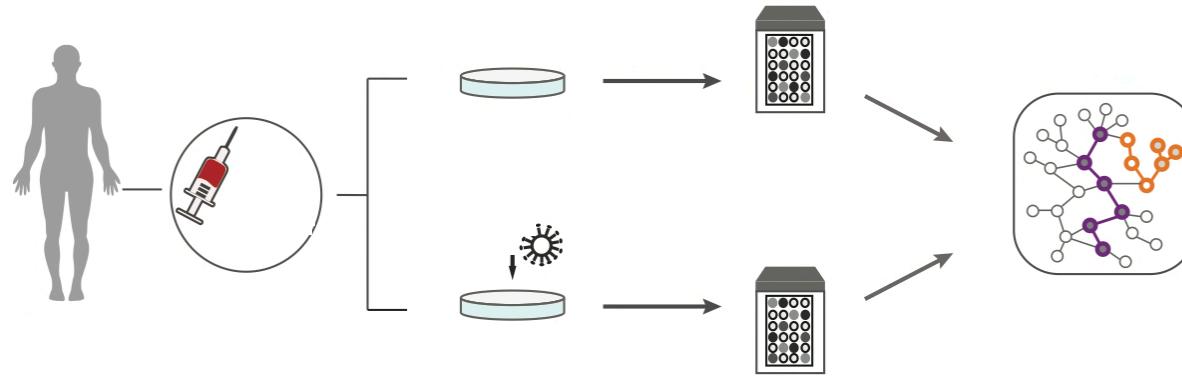


A genome-by-environment interaction (G×E) classifier for precision medicine: personal transcriptome response to rhinovirus identifies children prone to asthma exacerbations

Gardeux V, ..., Schissler AG, ..., Martinez FD*, Lussier YA*. *J Am Med Inform Assoc*, 2017 ocx069



University of Nevada, Reno



THE UNIVERSITY OF ARIZONA HEALTH SCIENCES
Center for Biomedical
Informatics & Biostatistics



Overall framework

- 1) Design clinically-relevant ASSAY
- 2) Use statistical modeling to QUANTIFY
- 3) Focus on PREDICTION through machine learning
- 4) INTERPRET results to enable precision medicine

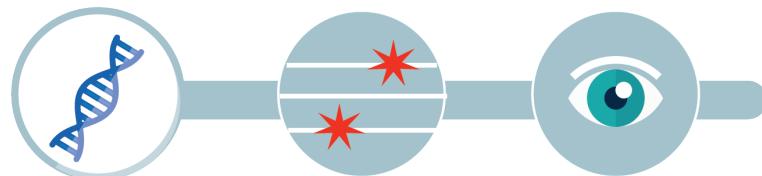
How can gene expression support clinical decisions?



Biochemistry



Genetics



Transcriptome (mRNA)

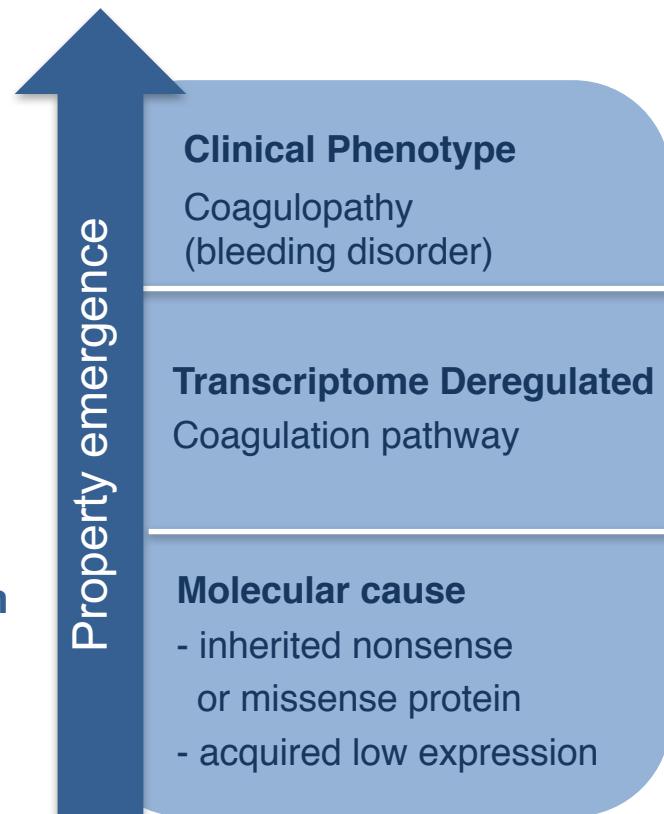


The same clinical phenotype may emerge from distinct molecular factors

Convergent pathway deregulation of diseases with **distinct causes (genetic, epigenetic, environmental)**

- coagulopathies can be inherited (Mendelian)
- or acquired (G × E)

In other words, **convergent phenotypes** attributable to **distinct gene products dysregulation** within the same pathway



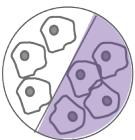
Design the right tool: N-of-1-pathways

1.



N-of-1
Individual

2.



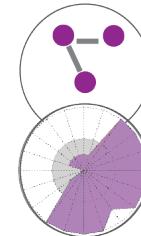
Paired
Samples

3.



Dynamic
Gene
Expression

4.



Pathways
Analysis



- . Predicting or monitoring response to therapy
- . Understanding personal disease mechanisms

Extreme p >> n

Only one observation in
each condition?!



Statistician's
Nightmare

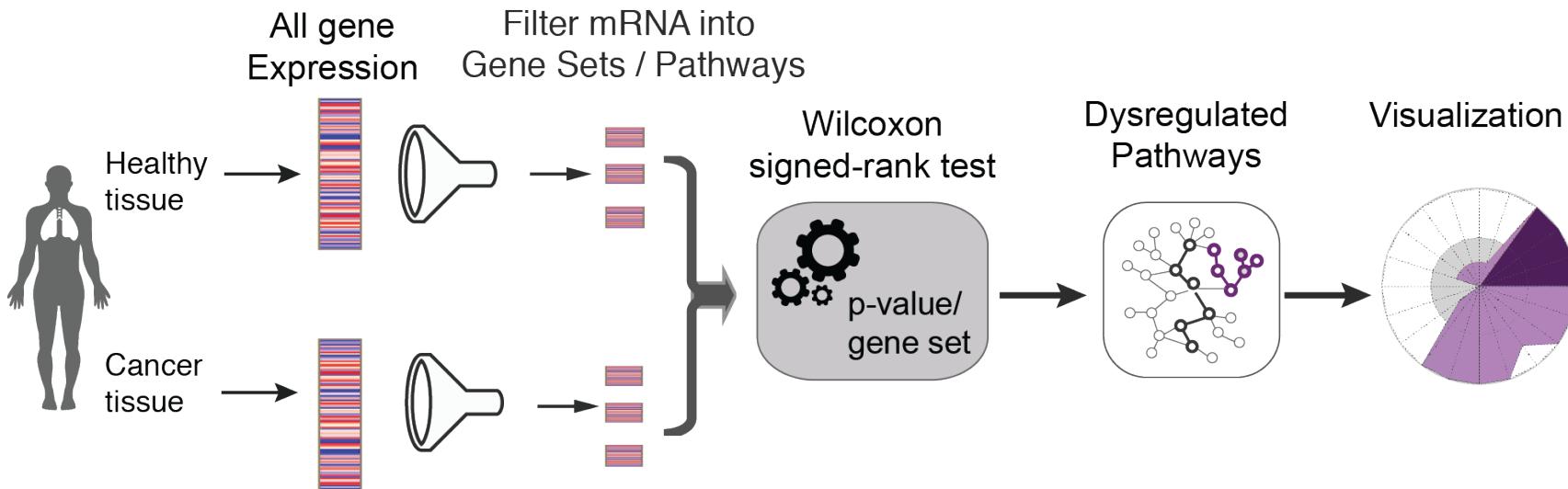
Introducing N-of-1-pathways Wilcoxon

Gardeux V, Achour I, (...) Lussier YA*. J Am Med Inform Assoc 2014 21:1015-1025

RNAseq (TCGA)
Paired Samples

N-of-1-Pathways
Single-subject analysis

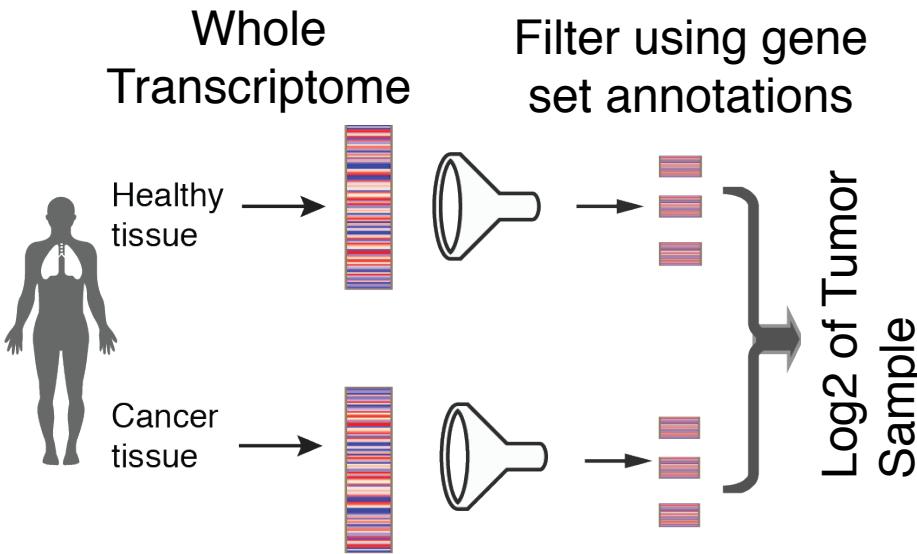
Personal
Profile



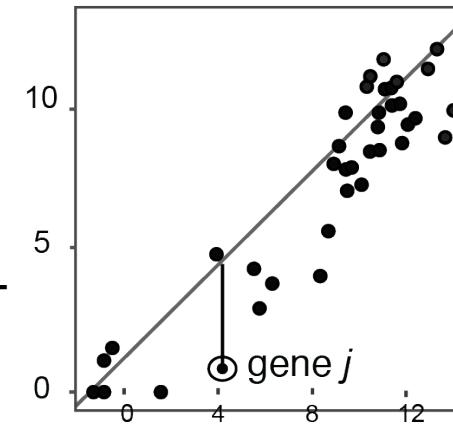
Introducing N-of-1-pathways Mahalanobis Distance (MD)

Schissler AG, ..., Piegorsch WW, Lussier YA, *Bioinformatics J*, 2015 Jun 15;31(12):i293-302.

RNAseq (TCGA)
Paired Samples



N-of-1-pathways
Single-subject analysis



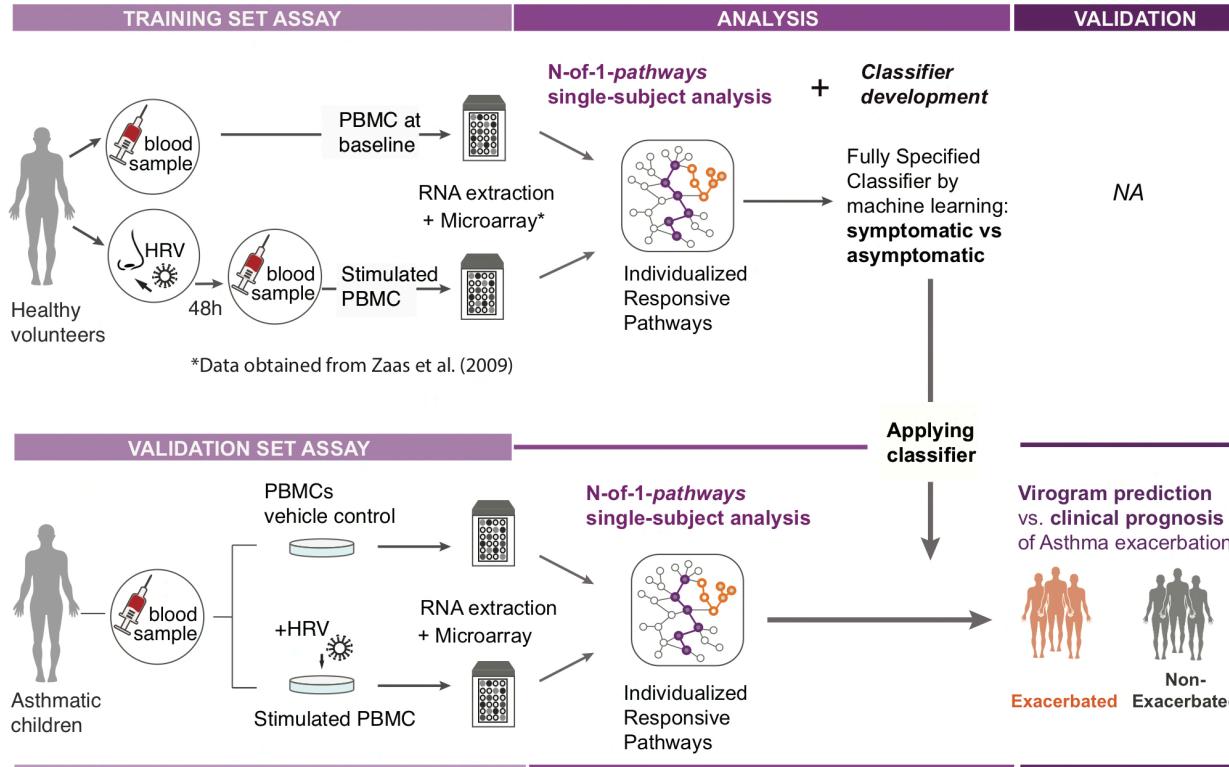
Correlation-adjusted differential expression

Log₂ of Normal Sample

$$d_j = \sqrt{\frac{1}{S_N^2(1 - r_{NT}^2)}} (T_j - N_j)$$

A genome-by-environment (GxE) interaction classifier for precision medicine: personal transcriptome response to rhinovirus identifies children prone to asthma exacerbations

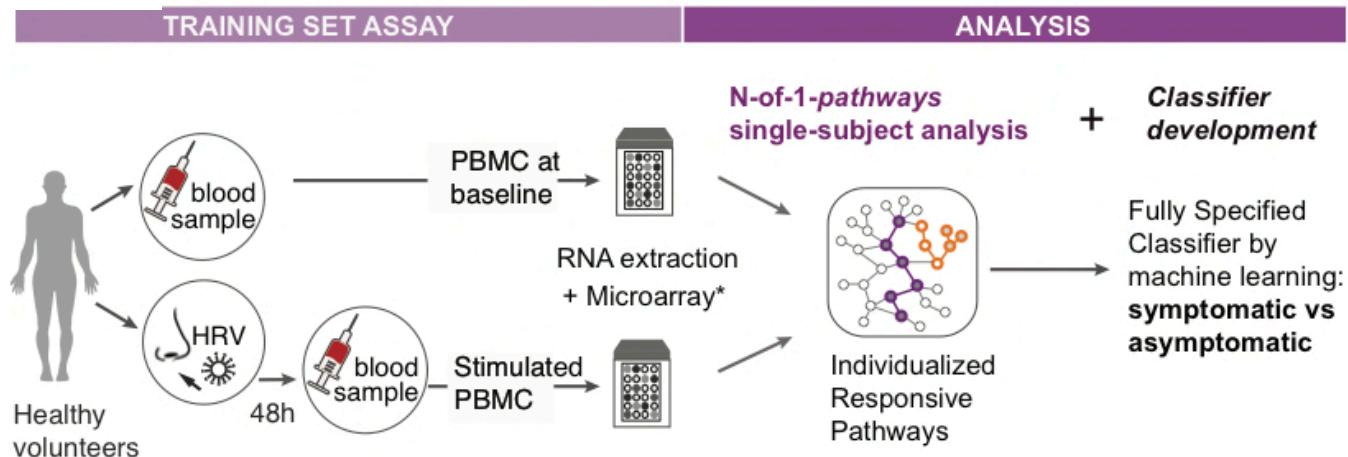
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A genome-by-environment interaction classifier for precision medicine:

personal transcriptome response to rhinovirus identifies children prone to asthma exacerbations

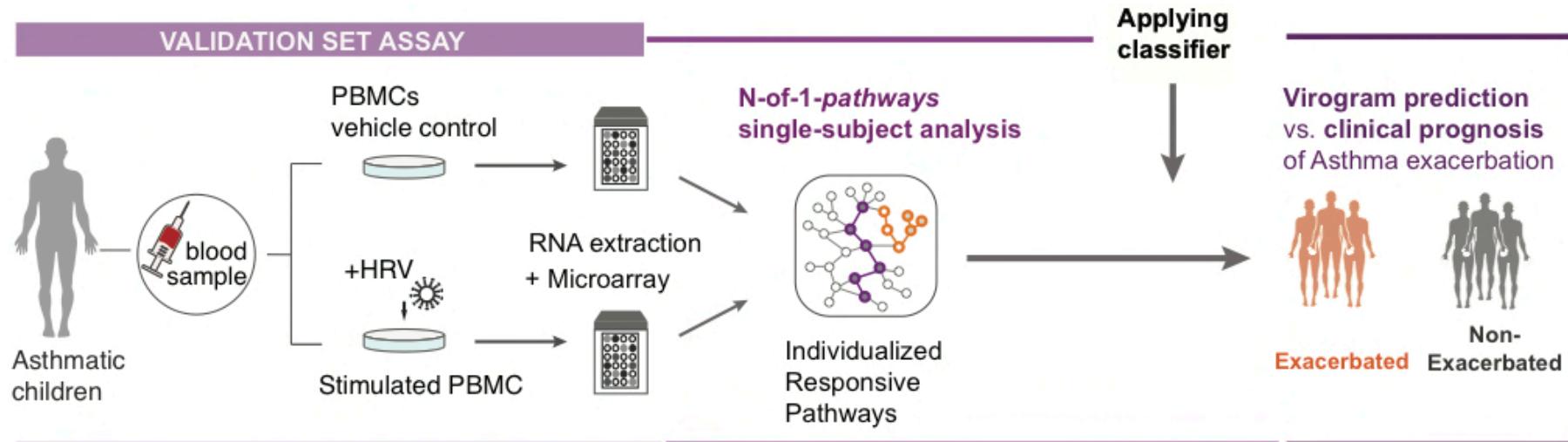
Gardeux V, ..., Schissler AG, ..., Martinez FD*, Lussier YA*. J Am Med Inform Assoc, 2017 ocx069



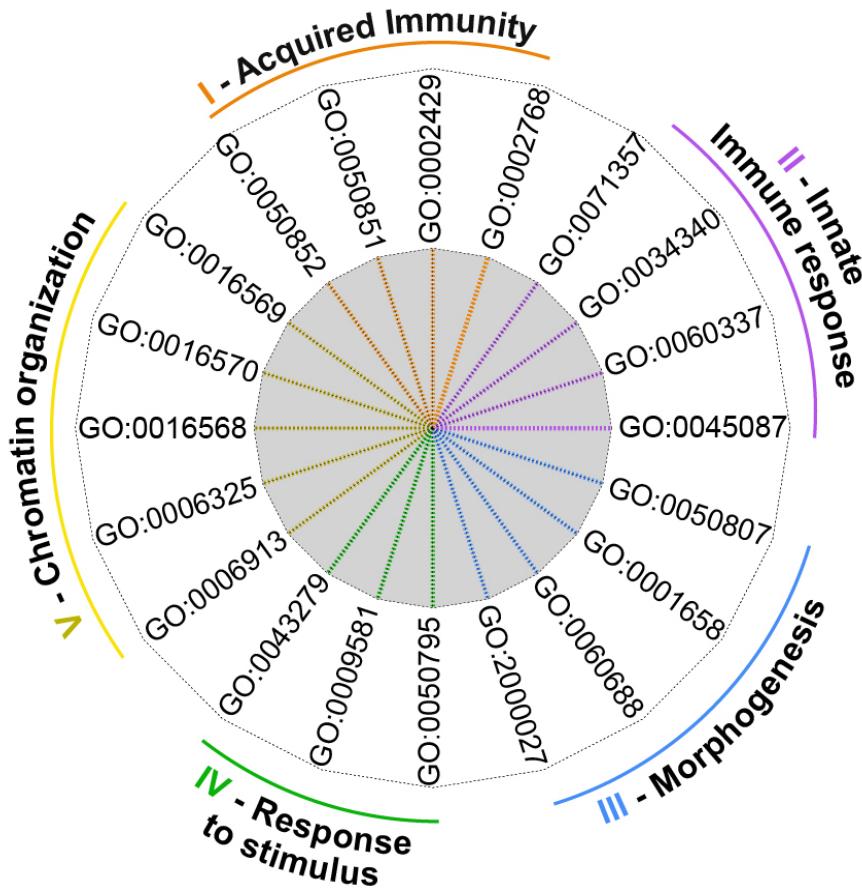
*Data obtained from Zaas et al. (2009)

A genome-by-environment interaction classifier for precision medicine: personal transcriptome response to rhinovirus identifies children prone to asthma exacerbations

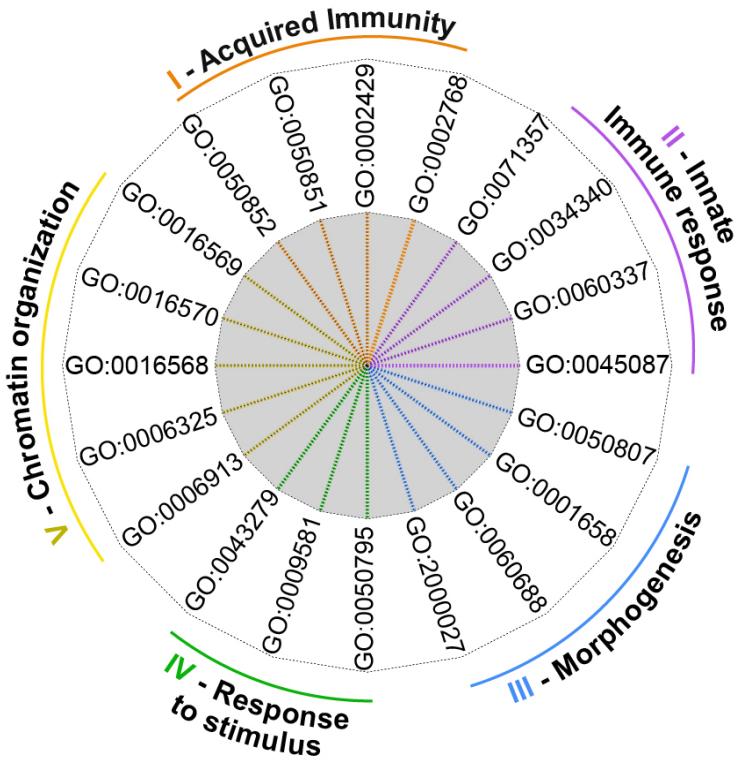
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Visualizing N-of-1 pathway dysregulation



Classification performance



Virogram assay + Classifier prediction

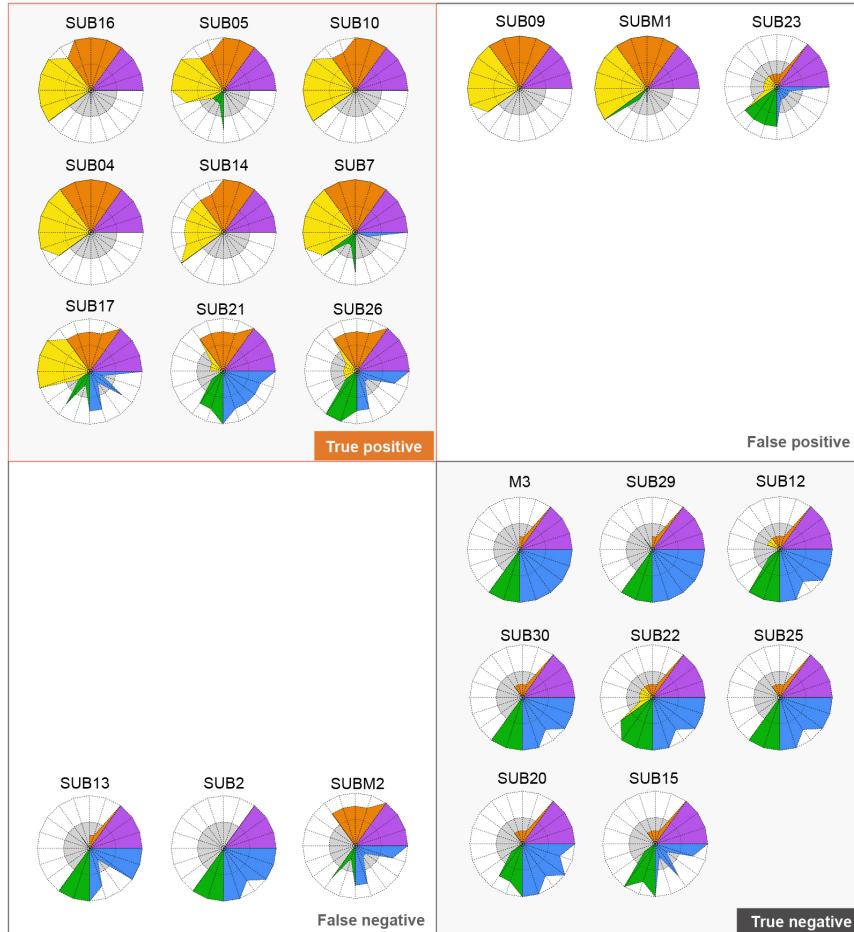


Exacerbated

Clinical phenotype



Non-Exacerbated



Funding



Computation
Institute

BEAGLE Cray
Super Computer



THE UNIVERSITY OF
CHICAGO



1S10RR029030-01



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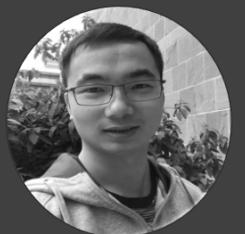
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LM009012
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I Foster, PhD



J Moore, PhD



JC Denny, PhD



Fernando Martinez, MD



Helen Zhang, PhD



WW Piegorsch, PhD

Collaborators

Take-home points

- Development of statistical informatics tools to interpret the transcriptome.
- Applied to GxE-informed asthmatic exacerbation classification.
- Interdisciplinary focus on precision medicine.

Alone we can do so little.
Together we can do so much.