viral targets
  - Colonization vs. Infection
  - Limited to pathogens on the panel



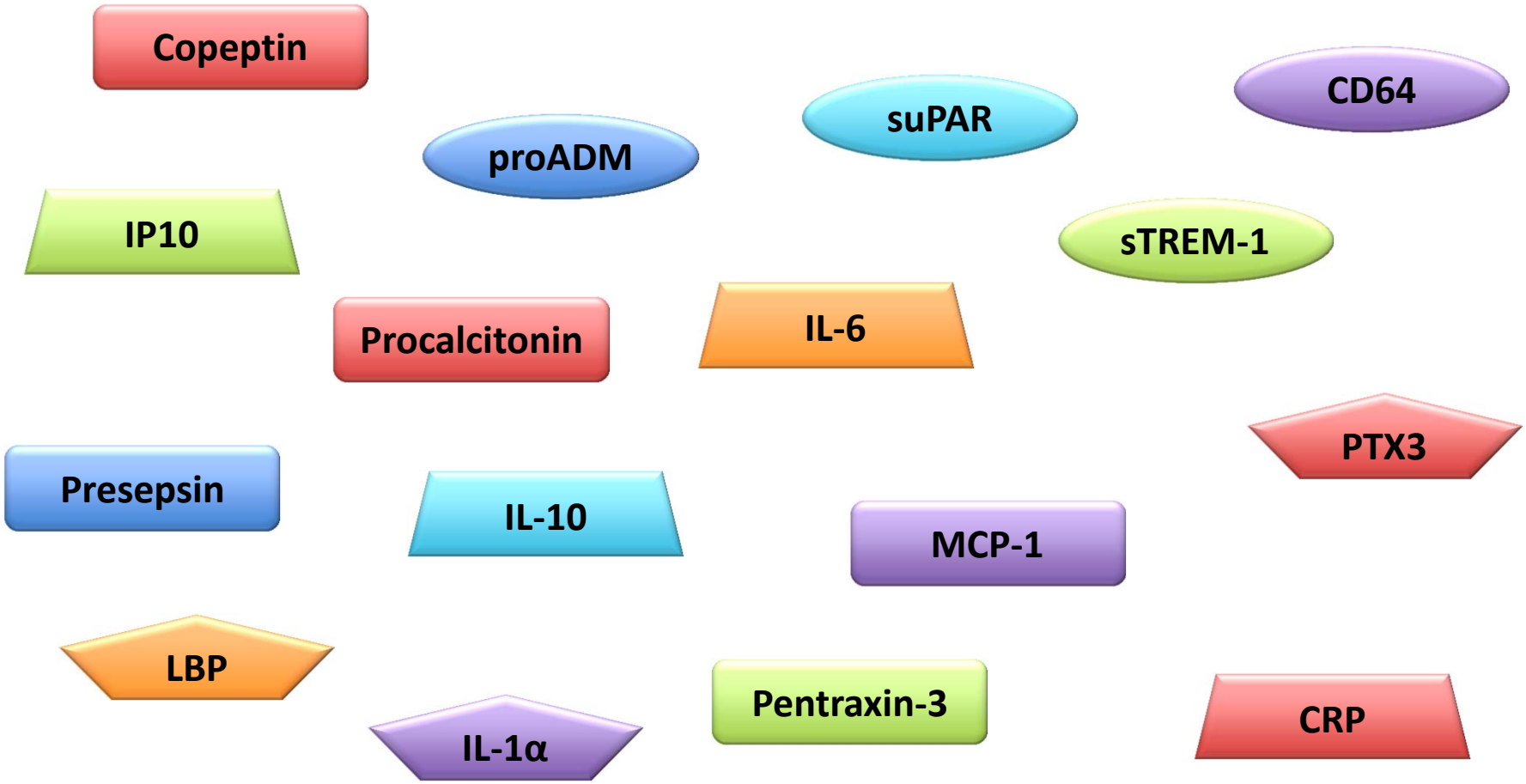
BioFire

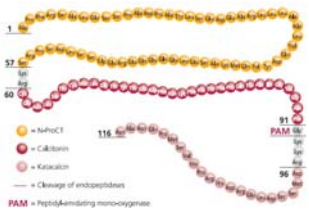
Pathogen Detection

- Culture
  - Insensitive
  - Not timely
- Multiplex PCR
  - Primarily viral targets
  - Colonization vs. Infection
  - Limited to pathogens on the panel
- Antigen detection
  - Insensitive
  - Single pathogen/assay
  - Requires *a priori* suspicion

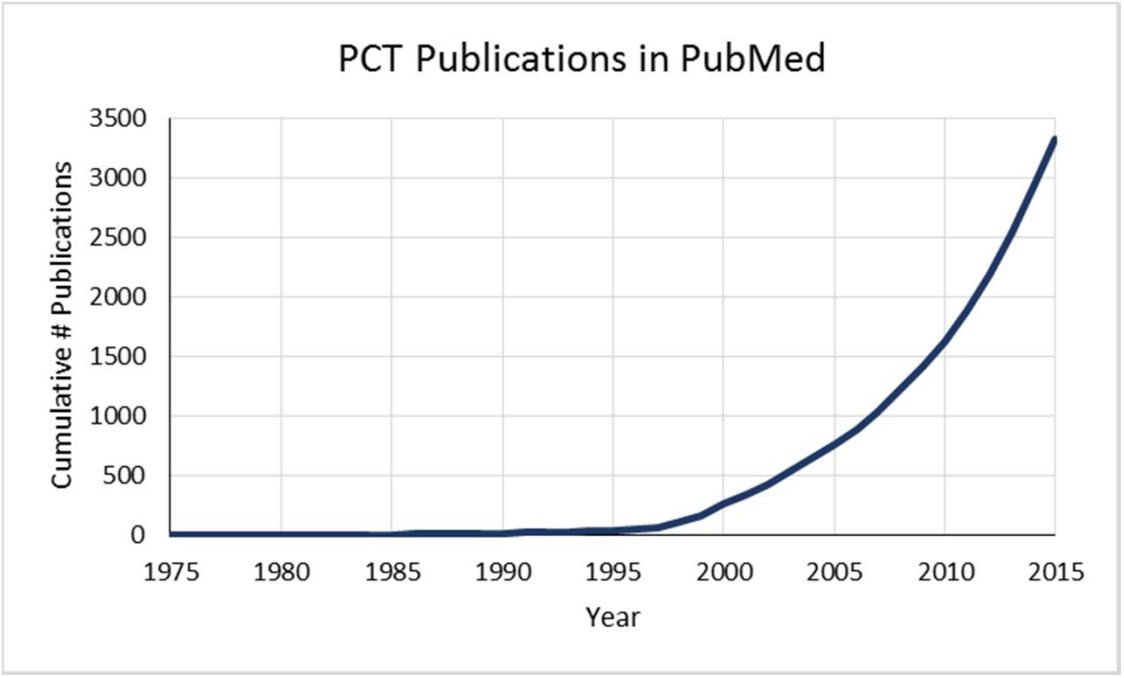
Can we **improve** our ability to ‘know’ what is happening with such patients?

Sepsis Biomarkers Galore





State of the Available Art – PCT



- Secreted by tissues in response to inflammation, particularly bacterial infection
- Inhibition by IFN-ɣ allows for bacterial vs. viral discrimination

- Whereas sepsis-related studies describe performance characteristics
- Most ARI-related studies describe PCT-directed therapy

Le Moullec et al., FEBS Lett. 1984, 167: 93-7.
Linscheid, et al., Endocrinology. 2005 Jun;146(6):2699-708.

Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections (Review)

Schuetz P, Müller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, Luyt CE, Wolff M, Chastre J, Tubach F, Kristoffersen KB, Burkhardt O, Welte T, Schroeder S, Nobre V, Wei L, Bhatnagar N, Bucher HC, Briel M

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Cochrane Database Syst Rev. 2012 Sep 12;9:CD007498.

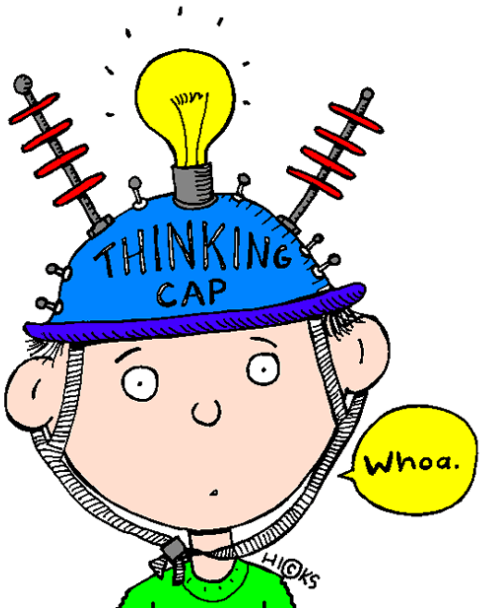
Procalcitonin algorithm compared to standard care for guiding antibiotic therapy in acute respiratory tract infections

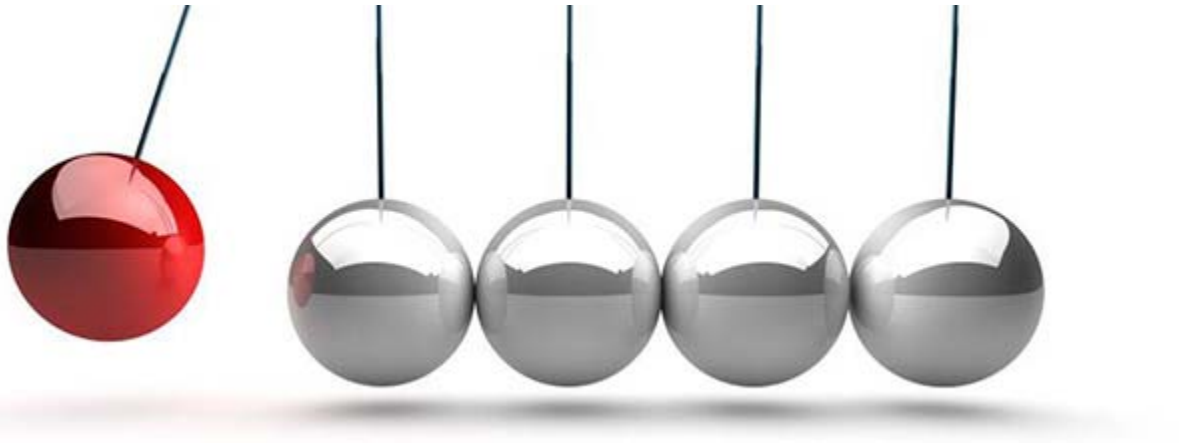
Patient or population: patients with acute respiratory tract infections
Settings: primary care, emergency department, intensive care unit
Intervention: procalcitonin algorithm
Comparison: standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard care	Procalcitonin algorithm				
Mortality Follow-up: 30 days	**Study population**		**OR 0.91** (0.7 to 1.19)	4211 (14 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
	63 per 1000	**58 per 1000** (45 to 74)				
	Moderate					
	22 per 1000	**20 per 1000** (16 to 26)				
Treatment failure Clinical assessment[3] Follow-up: 30 days	**Study population**		**OR 0.83** (0.71 to 0.97)	4211 (14 studies)	⊕⊕⊕⊖ **moderate**[4]	
	219 per 1000	**189 per 1000** (166 to 214)				
	Moderate					
	211 per 1000	**182 per 1000** (160 to 206)				
Antibiotic exposure Total days of antibiotic therapy in all randomised patients	The mean antibiotic exposure in the control groups was **8 days**	The mean antibiotic exposure in the intervention groups was **3.47 lower** (3.78 to 3.17 lower)		4211 (14 studies)	⊕⊕⊕⊖ **moderate**[4]	

Cochrane Database Syst Rev. 2012 Sep 12;9:CD007498.

Can we do better still?





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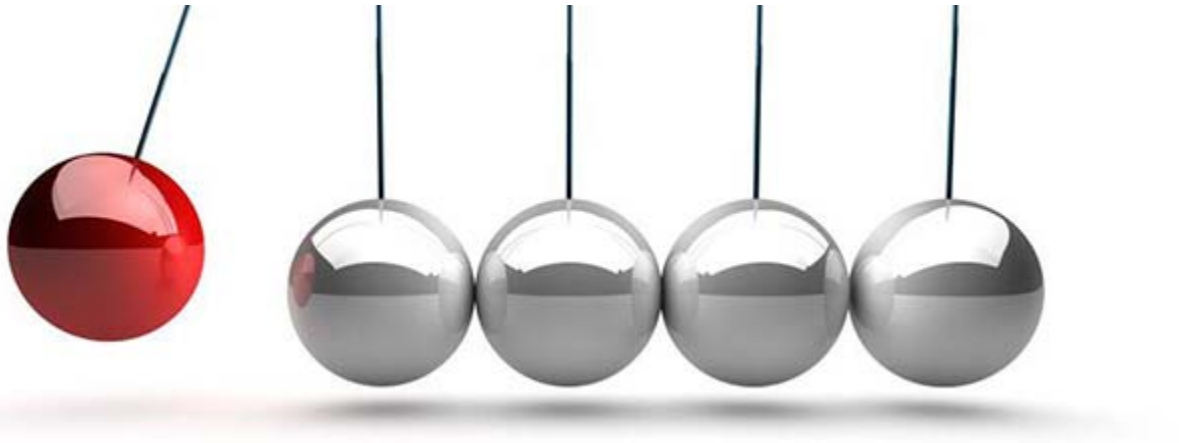

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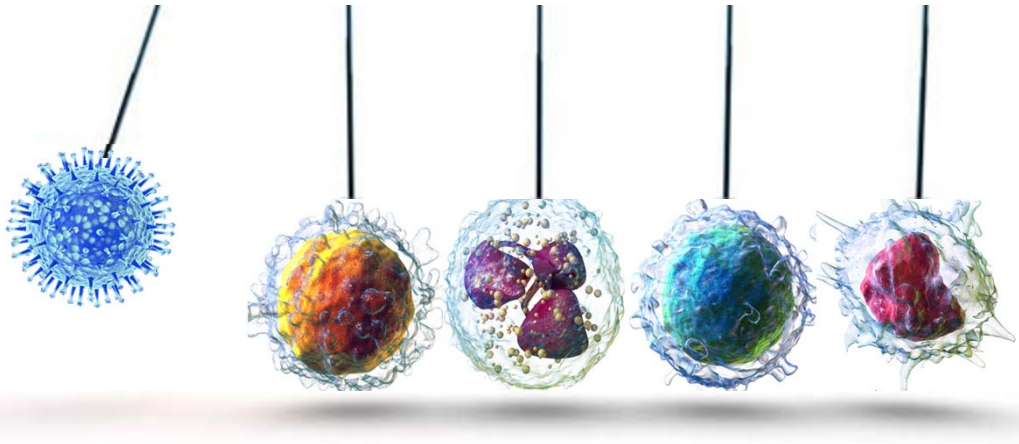

Transcriptome Proteome

Clinical Predictors Metabolome

Candidate Biomarkers

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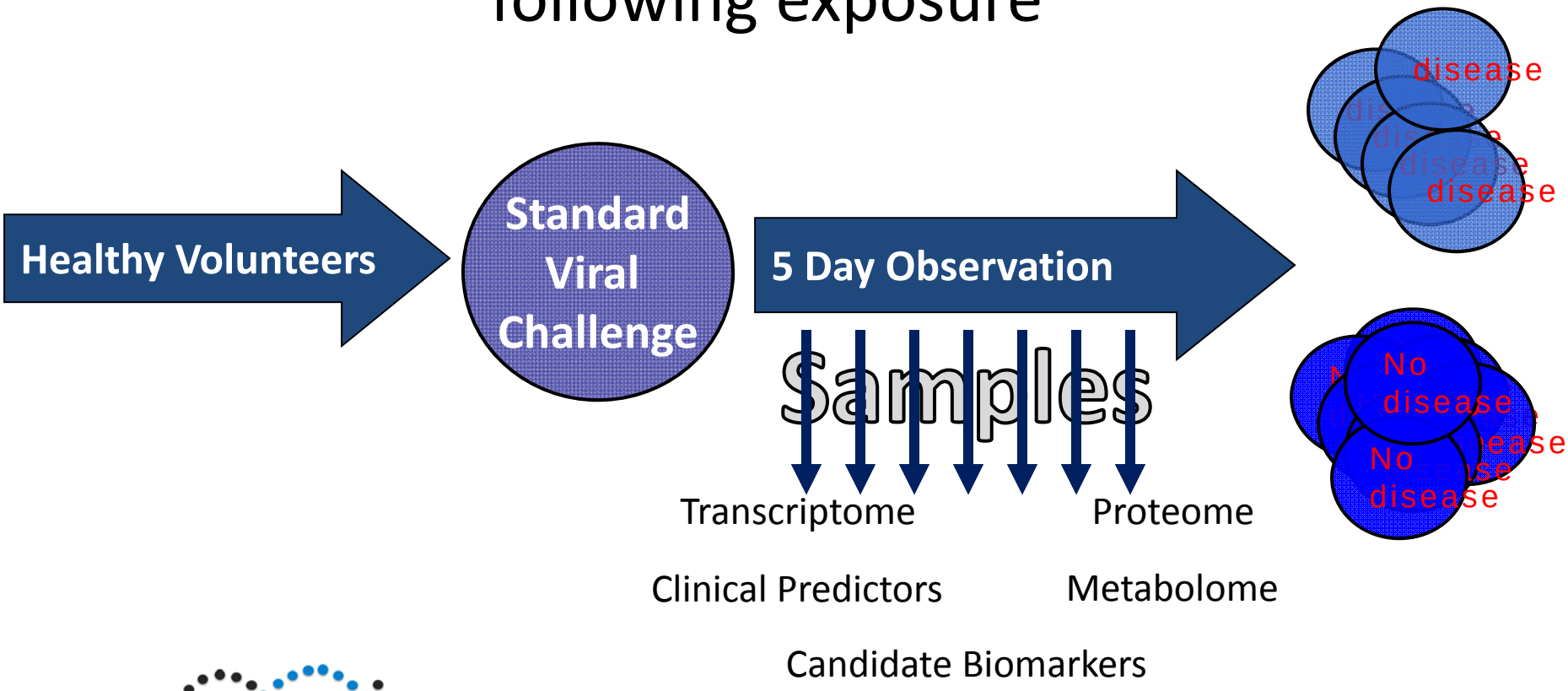
Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine.
DOI:10.15347/wjm/2014.010. ISSN 20018762. - Own work

DARPA Predicting Health and Disease

Develop a predictor of incipient viral infection following exposure



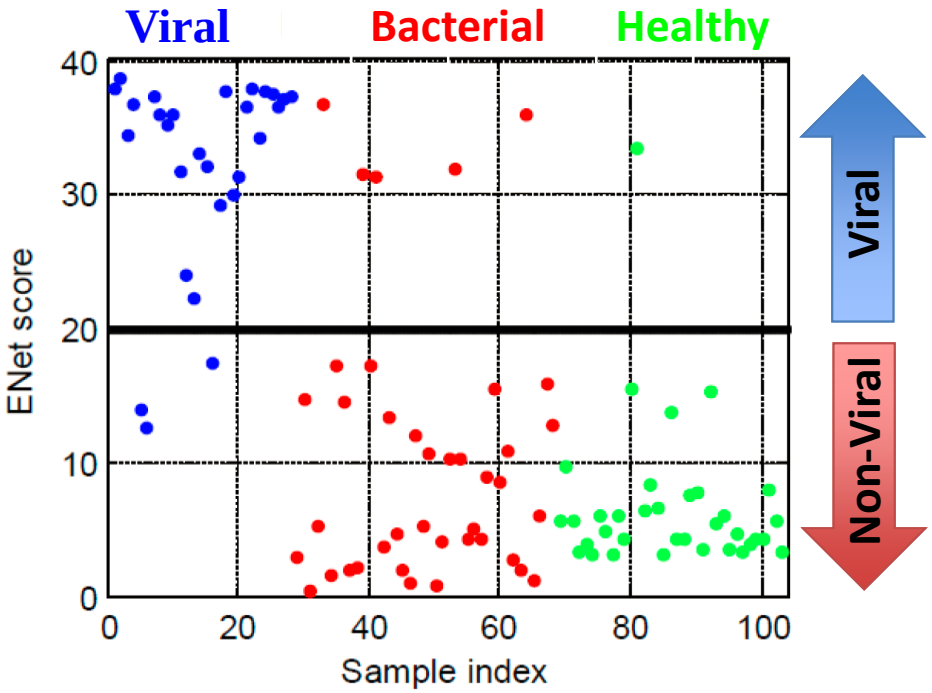
RT-PCR Diagnostic Classifies Community-Acquired Viral Respiratory Infection

48-probe classifier derived from challenge studies

Validated in 68 individuals presenting to ED with fever

Reference standard: Retrospective, blinded, adjudicated phenotypes including confirmed microbial etiology (n=29 viral, n=39 bacterial)

Controls: Healthy, uninfected adults (n =33)



Sensitivity 89%

Specificity 94%

Zaas et al., Sci Trans Med (2013)

DukeMedicine

OPEN ACCESS Freely available online

PLoS one

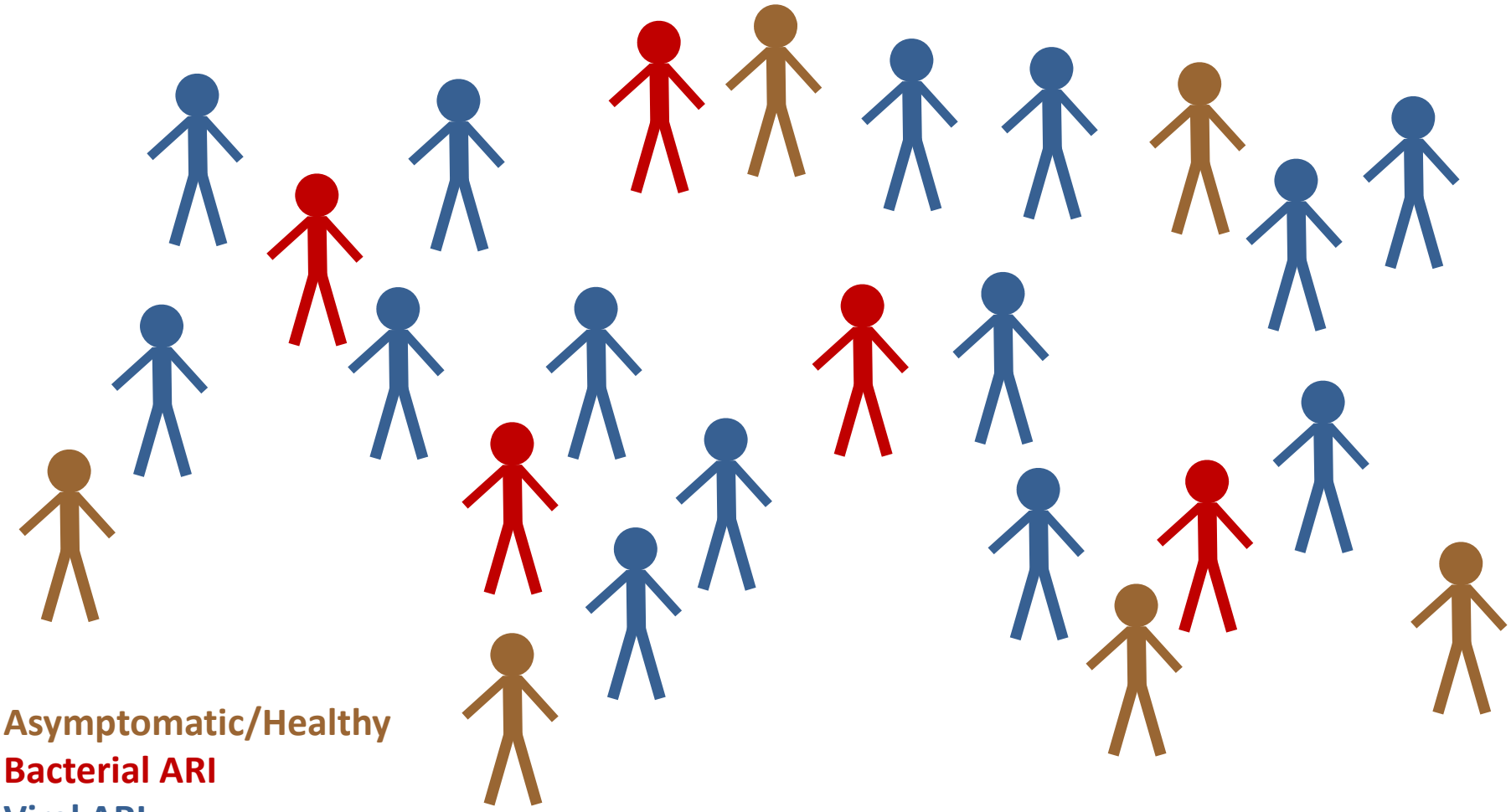
Expanding the Understanding of Biases in Development of Clinical-Grade Molecular Signatures: A Case Study in Acute Respiratory Viral Infections

Nikita I. Lytkin[1], Lauren McVoy[2], Jörn-Hendrik Weitkamp[3], Constantin F. Aliferis[1,2,4], Alexander Statnikov[1,5]*

"…molecular signatures developed and applied on different phenotypes and populations of patients should be treated with great caution."

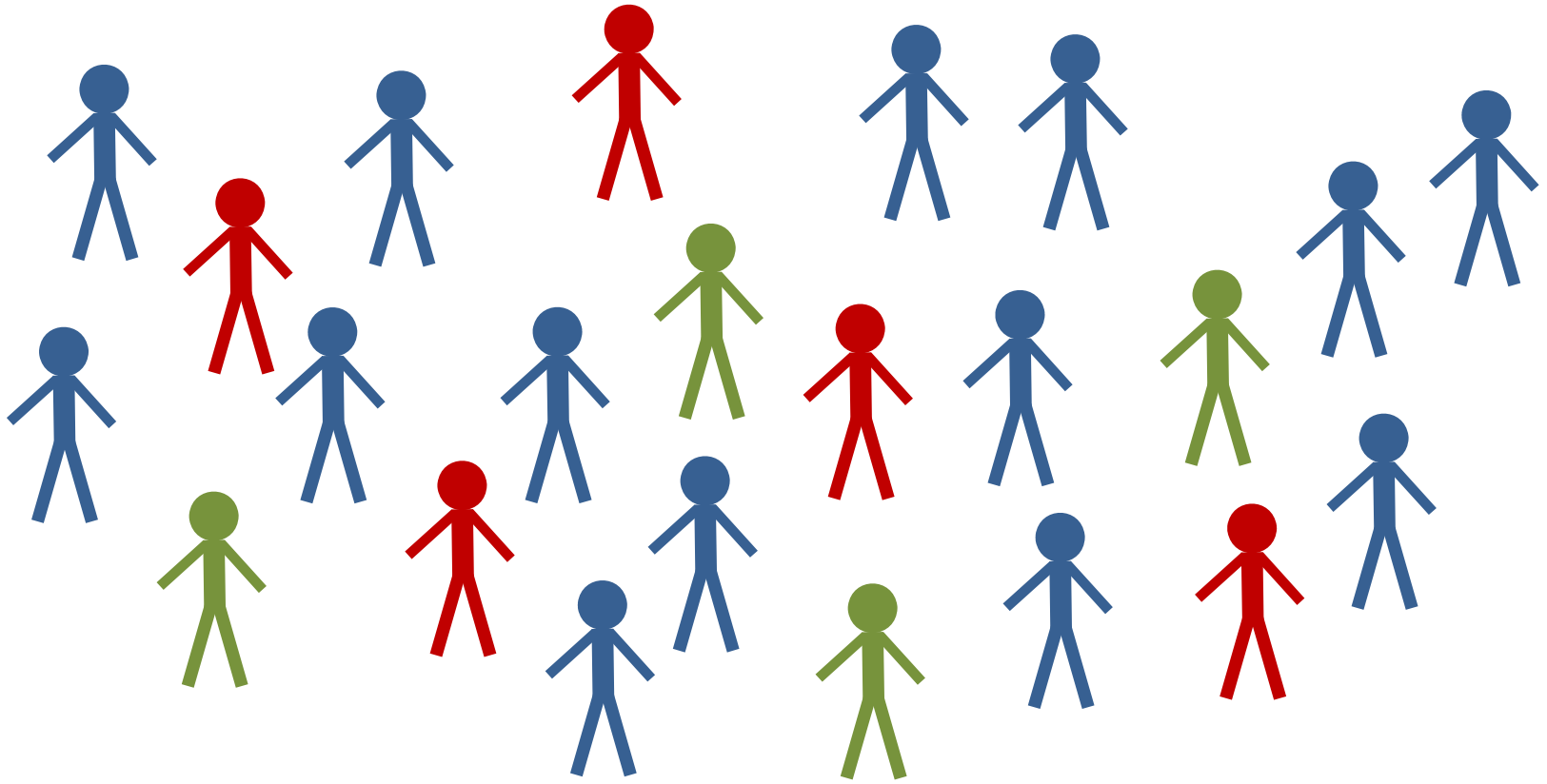
PLoS ONE 6(6): e20662. 2011.

Who is the Target Population?



Asymptomatic/Healthy
Bacterial ARI
Viral ARI

Those with Suspected ARI



Bacterial ARI
Viral ARI
Sick but not due to infection

Defining the Reference

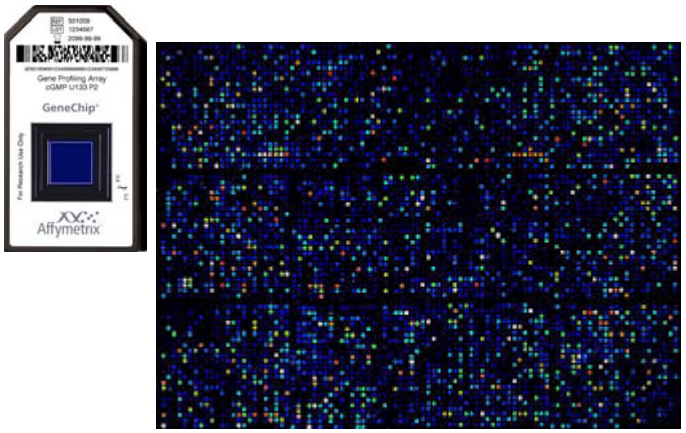
- Retrospective, blinded adjudications
- Patient symptoms, physical examination, radiographic findings, routine laboratory testing, augmented pathogen detection
- Bacterial or Viral ARI required a compatible clinical syndrome and positive microbiology
- No Infection/SIRS subjects had a clinically confirmed alternative, non-infectious diagnosis

Deriving a Host Response ARI Classifier

- Bacterial ARI (n=70)
  - Pneumonia, GAS pharyngitis
- Viral ARI (n=115)
  - Coronavirus, Coxsackie/Echovirus, CMV, Enterovirus, Metapneumovirus, Influenza, Parainfluenza, Rhinovirus, RSV
- SIRS due to Non-Infectious Etiologies (n=88)
- Healthy controls (n=44)

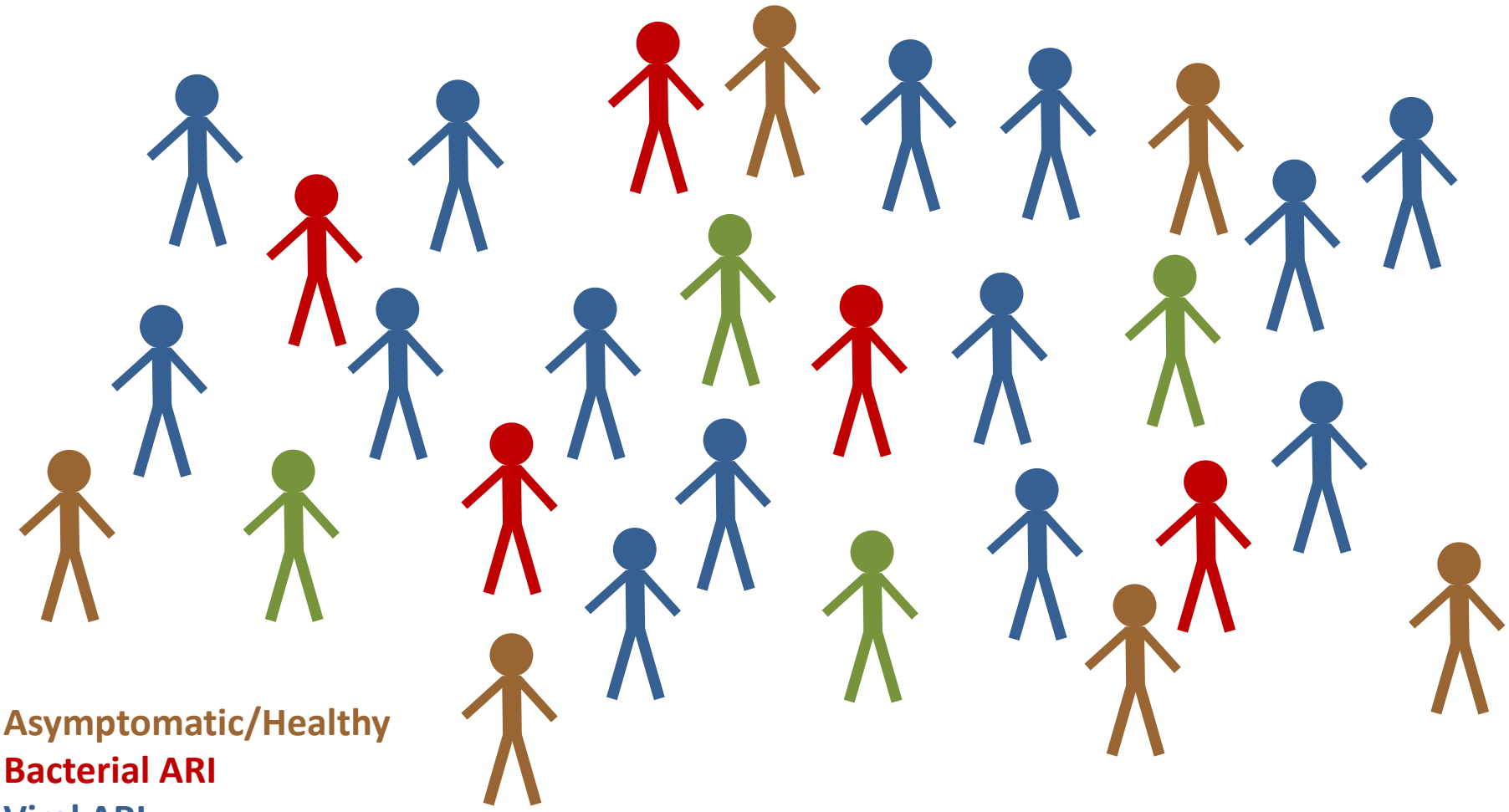
Deriving a Host Response ARI Classifier

- Host gene expression measured by microarray



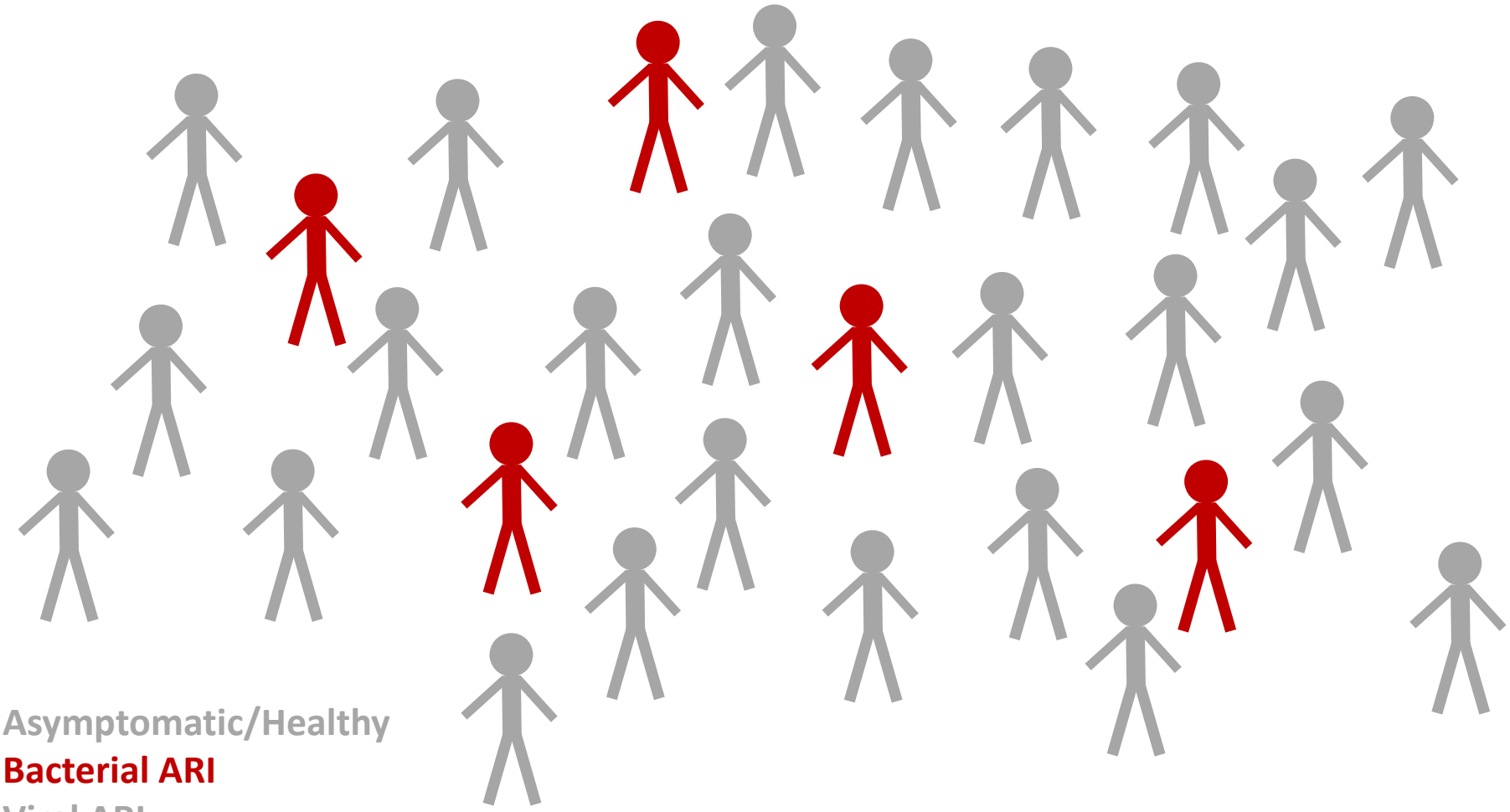
- Generate binary classifiers
  - Bacterial vs. Non-Bacterial
  - Viral vs. Non-Viral
  - Non-Infection vs. Infection

Study Population



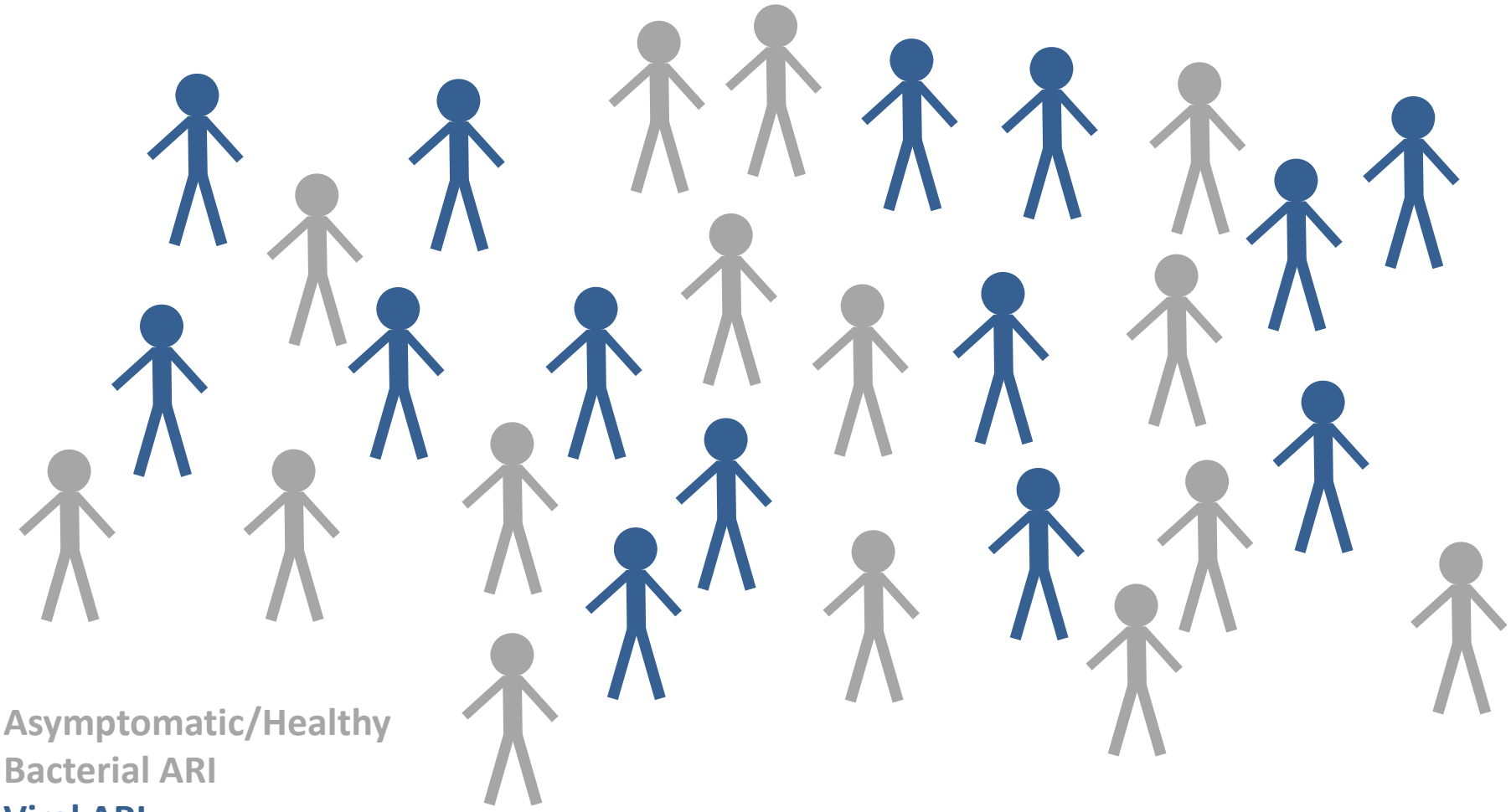
Asymptomatic/Healthy
Bacterial ARI
Viral ARI
Sick but not due to infection

Bacterial ARI Classifier



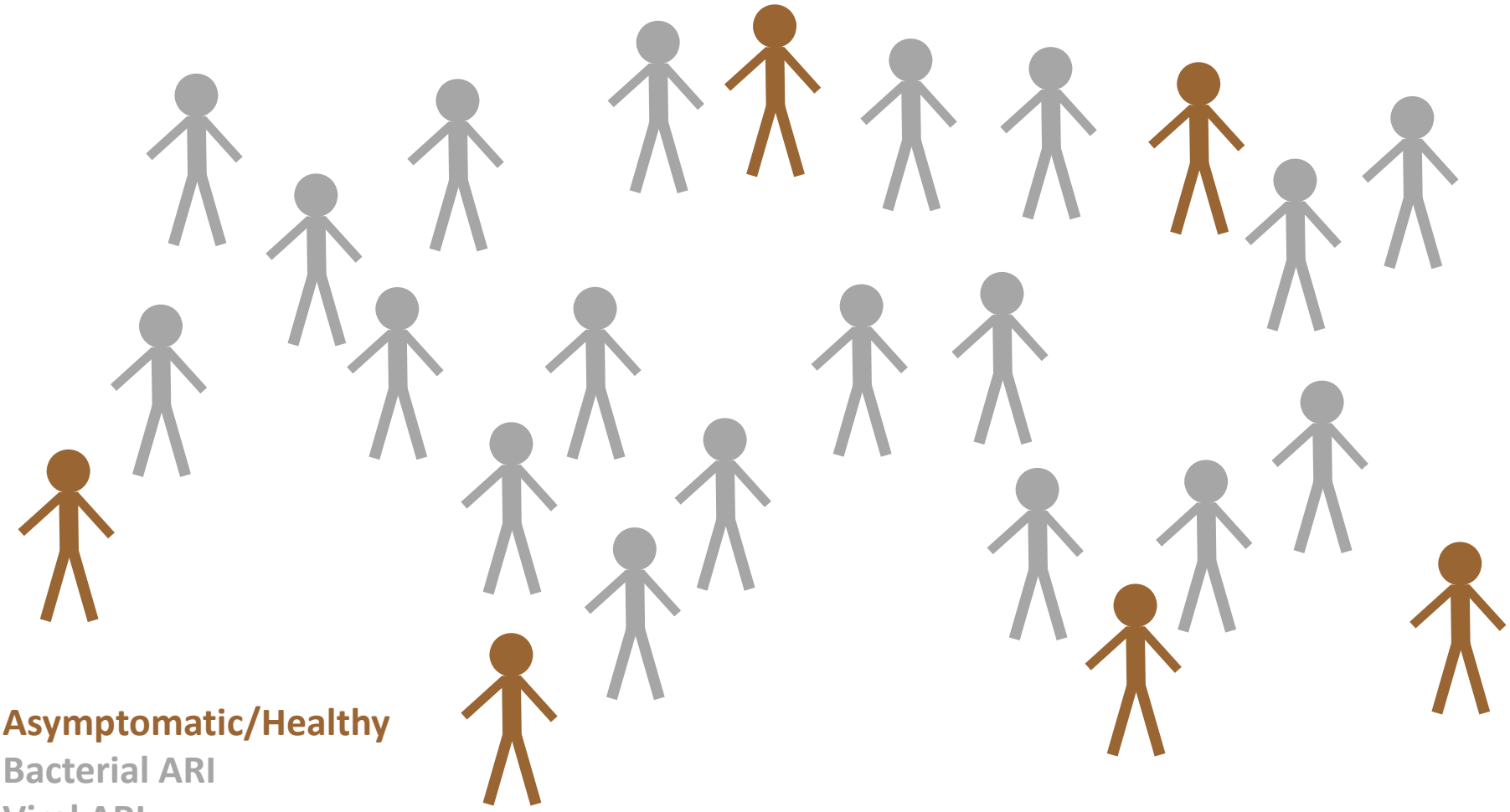
Asymptomatic/Healthy
Bacterial ARI
Viral ARI
Sick but not due to infection

Viral ARI Classifier



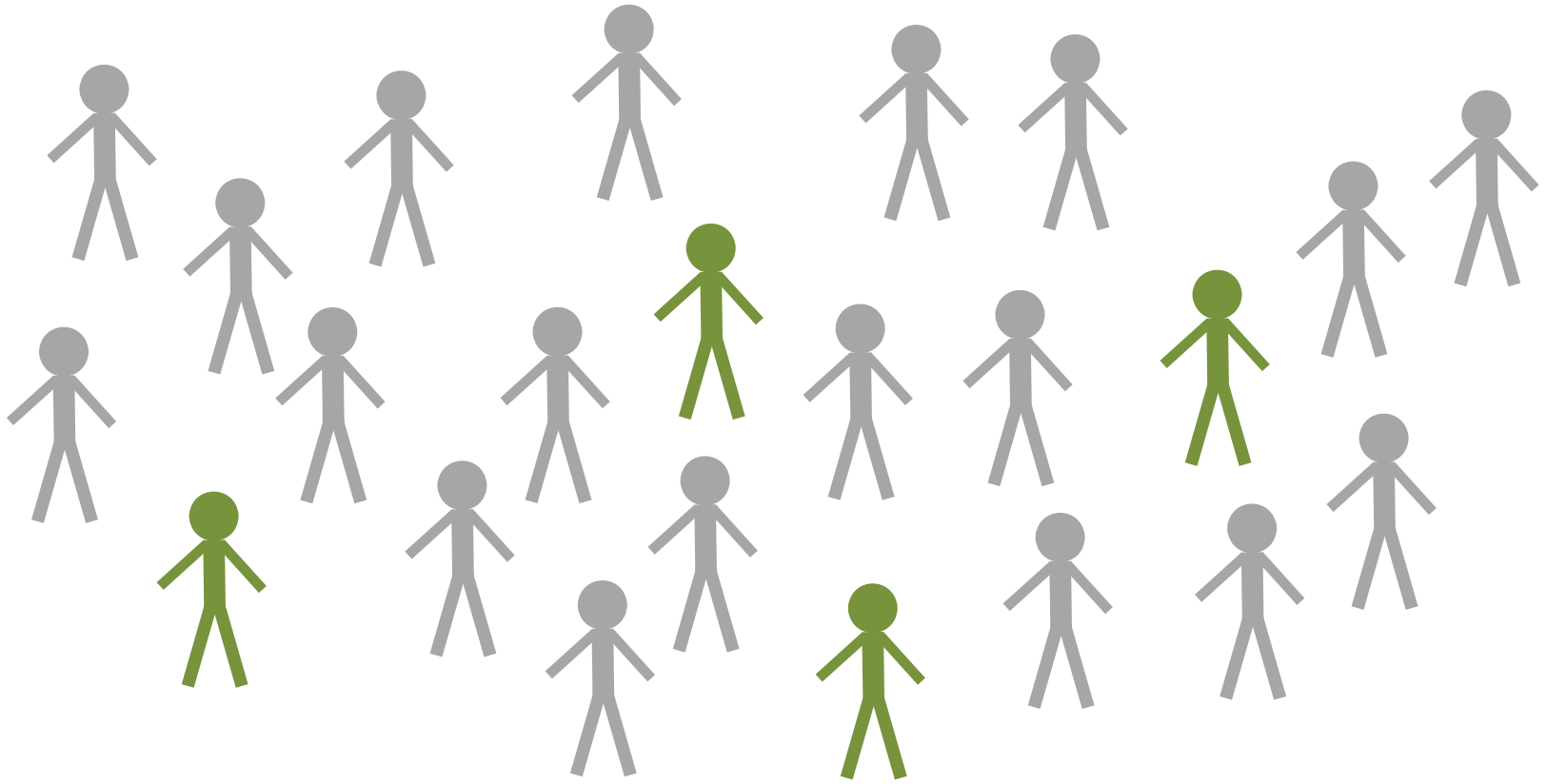
Asymptomatic/Healthy
Bacterial ARI
Viral ARI
Sick but not due to infection

Healthy Controls?



Asymptomatic/Healthy
Bacterial ARI
Viral ARI

Or Ill Controls?



Bacterial ARI

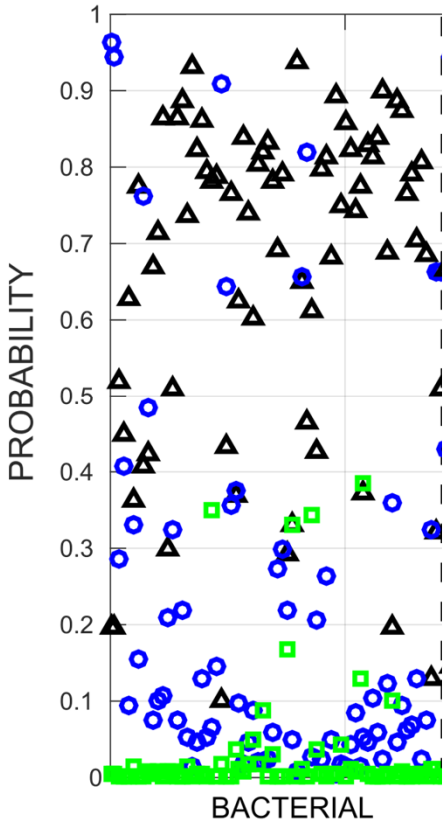
Viral ARI

Sick but not due to infection

Control – Healthy or Sick?

- Generate three classifiers
  - Bacterial vs. Non-Bacterial (Viral + Healthy)
  - Viral vs. Non-Viral (Bacterial + Healthy)
  - Healthy vs. Infected (Bacterial + Viral)
- Validate in patients with SIRS

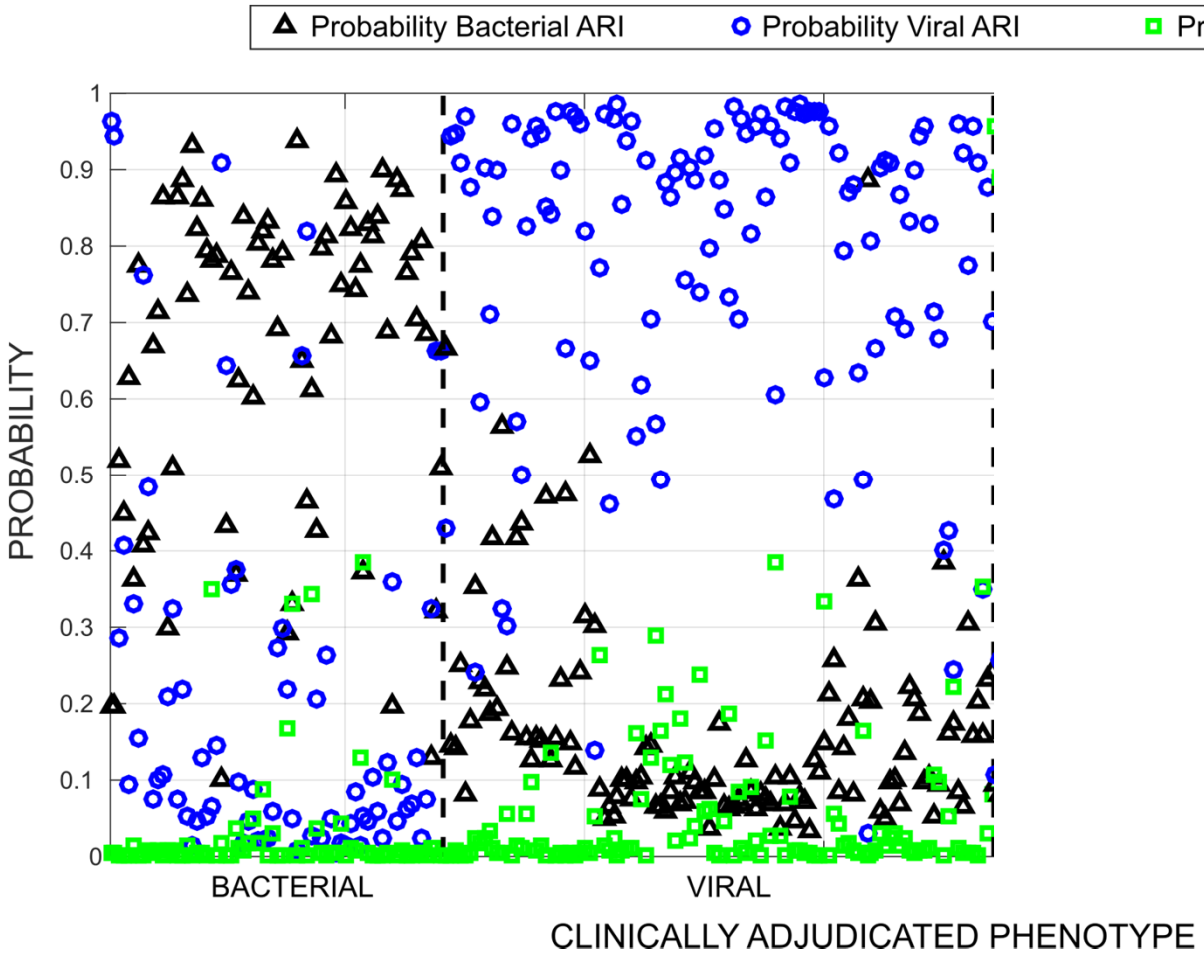
Patients with Bacterial ARI



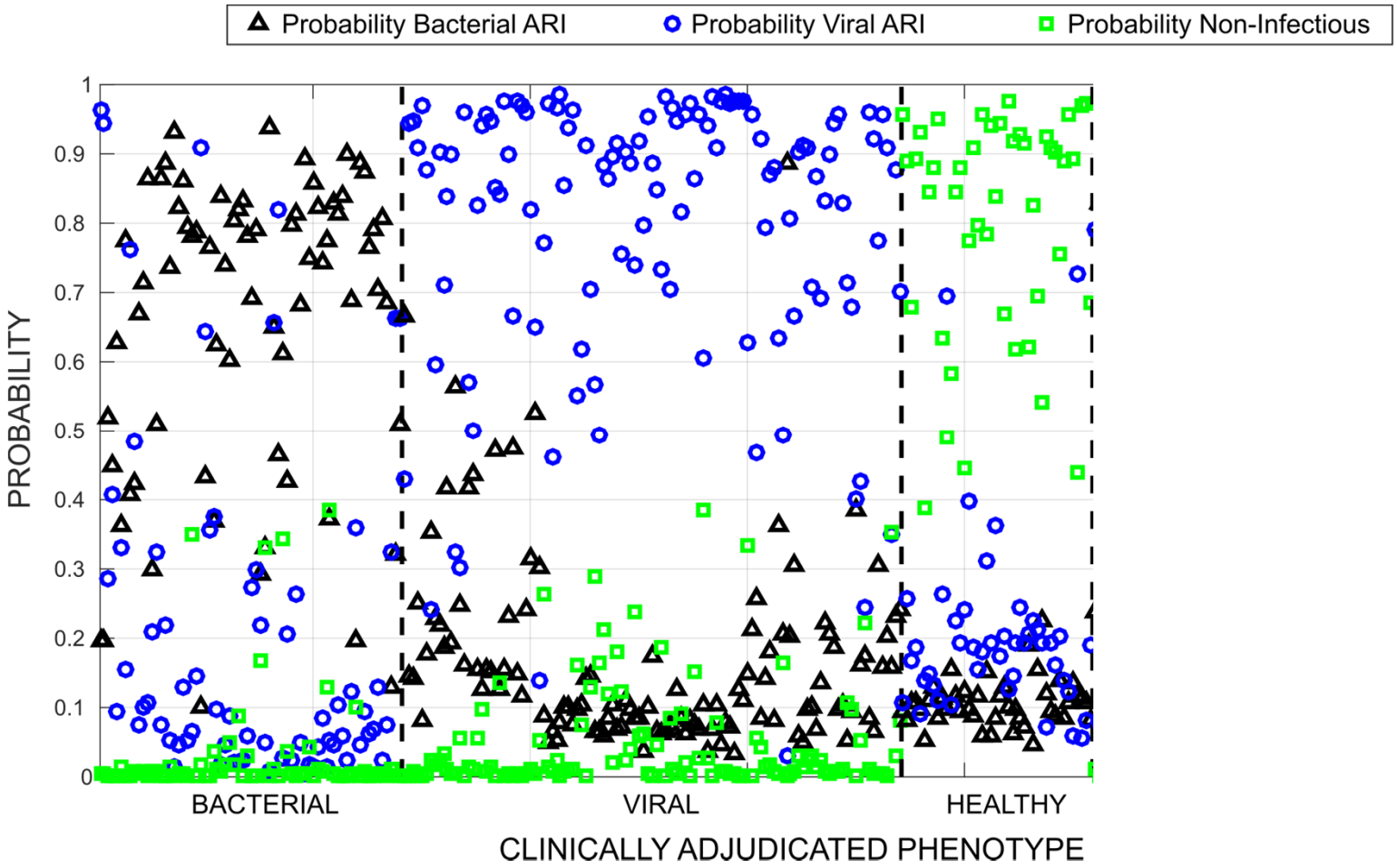
Each subject receives 3 non-mutually exclusive probabilities:

1. p(Bacterial ARI)
2. p(Viral ARI)
3. p(No Infection)

Patients with Viral ARI



Healthy



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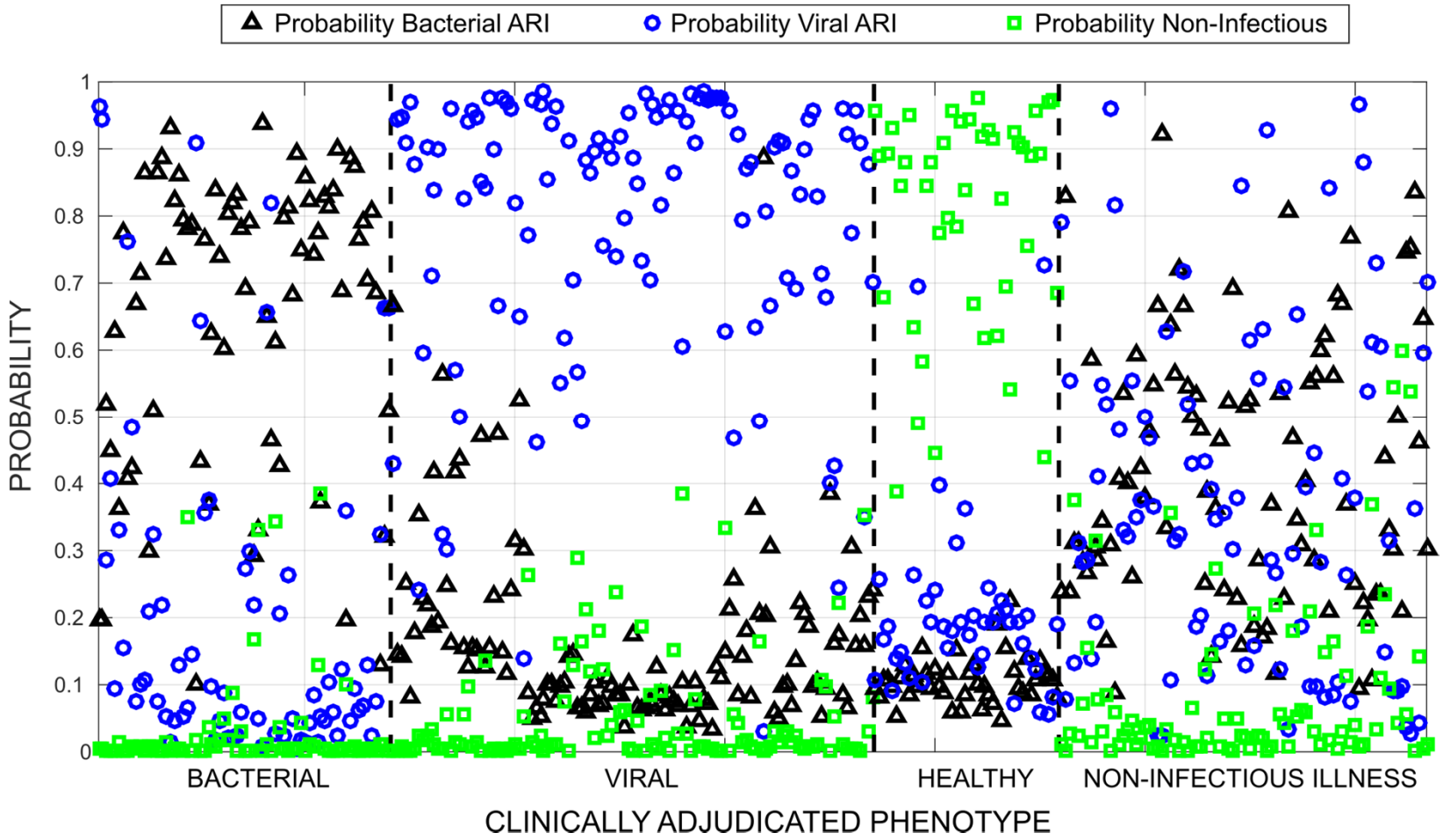
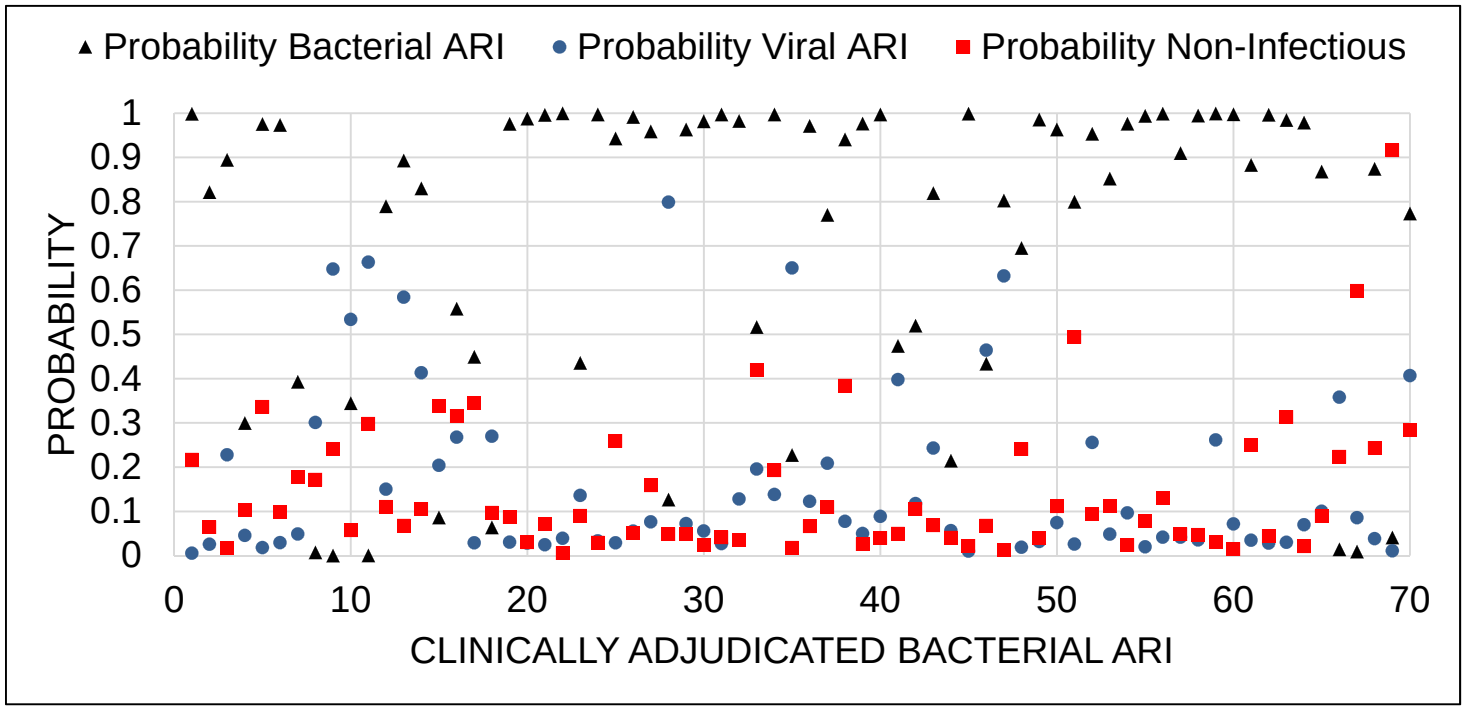
Non-Infectious Illness



ARI Classifier Without Healthy Controls

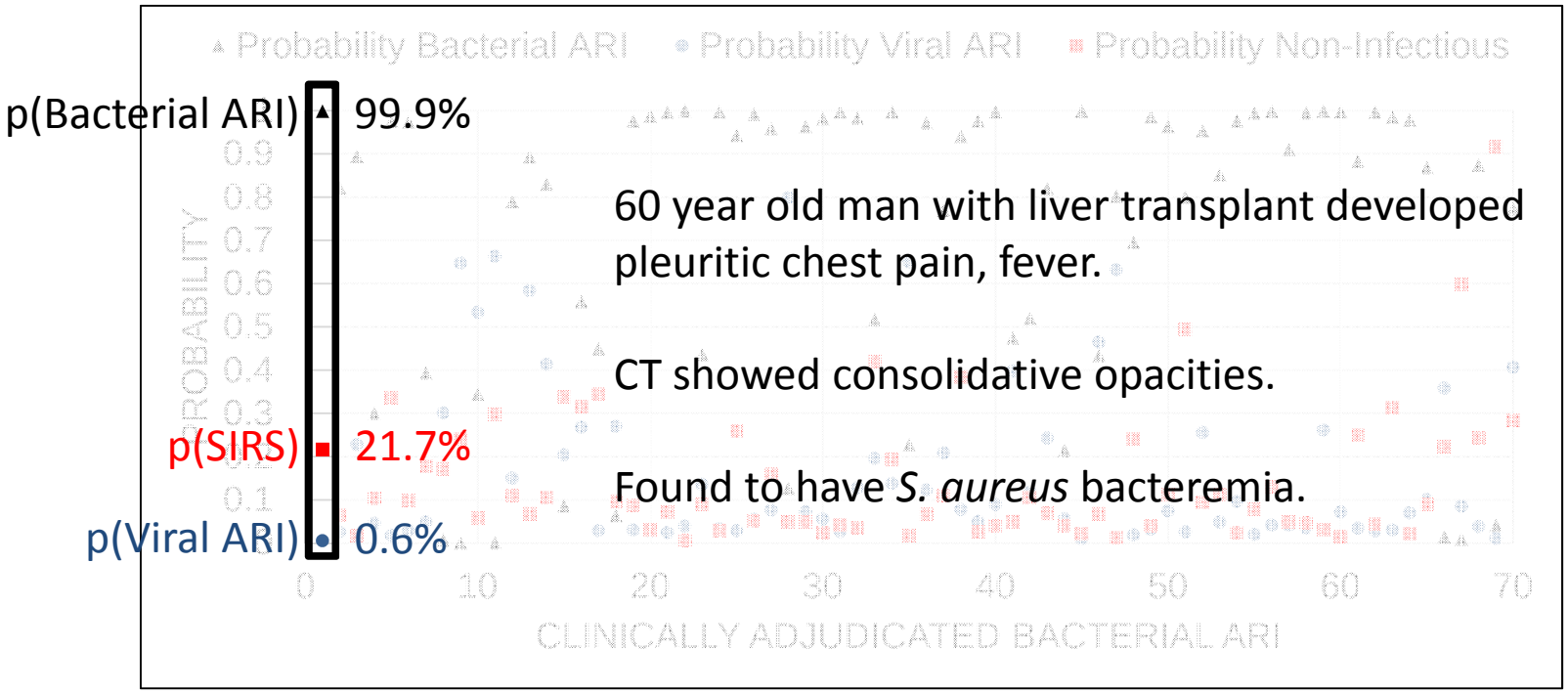
- Generate three independent classifiers:
  - Bacterial ARI (71 genes)
  - Viral ARI (33 genes)
  - Non-Infectious Illness/SIRS (26 genes)
- Apply all three classifiers to each individual
- Generate three discrete probabilities for each condition
- Highest probability wins

Bacterial ARI Classification

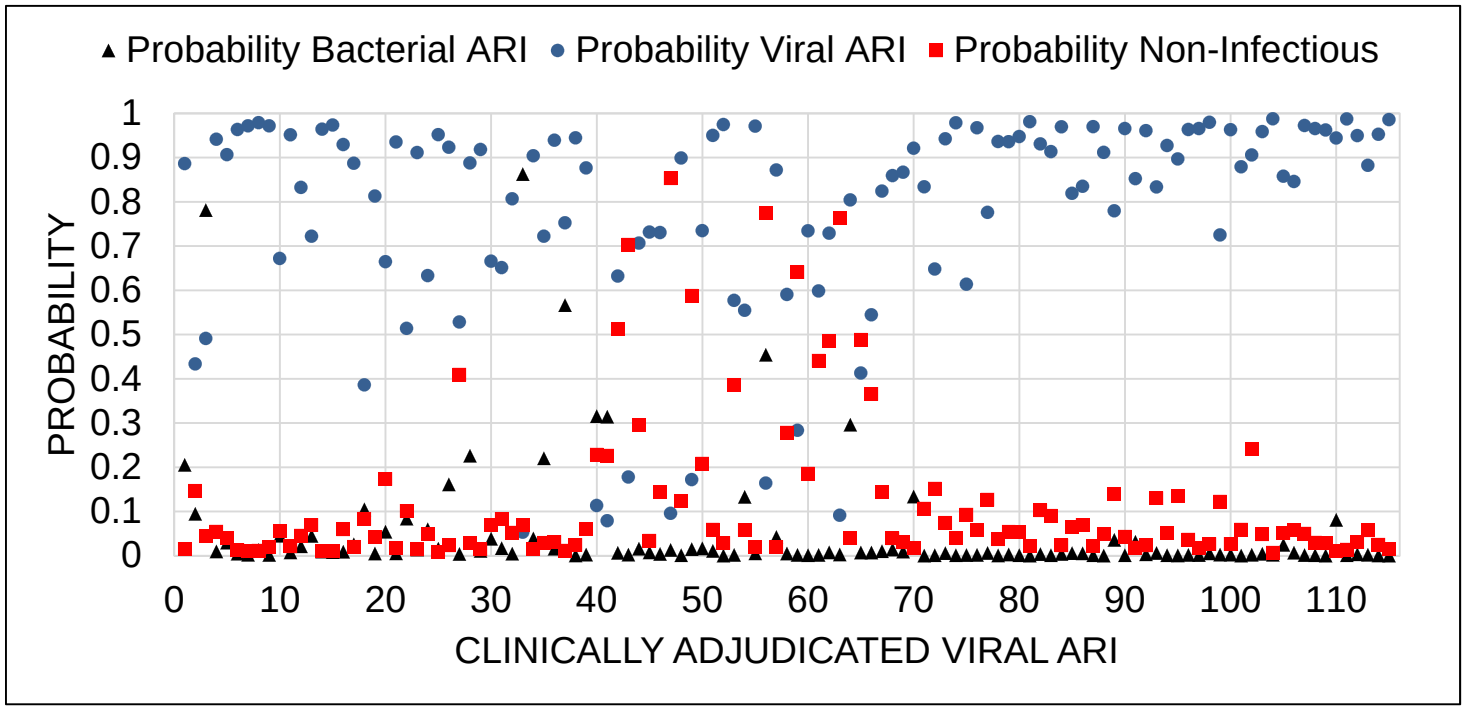


58/70 correctly identified (83%)
179/191 correctly excluded (94%)

Bacterial ARI Classification

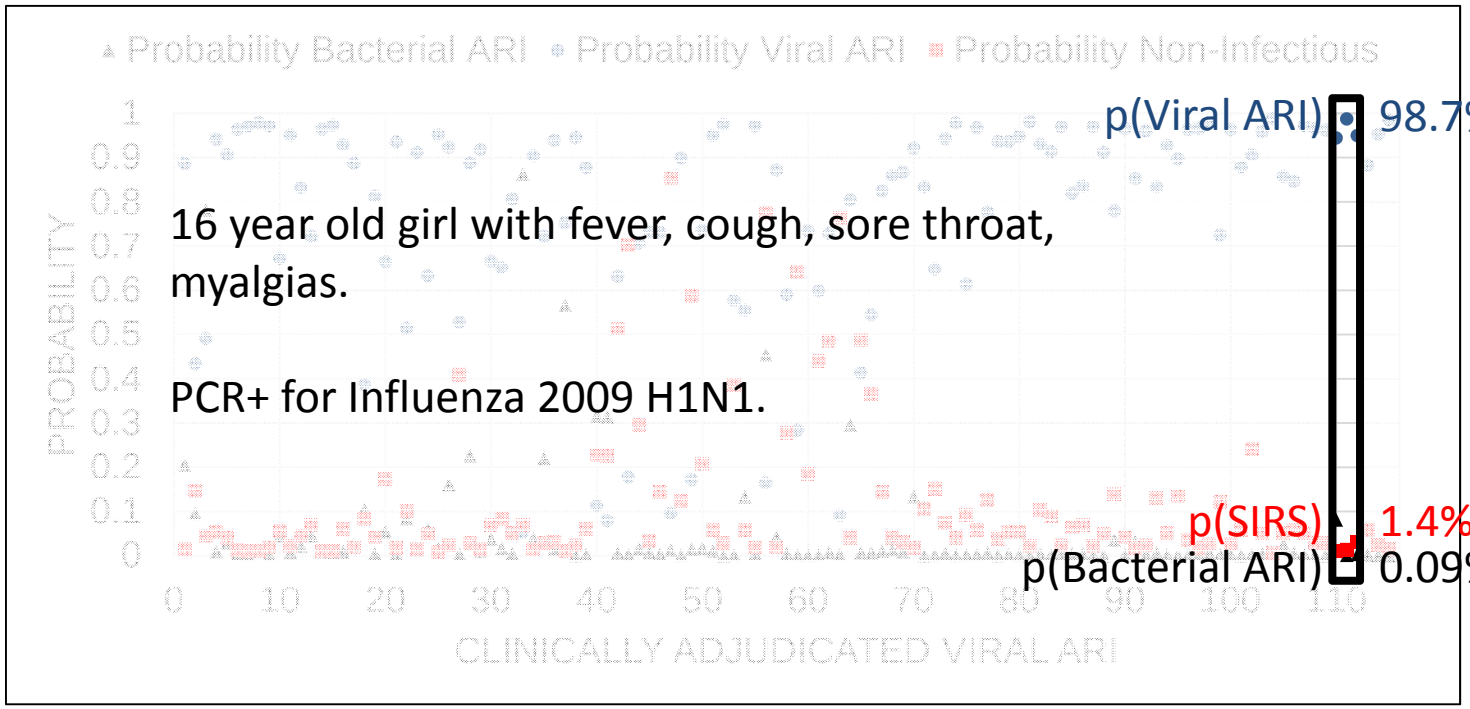


Viral ARI Classification

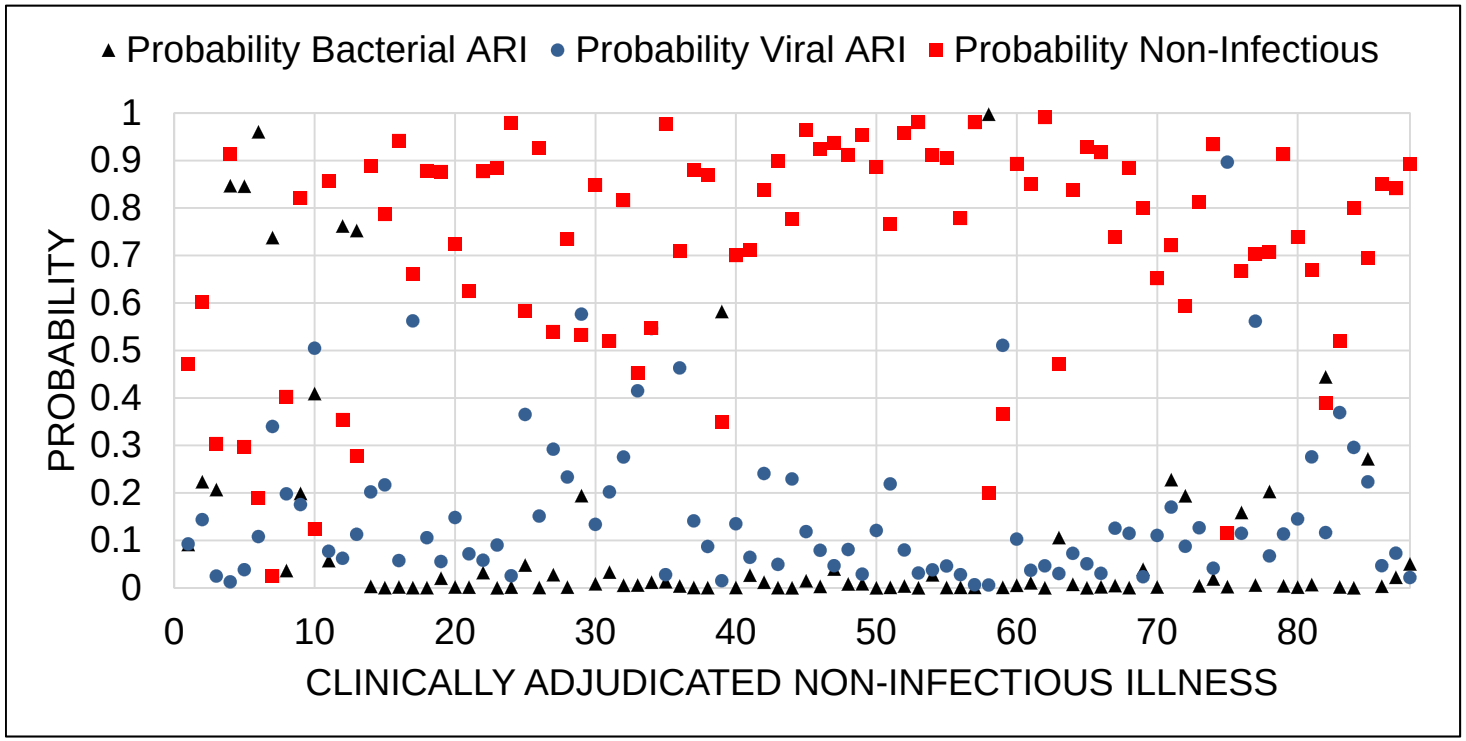


104/115 correctly identified (90%)
145/158 correctly excluded (92%)

Viral ARI Classification

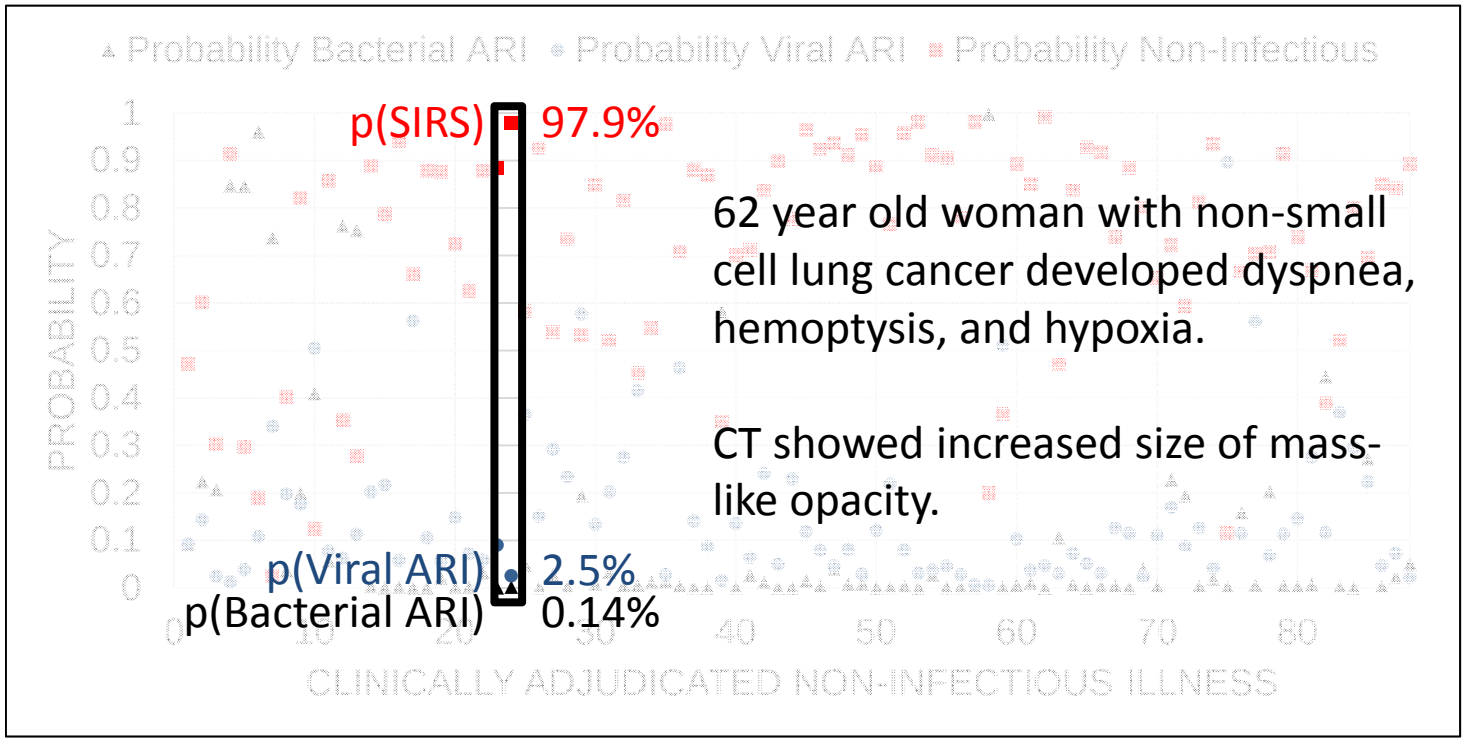


SIRS Classification



Infection excluded in 76/88 cases (86%)

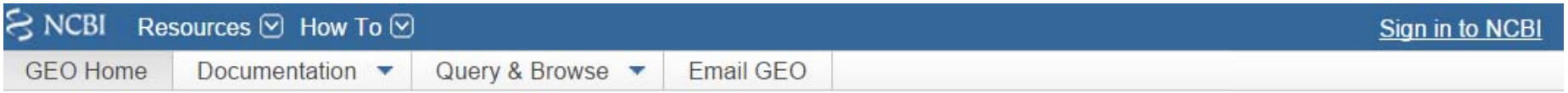
SIRS Classification



Best available alternative – PCT

- PCT 0.25 as threshold for bacterial vs. non-bacterial
- Accuracy defined as % correctly classified

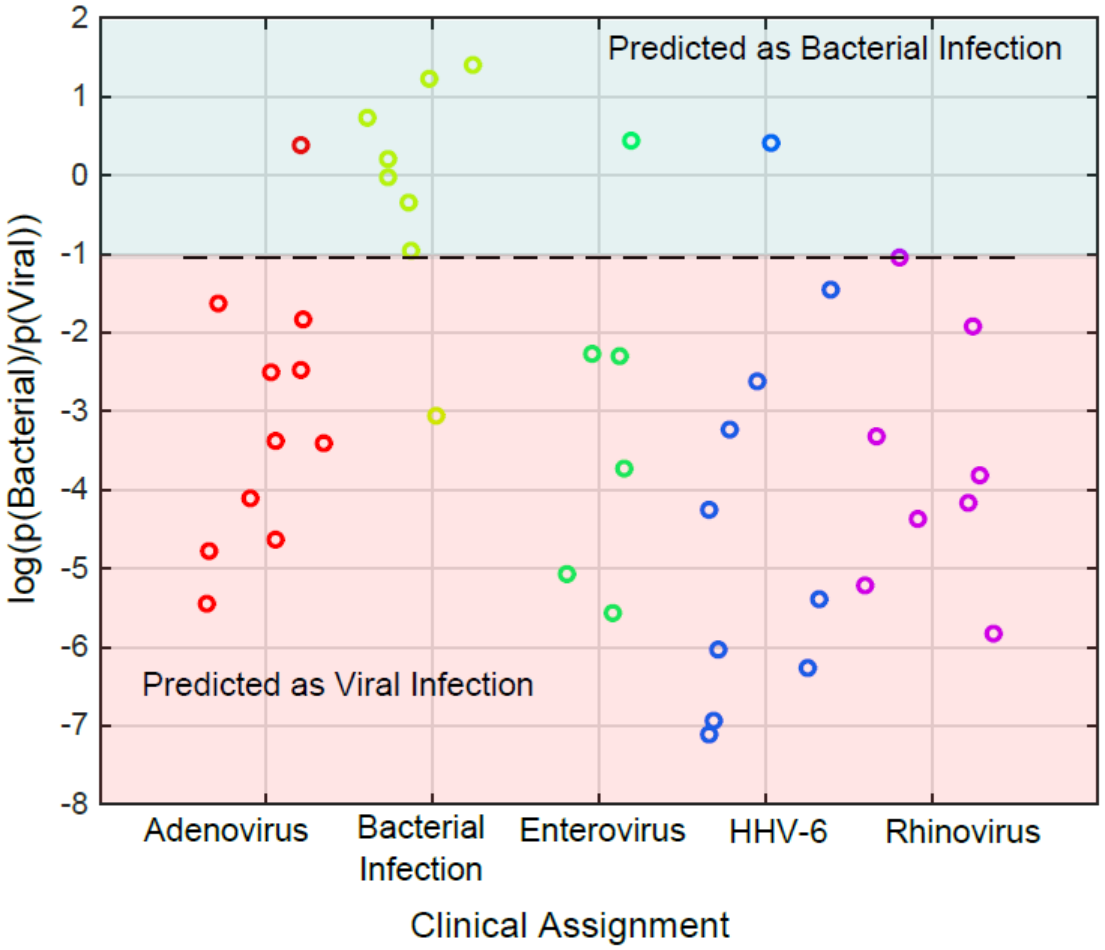
	Procalcitonin	Host Response Classifier
Bacterial ARI Dx*	78%	86%
Viral ARI Dx	88%	90%
SIRS Dx*	64%	85%



Gene Expression Omnibus

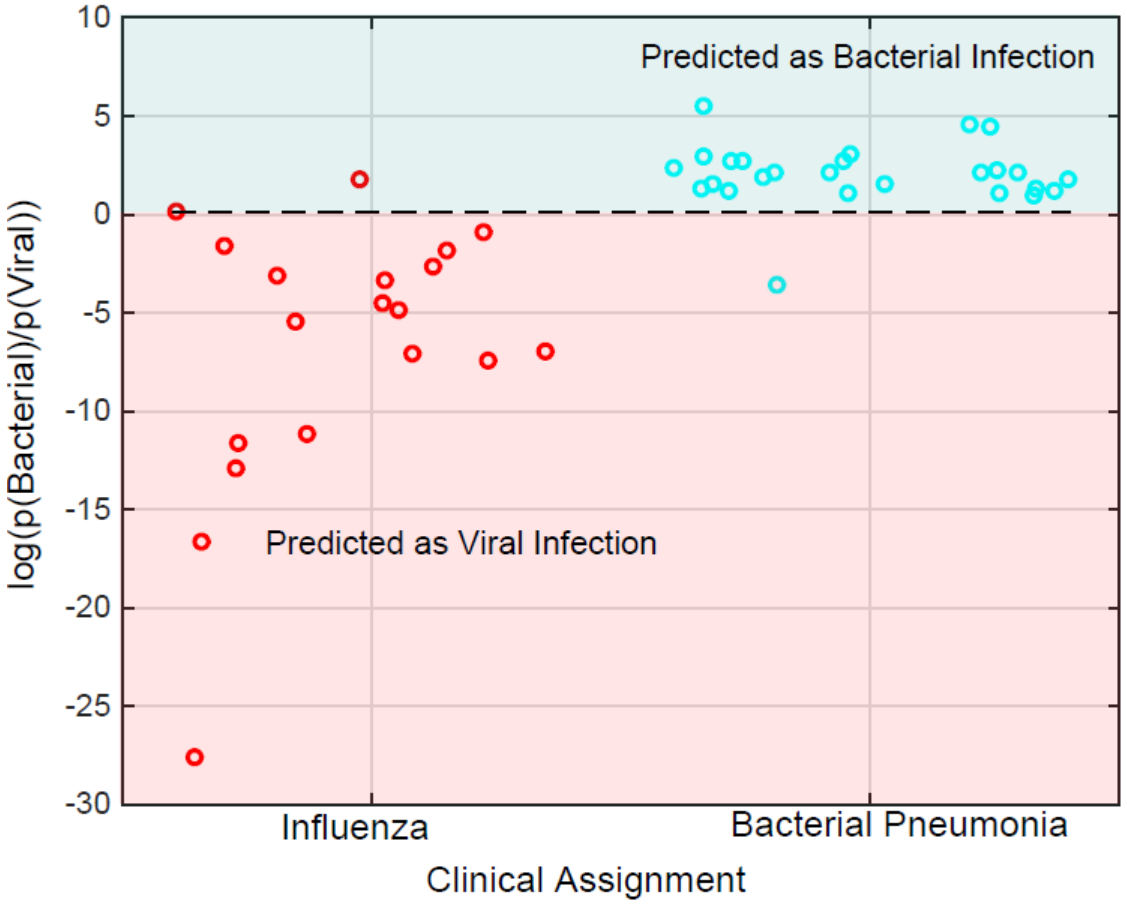
GEO is a public functional genomics data repository supporting MIAME-compliant data submissions. Array- and sequence-based data are accepted. Tools are provided to help users query and download experiments and curated gene expression profiles.

Validation GSE40396



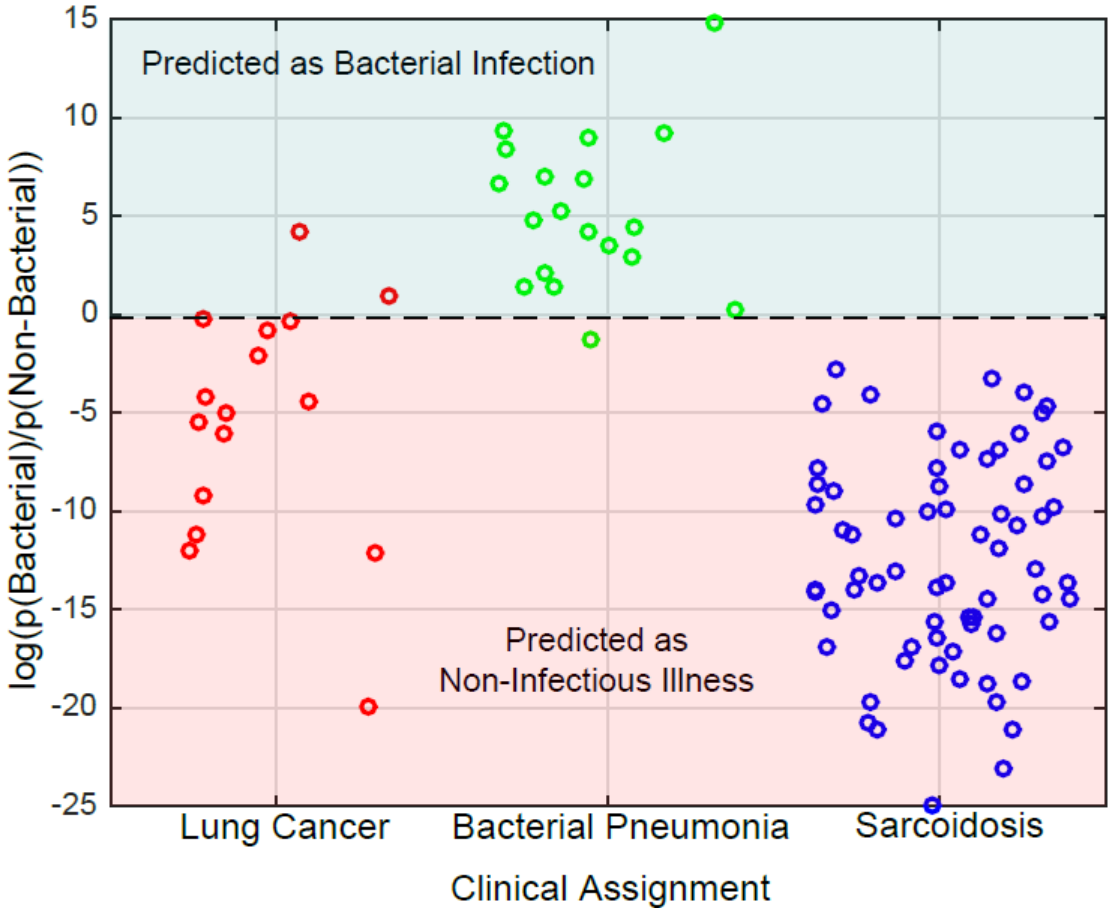
- Children with adenovirus, HHV-6, enterovirus, or bacterial infection
- AUC 0.93

Validation GSE20346



- Hospitalized adults with bacterial pneumonia or Influenza A
- AUC 0.99

Validation GSE42834



- Adults with bacterial pneumonia, lung cancer, or sarcoidosis
- AUC 0.99

Clinical Conundrum

- 31 yo man with Cystic Fibrosis, colonized with *Pseudomonas aeruginosa*
- Discharged 1 week ago for flare where he received limited course of anti-Pseudomonal antibiotics
- Then develops dyspnea, abdominal cramping, diarrhea. Reports close contact to someone with a “stomach virus”.
- Sputum culture reveals *Pseudomonas aeruginosa*
- He is treated with a prolonged course of anti-Pseudomonal antibiotics for another CF flare

p(Bacterial ARI) 0.05% **p(Viral ARI) 66.4%** p(SIRS) 29.8%

Trial Conundrum
To enroll or not to enroll?

- Phase 3 trial of Drug X to treat CABP identifies an 87 year old man with congestive heart failure and multiple myeloma
- 1 week of weakness and cough
- ER evaluation: Febrile, infiltrate on chest x-ray consistent with edema or atypical infection
- Troponin and BNP elevated indicating myocardial infarction and decompensated CHF
- All microbiology is negative

p(Bacterial ARI) 99.7% p(Viral ARI) 0.6% p(SIRS) 20.0%

Concluding Thoughts

- Non-microbial biomarkers should be fit for purpose
- Comparator – adjudicated phenotype
- Performance characteristics will not be perfect given an imperfect comparator
- Generalizability
  - Pediatrics – Yes
  - Neonates – ?
  - Immunocompromised – Yes (limited)
- Biomarkers are informative, not infallible
- **Novel host response biomarkers have the potential to change ID diagnostics**

Standing on the shoulders of giants


Octavio Ramilo


Greg Storch


Benjamin Tang


Stephen Gordon


Ron Turner


Broad Institute

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DukeMedicine

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