Multi-‘omics of host-microbiome interactions in ME/CFS

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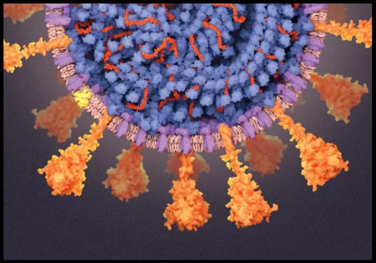
Associate Professor
The Jackson Laboratory

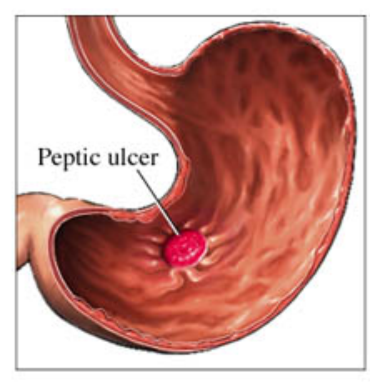
The Jackson Laboratory
Leading the search for tomorrow’s cures

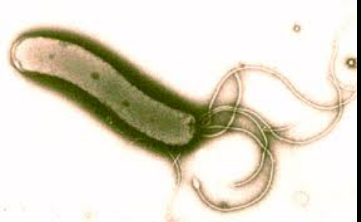
COVID-19



SARS-CoV-2

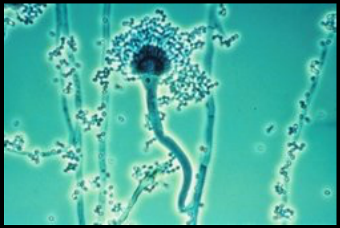
Ulcers





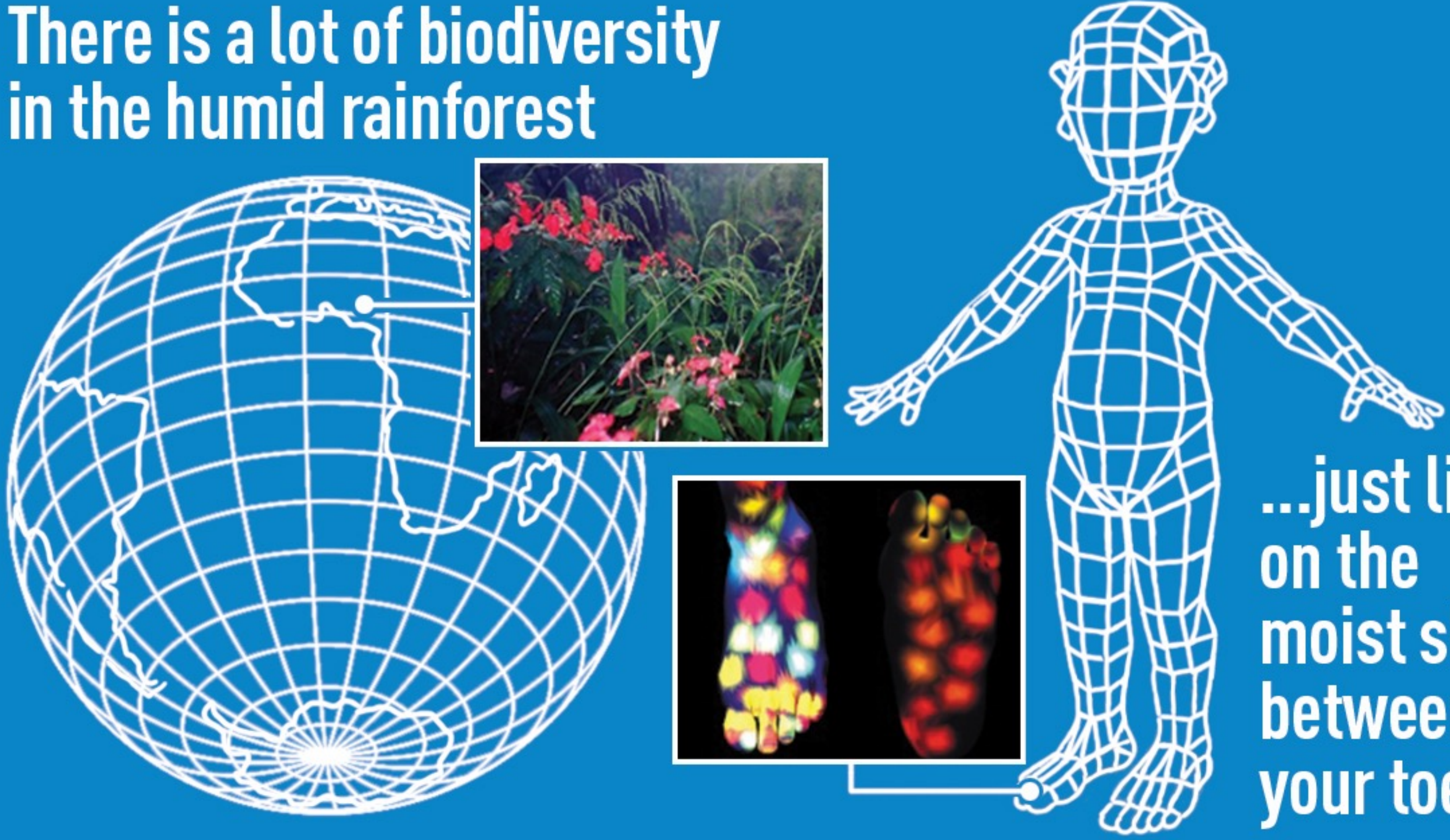
Helicobacter pylori

Lung infections



Aspergillus afumigatus

There is a lot of biodiversity in the humid rainforest



...just like on the moist skin between your toes!

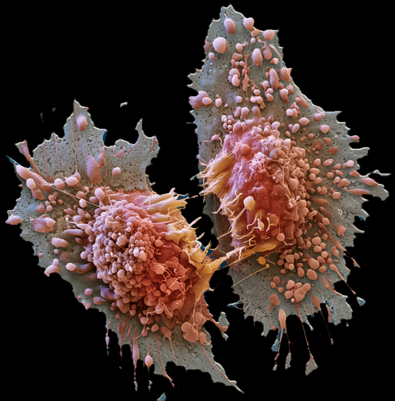
Obesity

Heart disease

Eczema

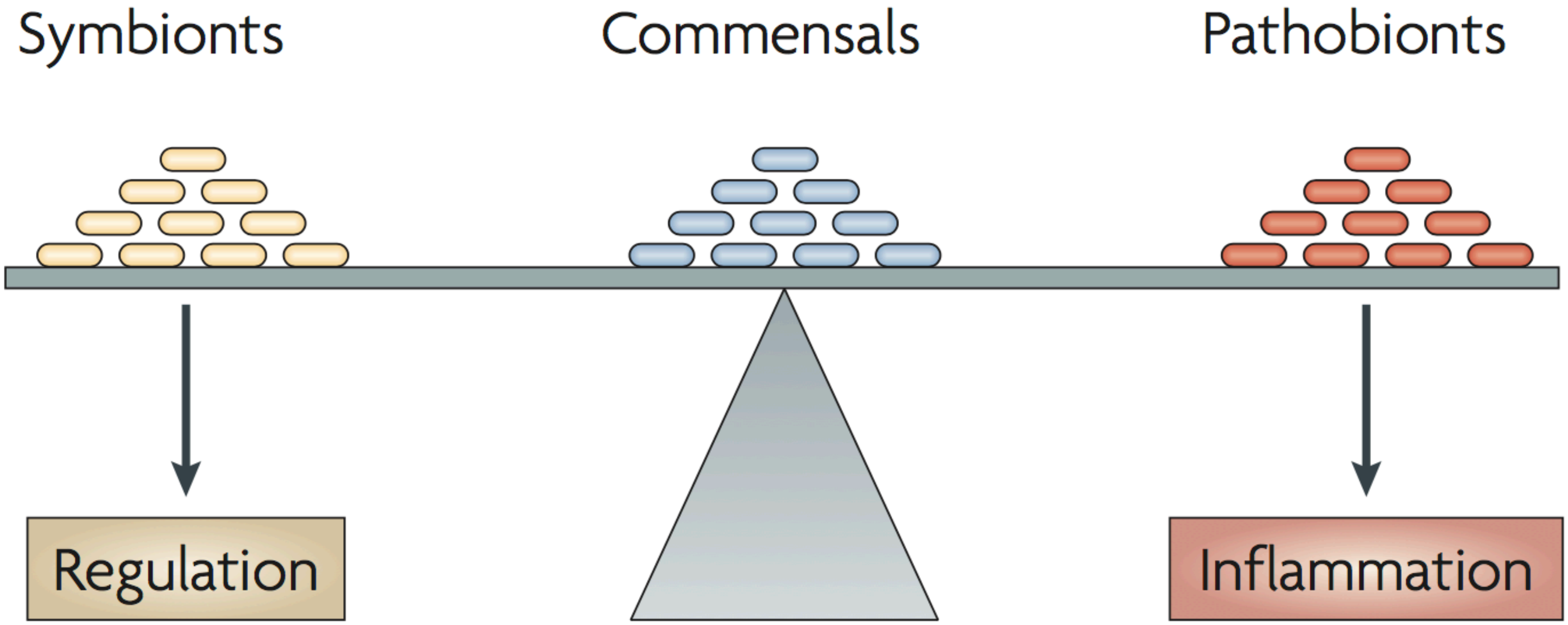
Diabetes

Cancer



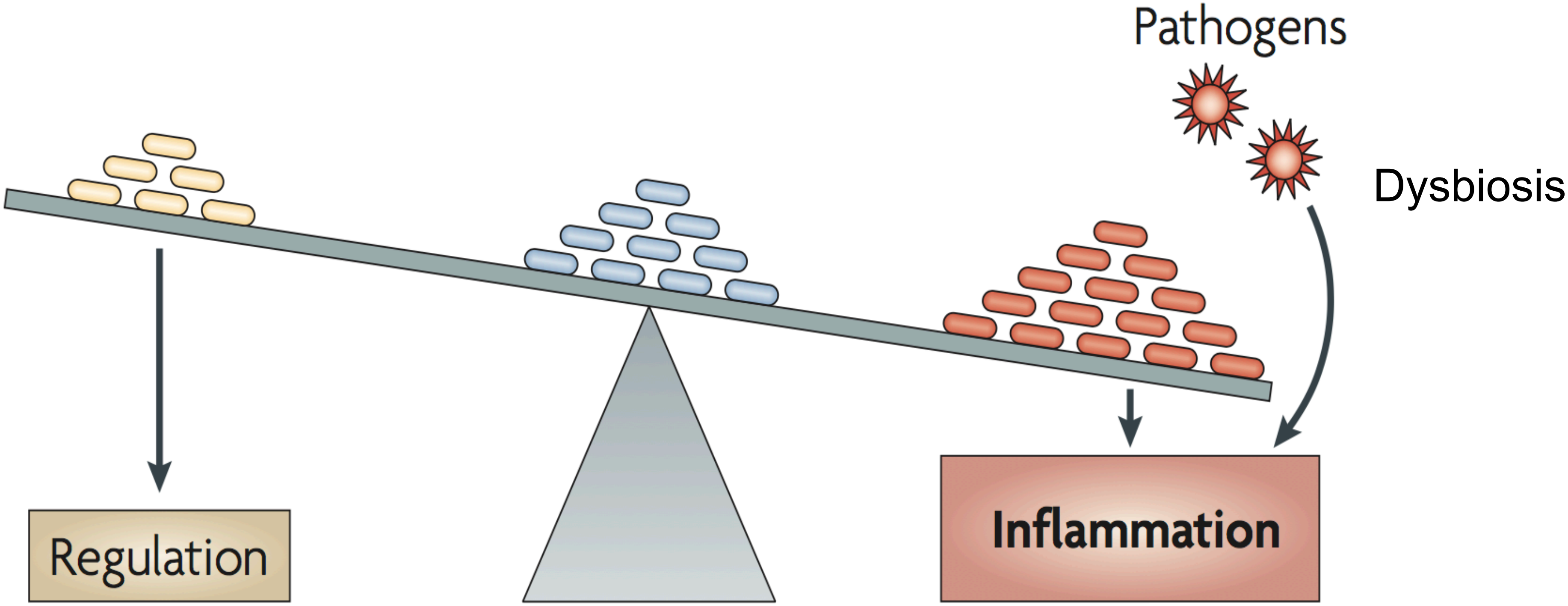
Mental health

Homeostatic microbiome-immune interactions
~ **healthy**



Round et al. Nature Reviews Immunology (May 2009)

Dysbiotic microbiome-immune interactions ~ diseased



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NIH Funded Collaborative Research Center for Chronic Fatigue Syndrome (ME/CFS)

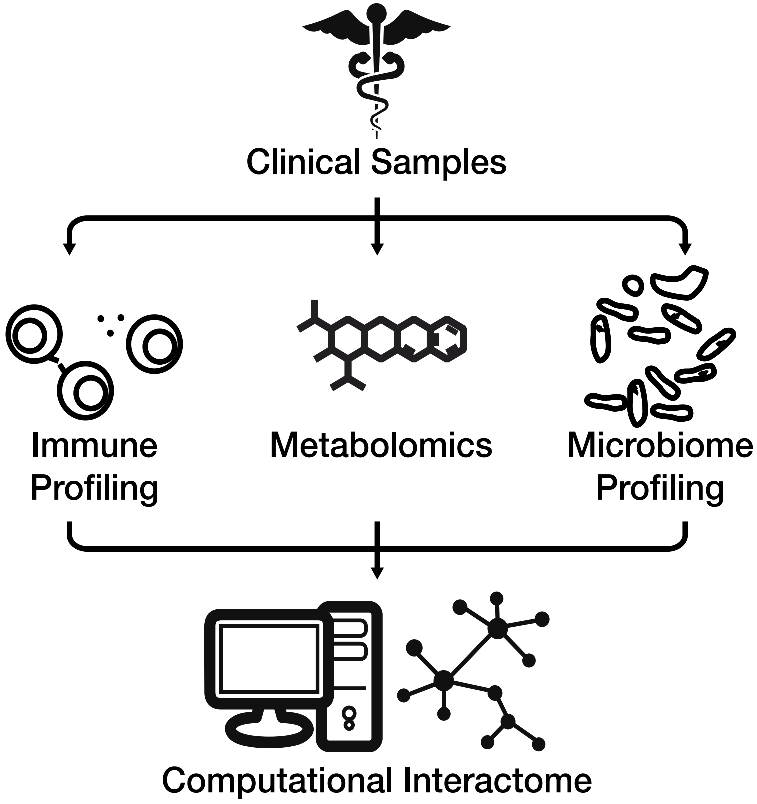
Overall Hypothesis:

ME/CFS caused by immune perturbation

- Microbiome
- Metabolism
- Infections

Our goal is precision medicine approach to:

➢ ID biomarkers
➢ ID novel targets



Clinical Samples

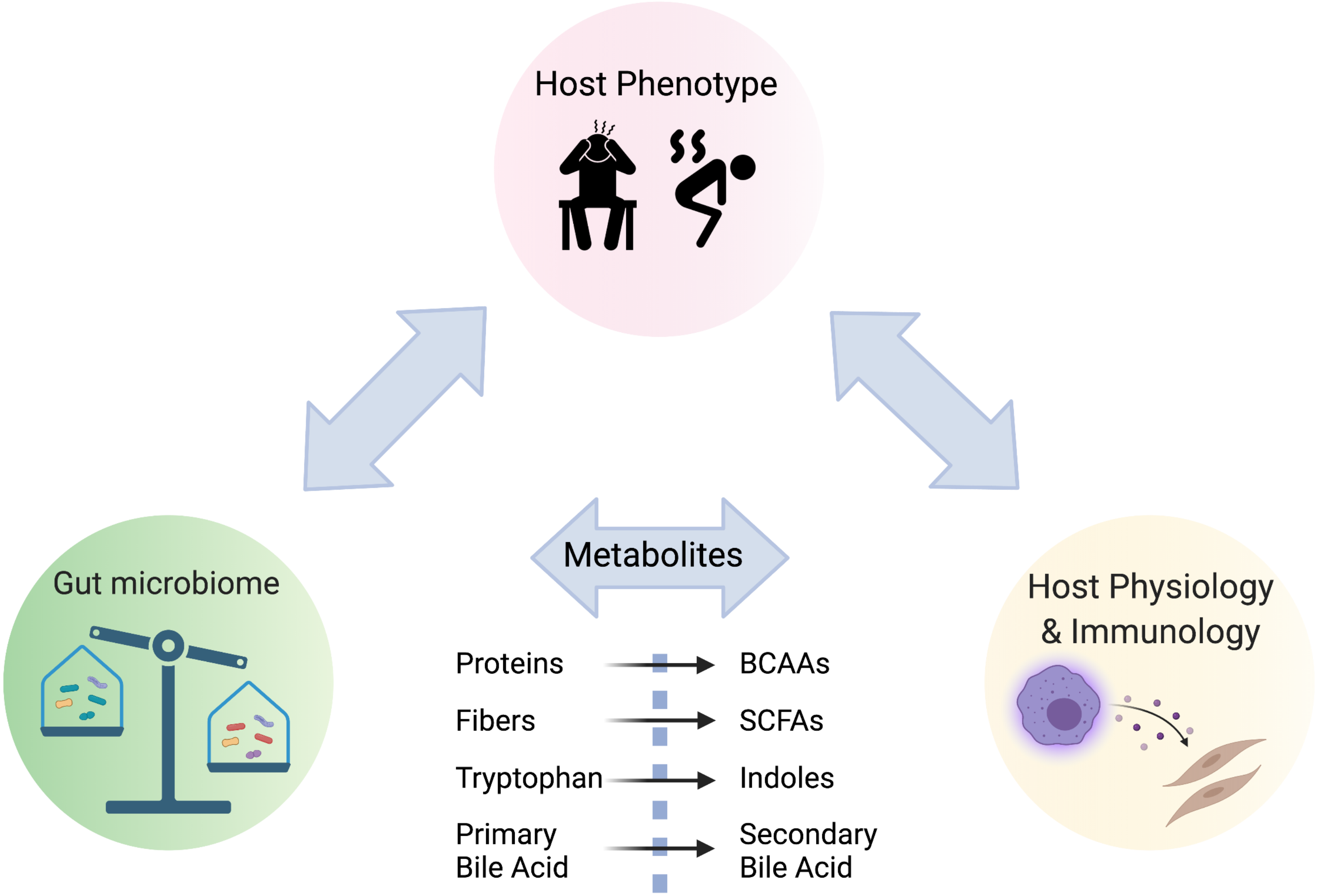
Immune Profiling

Metabolomics

Microbiome Profiling

Computational Interactome

Key mediators of host–microbiome interactions



Host Phenotype

Gut microbiome

Metabolites

Host Physiology & Immunology

Proteins → BCAAs

Fibers → SCFAs

Tryptophan → Indoles

Primary Bile Acid → Secondary Bile Acid

Rigor of prior research: microbial links to ME/CFS

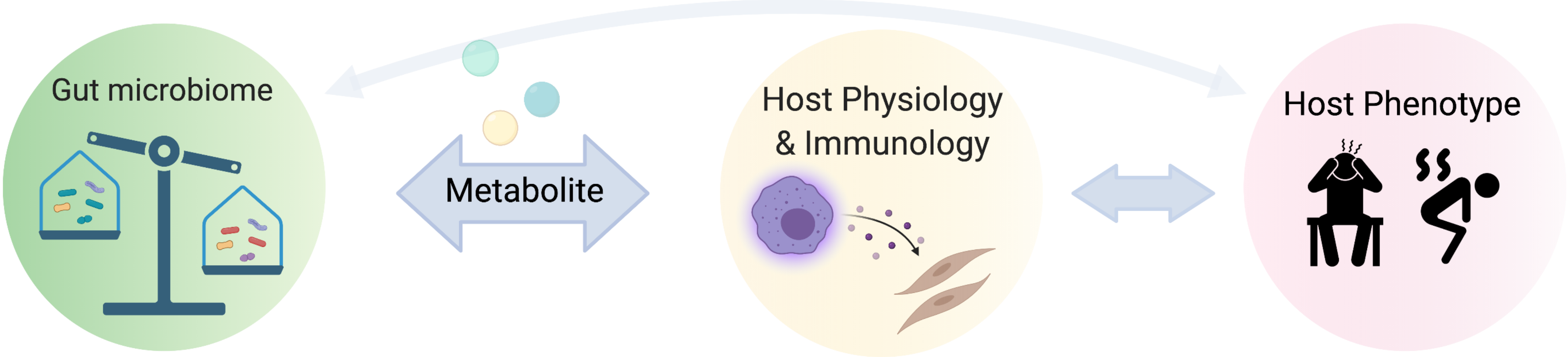
- Infection may trigger ME/CFS
    - Lyme disease (*Borrelia burgdorferi*), HIV, Q fevers (*Coxiella burnetii*)
- Fecal microbiota transplantation has anecdotal success in ME/CFS treatment
- Microbial dysbiosis is observed in ME/CFS in preliminary studies
    - Loss of diversity, reduction in putative anti-inflammatory species & increase in potential pro-inflammatory species

Rigor of prior research: metabolomic/immune manifestations of ME/CFS

- Metabolomic irregularities in ME/CFS
  - Disturbances in lipid and fatty acid metabolism
  - Broad profiling, lack of distinct, reproducible biomarkers

- Immune dysregulation in ME/CFS
  - Low-functioning natural killer (NK) cells
  - Tregs, Th17, mucosal associated invariant T cells

Our Framework: from multi-’omics to host-microbiome interactions



Decode the microbiome: metagenomics

Measure/Predict the metabolites

Host physiological changes

Epidemiology Model

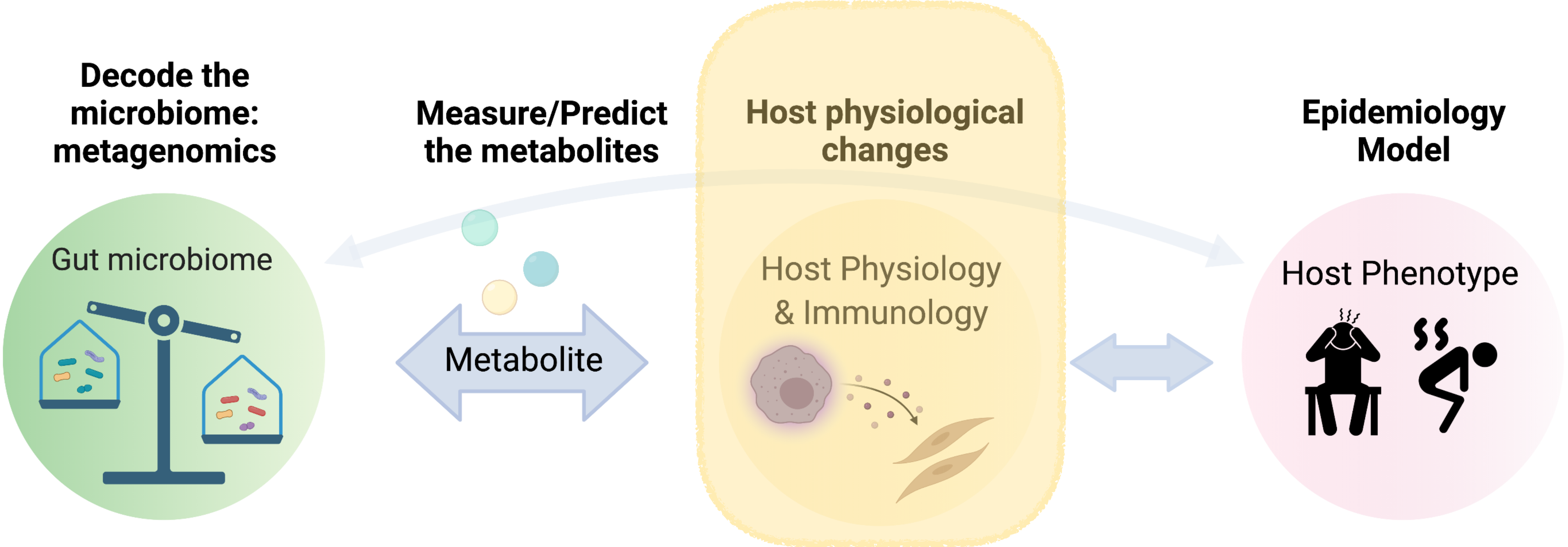
Gut microbiome

Metabolite

Host Physiology & Immunology

Host Phenotype

Our Framework: from multi-’omics to host-microbiome interactions



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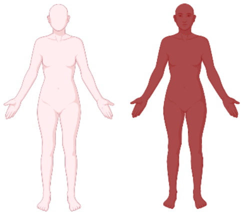
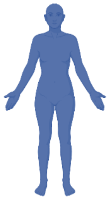
Project Design



MECFS Patient
(n = 149)

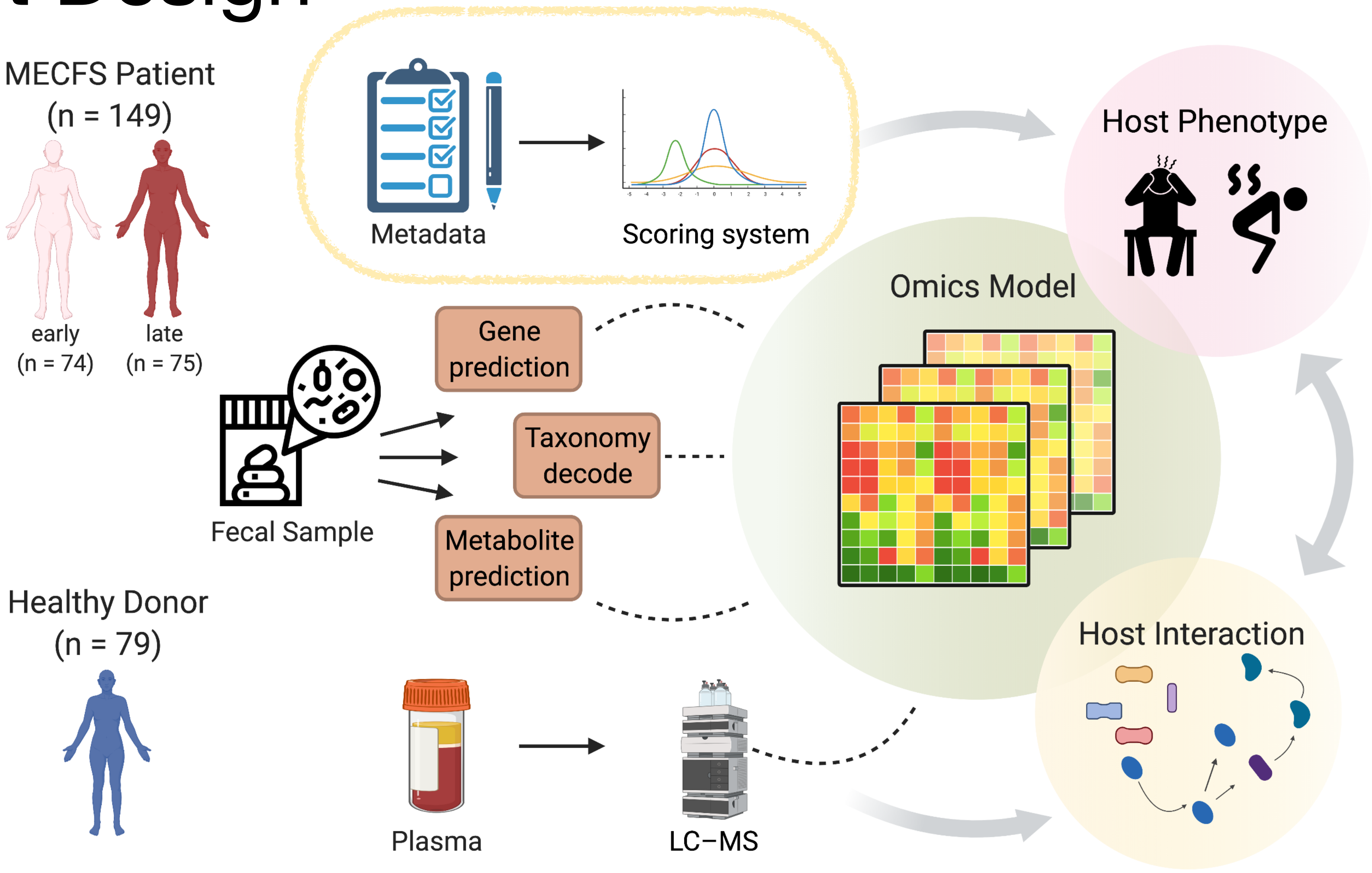
early
(n = 74)

late
(n = 75)



Healthy Donor
(n = 79)

Project Design



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Metadata

Scoring system

Host Phenotype

Omics Model

Gene prediction

Taxonomy decode

Metabolite prediction

Fecal Sample

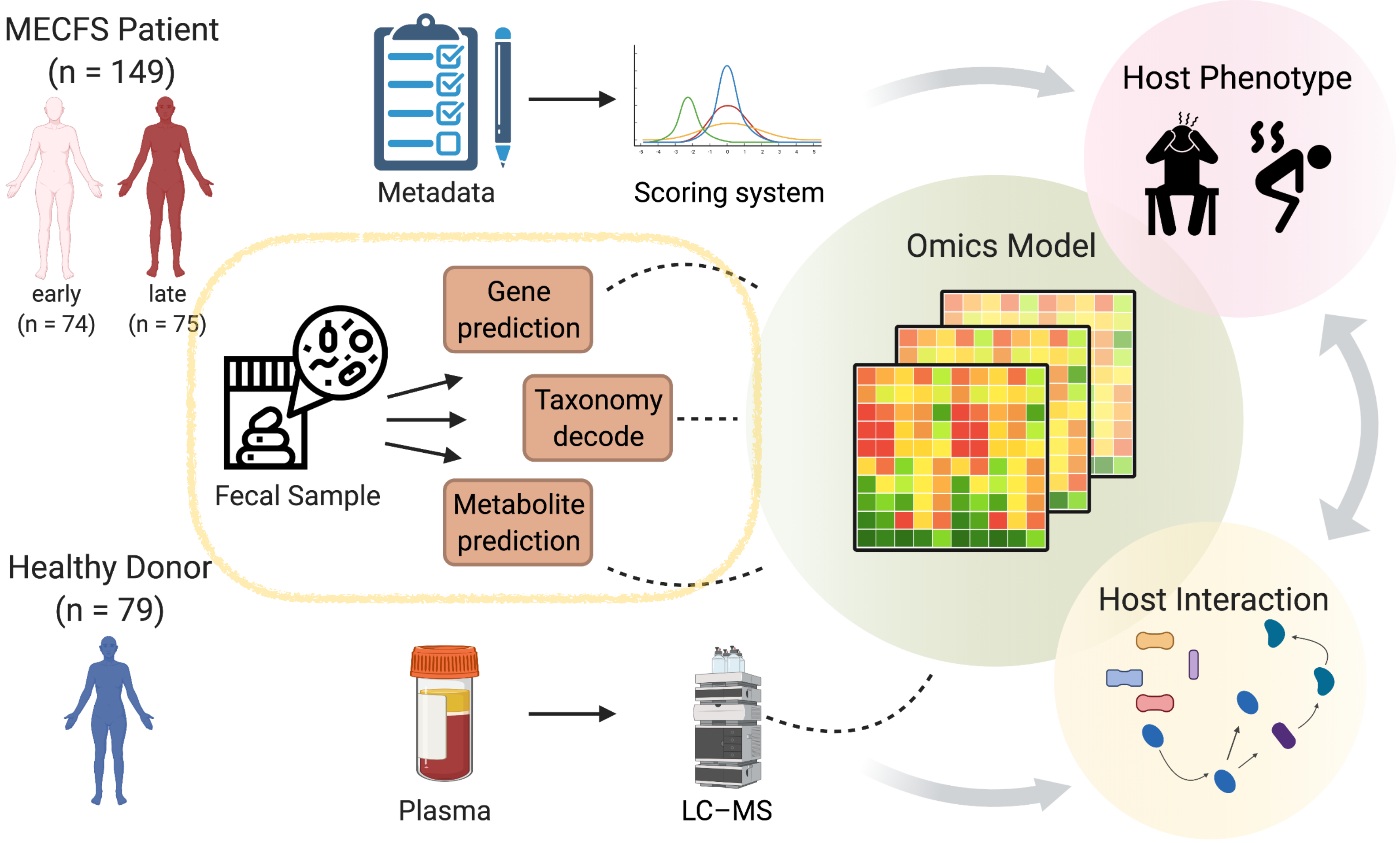
Healthy Donor
(n = 79)

Plasma

LC−MS

Host Interaction

Project Design



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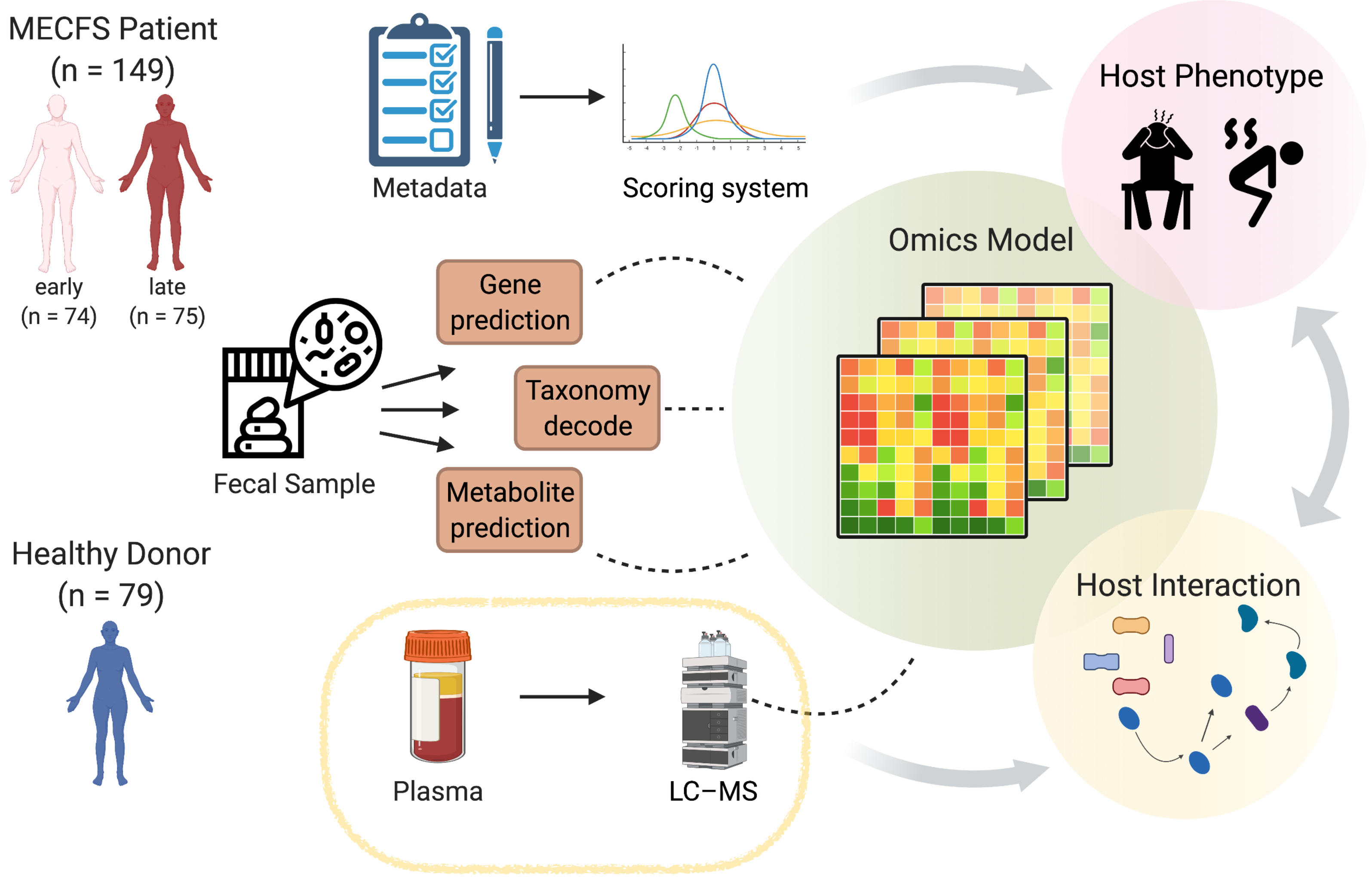

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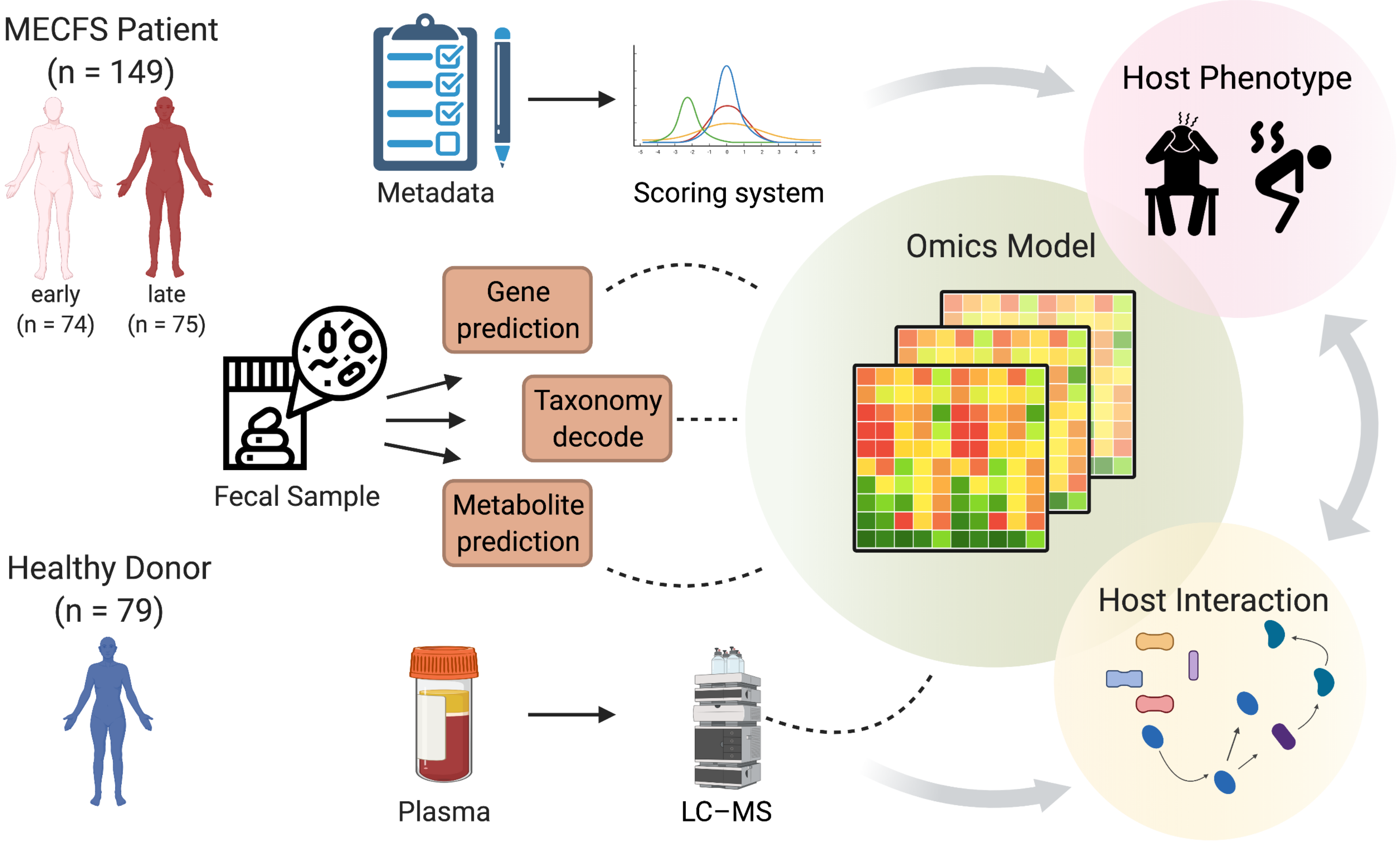

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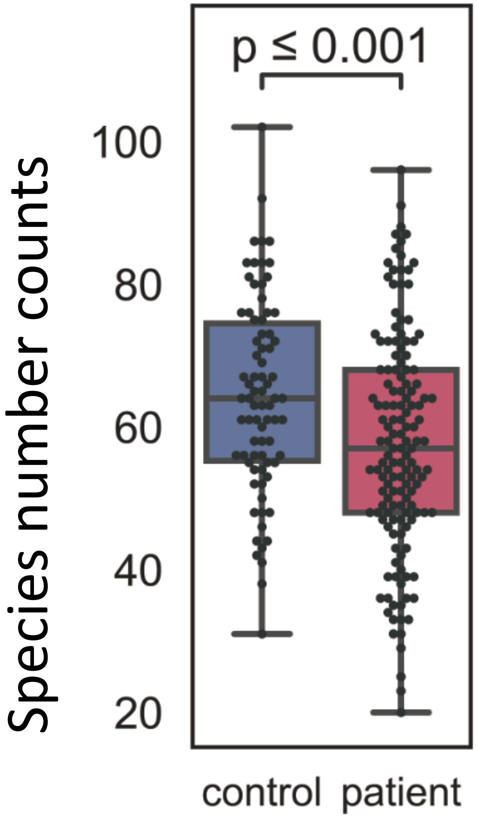
Xiong et al. Cell Host Microbe 2023 - major takehomes

- Short term patients show the most significant microbial dysbiosis
- Long term patients re-establish a healthy control lookalike microbiome, but have the most major metabolic dysbioses
- ‘Omics + clinical data -> most robust classification of cohorts
- Value of multi-omics analyses and multiple cohorts

ME/CFS patients, especially short-term, have decreased gut microbial diversity



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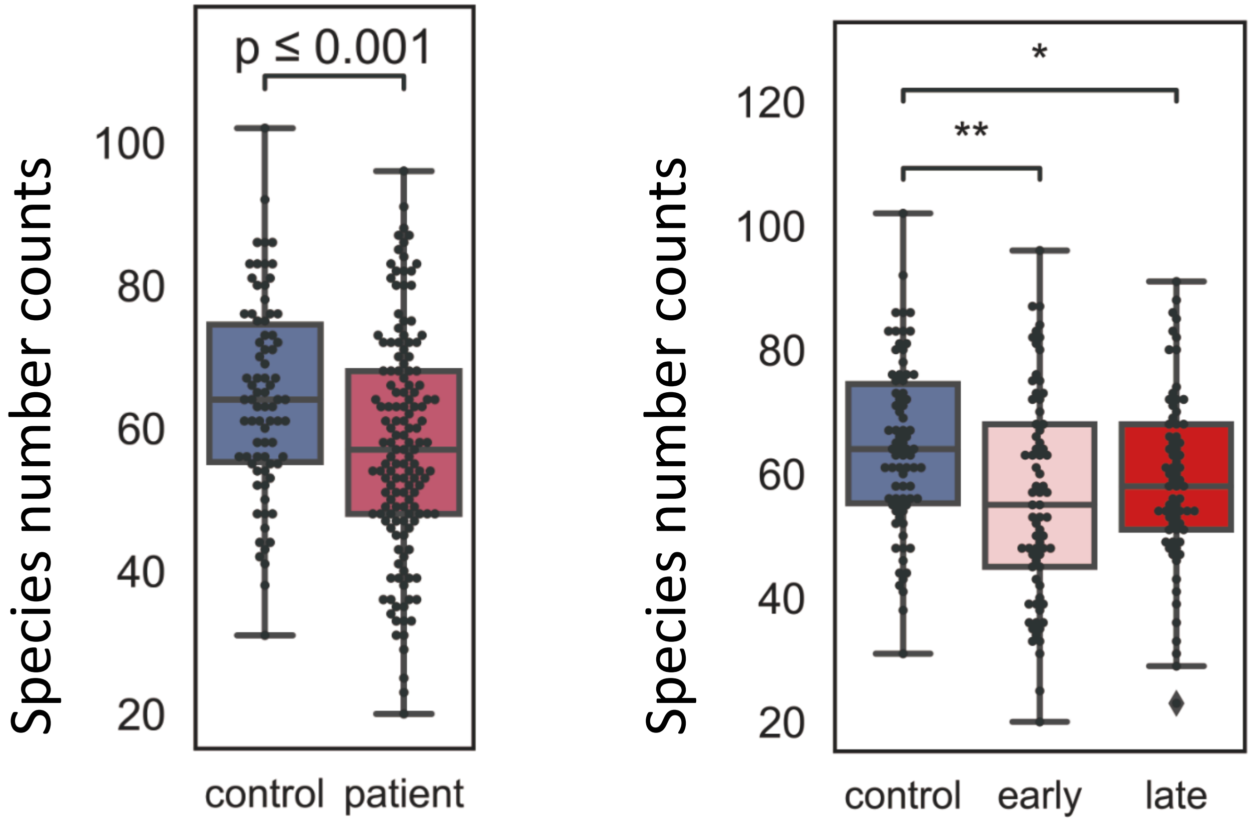
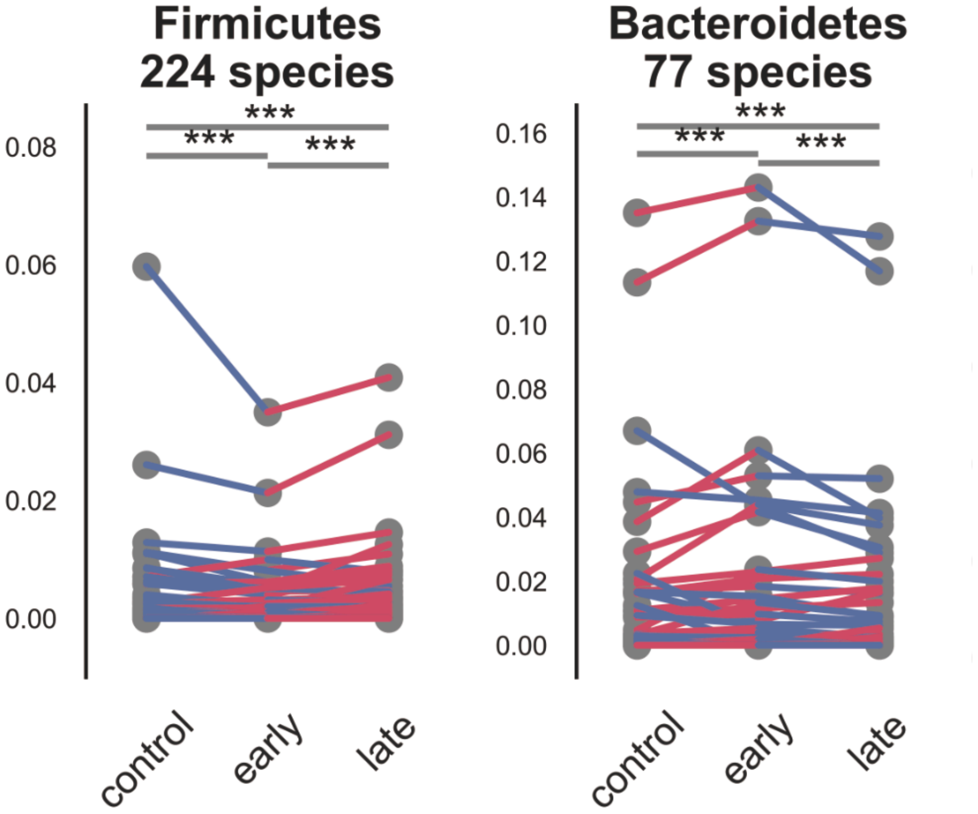


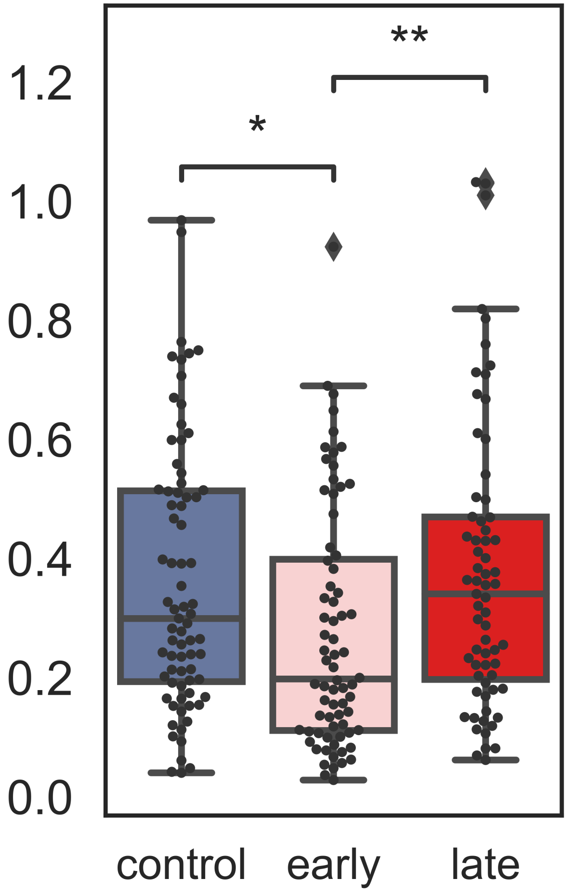
Key Firmicutes and Bacteroidetes are differentially abundant in early stage disease

Species relative abundance

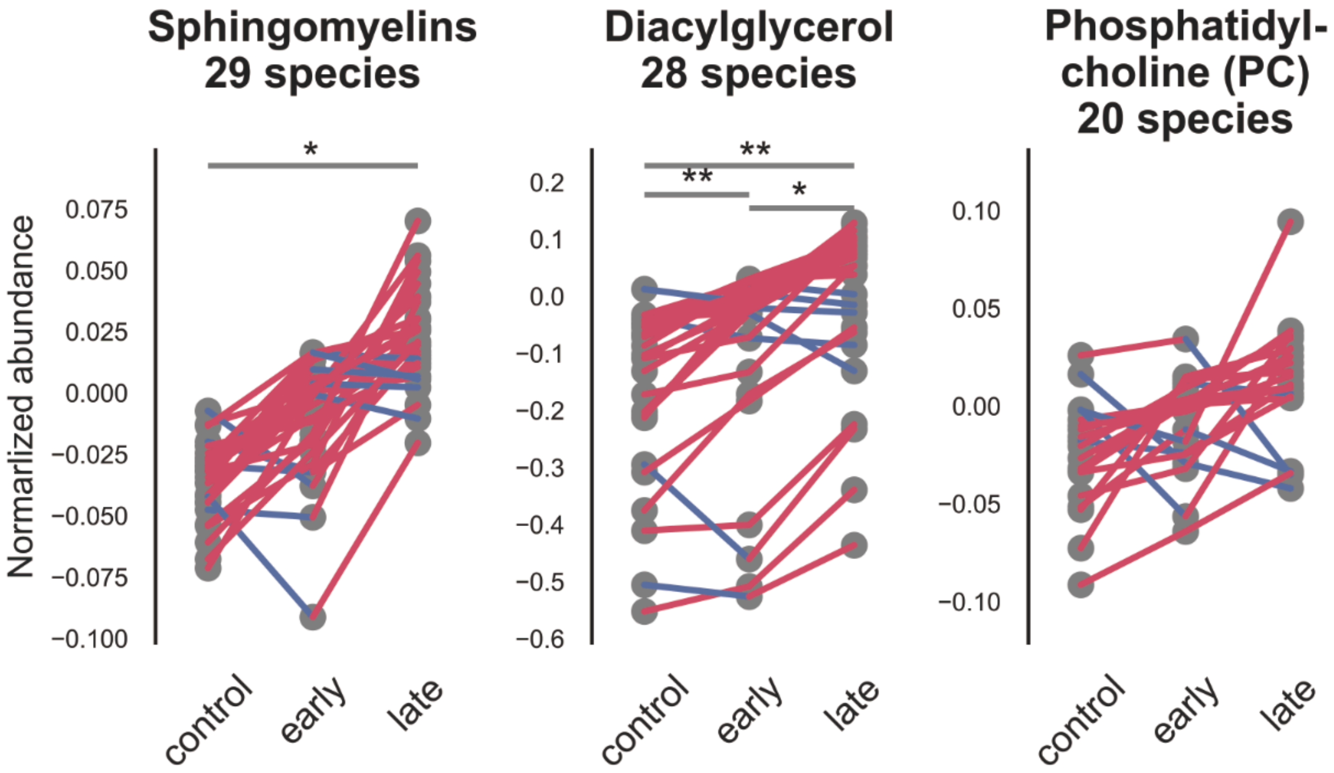


Key Firmicutes and Bacteroidetes are differentially abundant in early stage disease

Firmicutes:
Bacteroidetes
ratio



Signatures of differentially expressed blood metabolites manifest in late-stage disease



Xiong et al. Cell Host Microbe 2023 - major takehomes

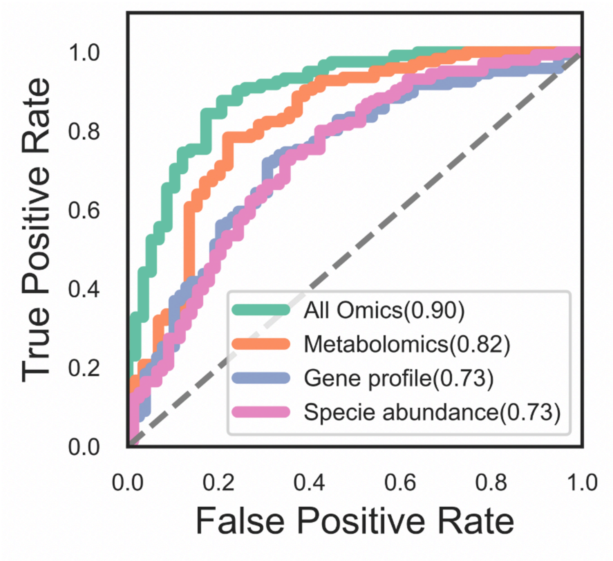
- Short term patients show the most significant microbial dysbiosis

- Long term patients re-establish a healthy control lookalike microbiome, but have the most major metabolic dysbioses
    - Iterative lifestyle changes? GI disturbances? Microbial changes lead to long-term dysbiosis?

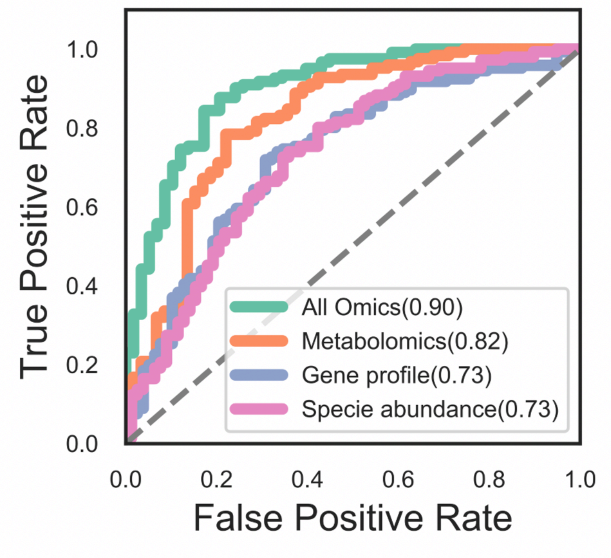
- ‘Omics + clinical data -> most robust classification of cohorts

- Value of multi-omics analyses and multiple cohorts

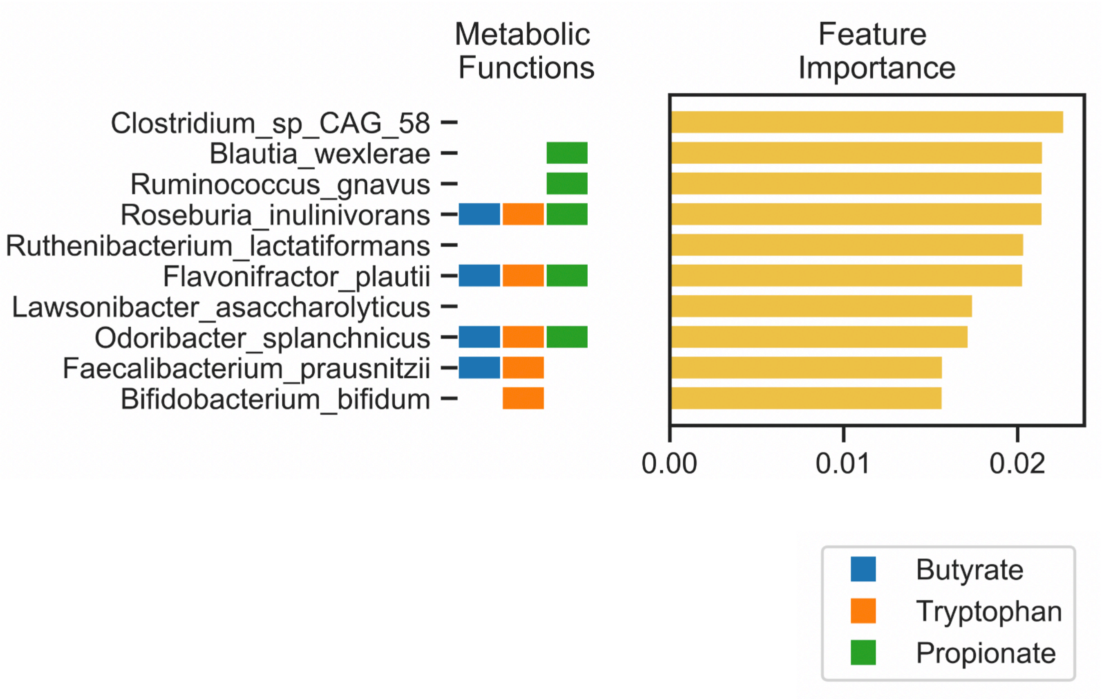
Multi-omics model accurately predict ME/CFS;



Multi-omics model accurately predict ME/CFS; biomarkers include butyrate pathway



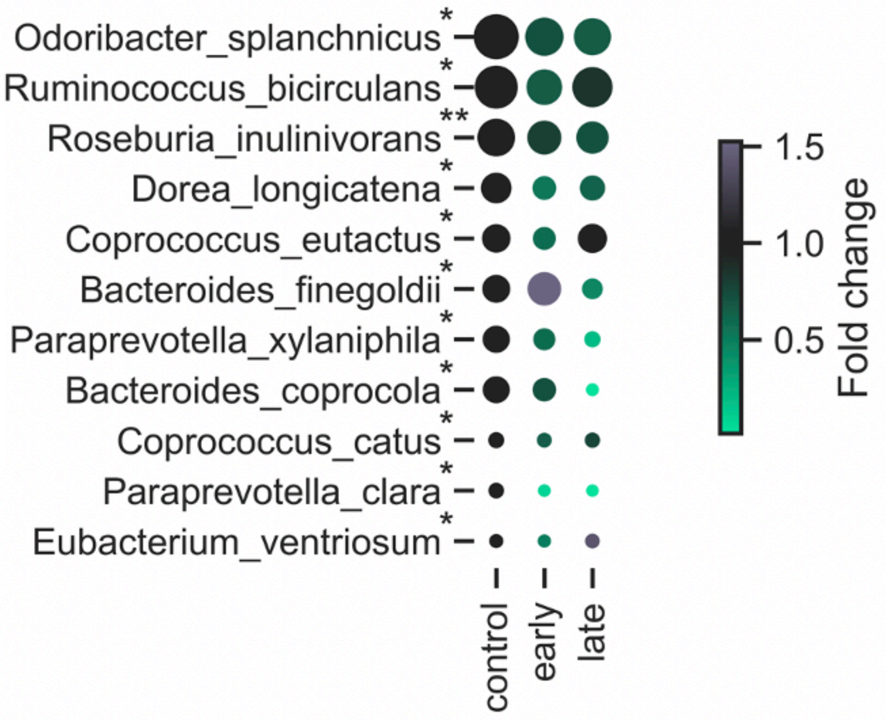
Species Abundance Gradient Boosting model



Host interactions point to reduced butyrate in gut in metabolomic data

Fold change

Butyrate producers



Relative abundance

Research opportunities and knowledge gaps

- No good animal model exists for MECFS (and similar complex diseases)
- Need: in human clinical studies paired with high resolution ‘omics to identify causal links (think immunotherapy studies)
    - Supplementation of butyrate producers
    - Butyrate and other SCFA
    - Dietary modulation
- Stay tuned for integration of high resolution immune data

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Courtney Gunter

Bateman Horne Center
Suzanne Vernon
Lucinda Bateman

Patients!

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NIH National Institute of Neurological Disorders and Stroke

NIH National Institute on Aging

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