

Microbe-Aware Precision Medicine

Katherine S. Pollard, PhD

Gladstone Institutes

UCSF Department of Epidemiology/Biostatistics, Institute for
Human Genetics, & Institute for Computational Health Sciences

Chan Zuckerberg Biohub Investigator

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Personal Path to Studying the Microbiome

Math, computer science, and anthropology:

- The field of bioinformatics didn't exist when I was in college

Career beginnings:

- Comparing human and chimp DNA
- Found the same building blocks are being assembled differently

Personal relevance:

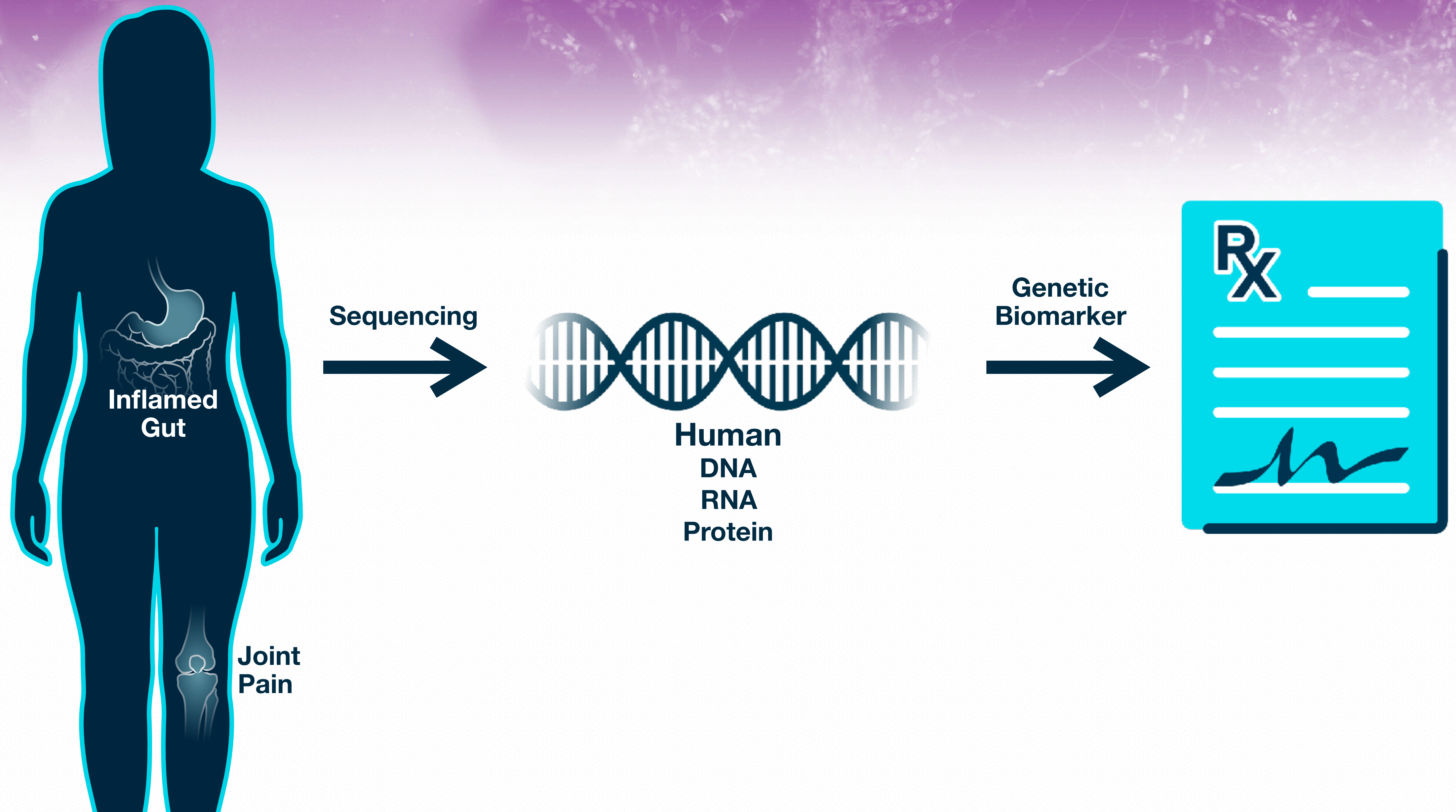
- Living with two autoimmune diseases

The Human Microbiome

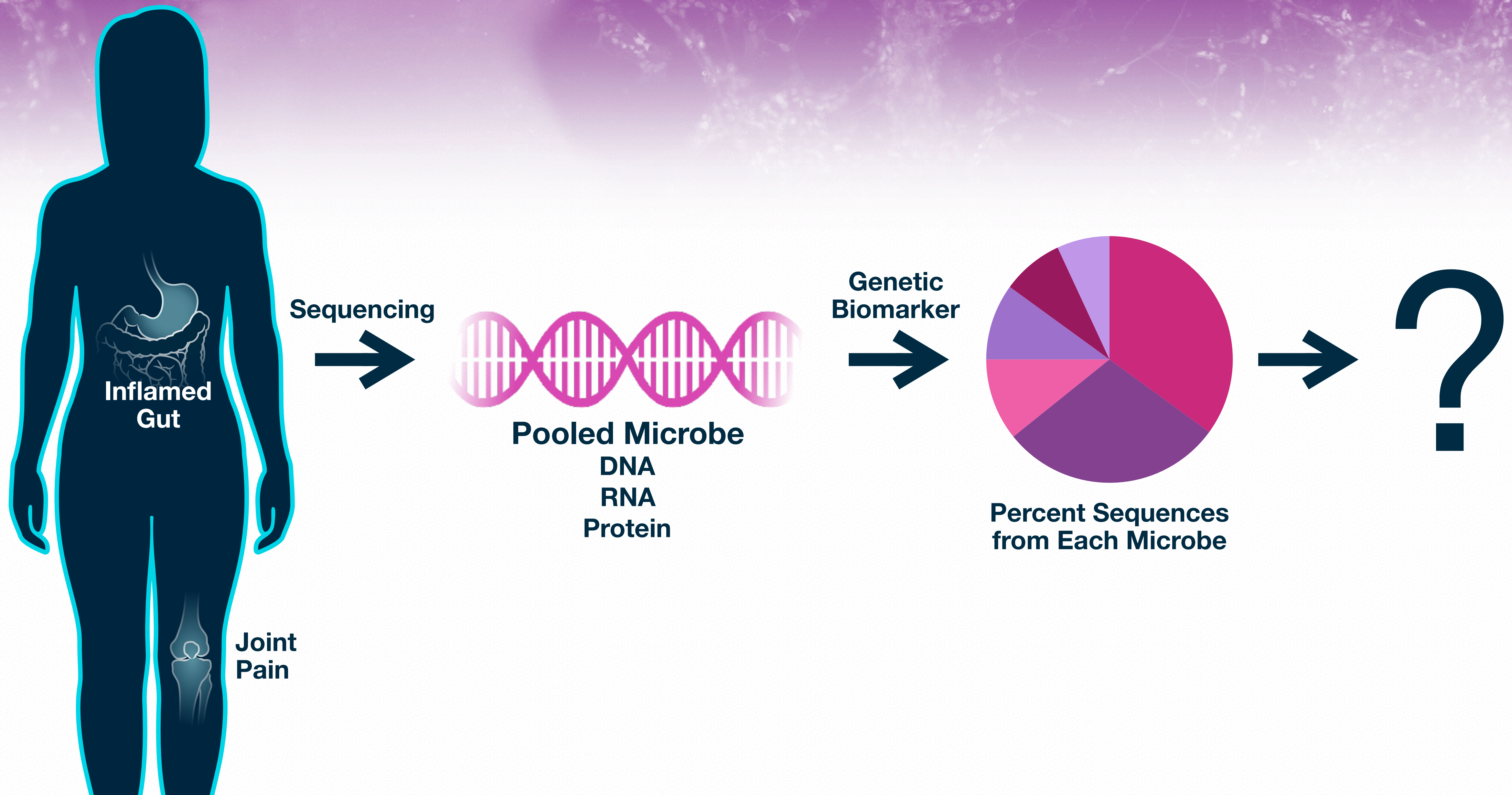
Microbes in our bodies:

- Contribute 300x more genes than human cells do
- Make up ~5 lbs. of body weight (most of which are gut microbes)
- Communicate and exchange molecules with human cells
- Integral to immune system
- Metabolize diet and drugs
- Interact with human genetics to make us who we are

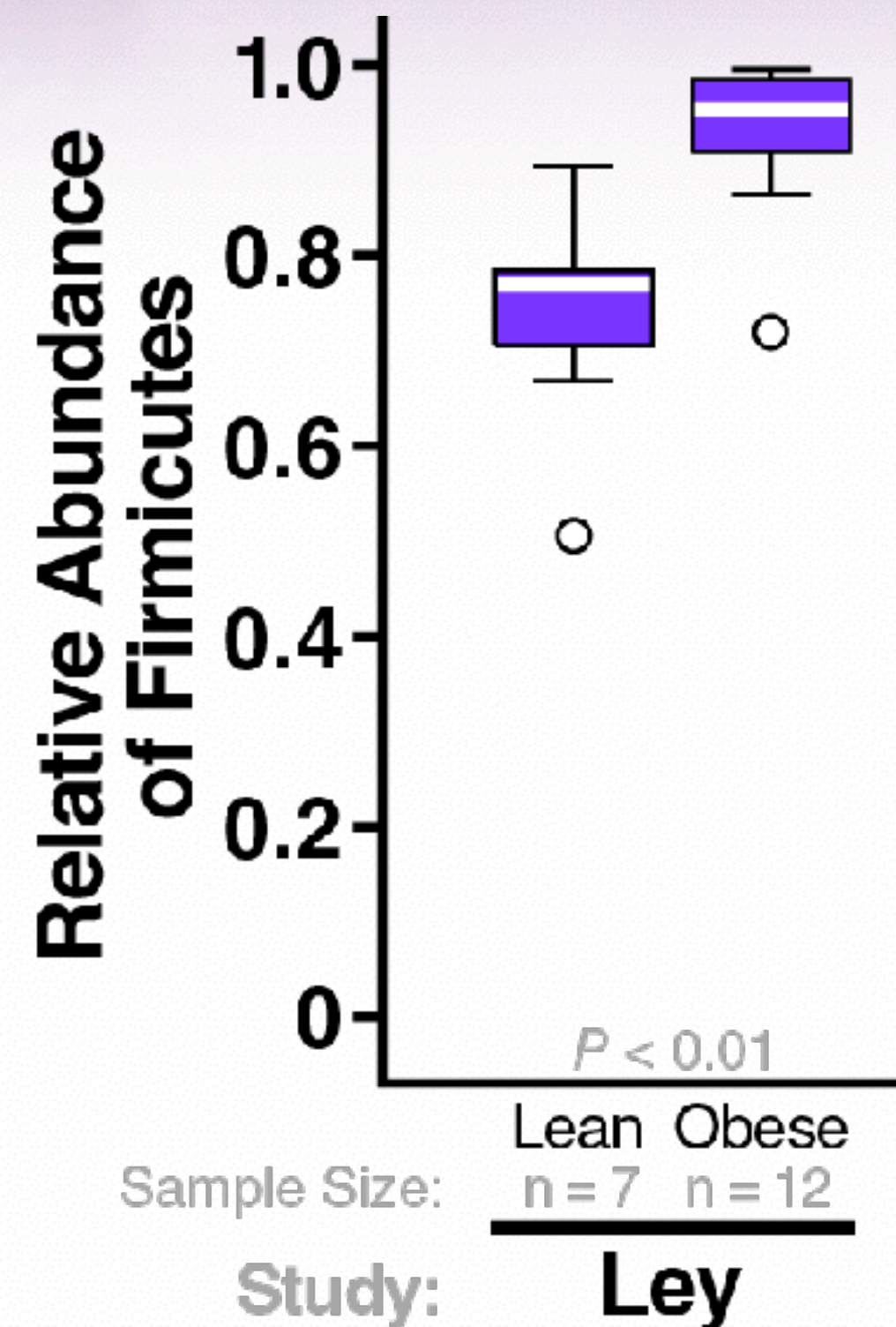
Precision Medicine 1.0



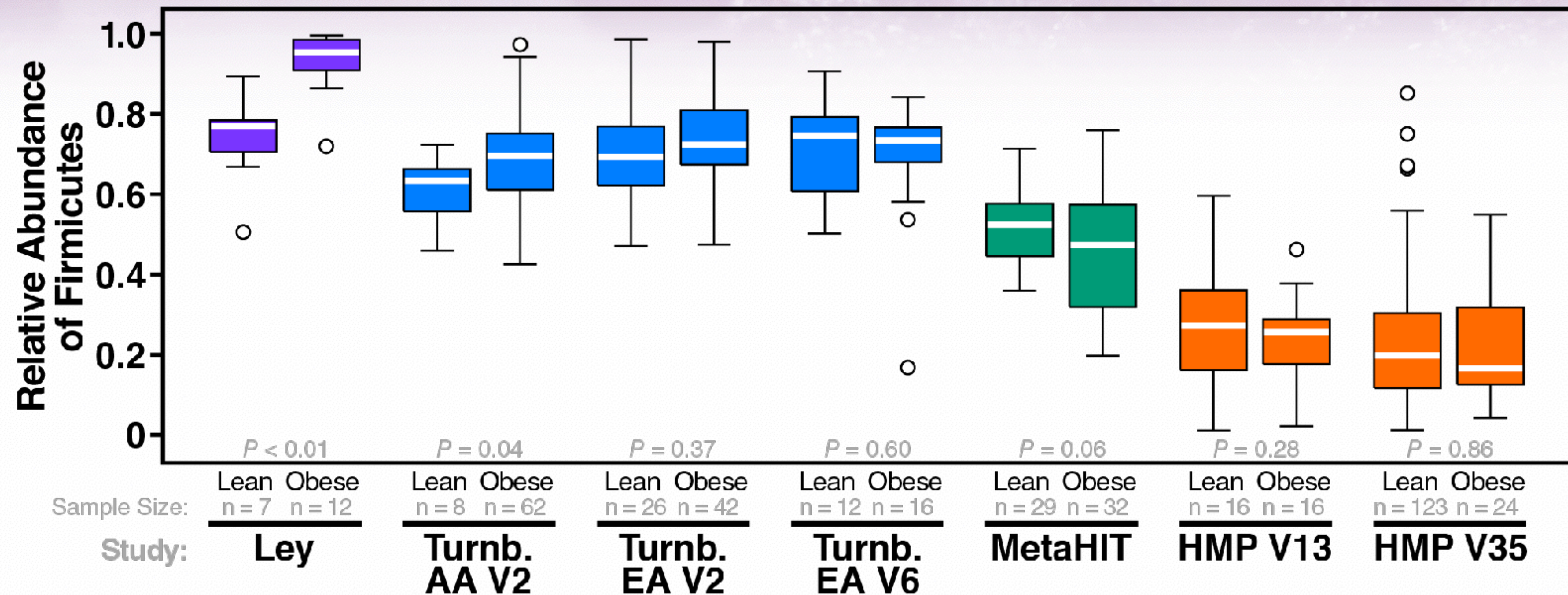
Microbiome Clinical Research



Microbe Abundance Fails as a Disease Biomarker



Microbe Abundance Fails as a Disease Biomarker



- Inconsistent association between obesity and phylum level composition of gut microbiome
- Much more variation across studies than between lean and obese groups within studies

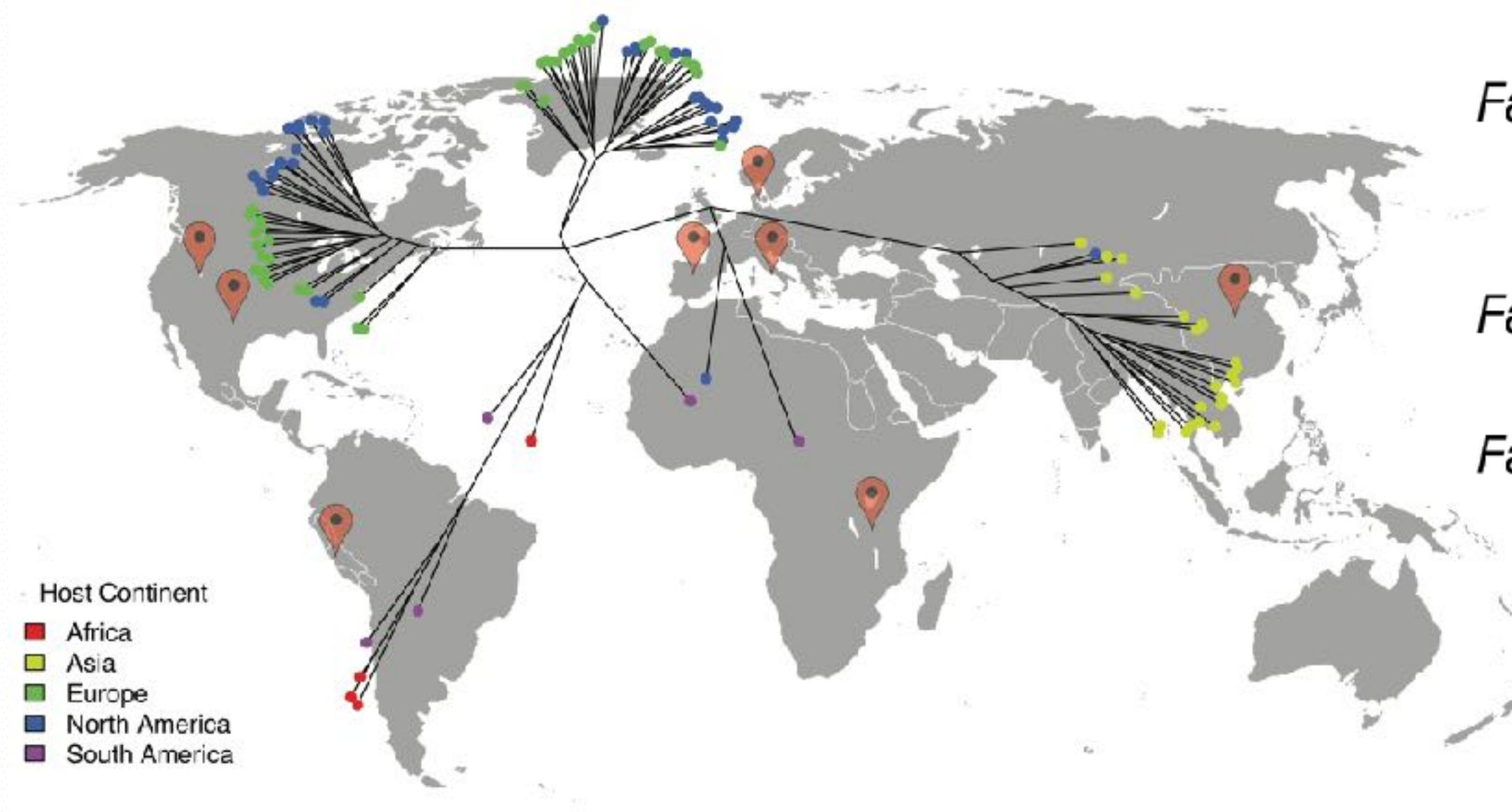
Strains of Same Species Have Different Genes

25-50% of genes differ between strains in two people

Stool metagenomes from 2 people

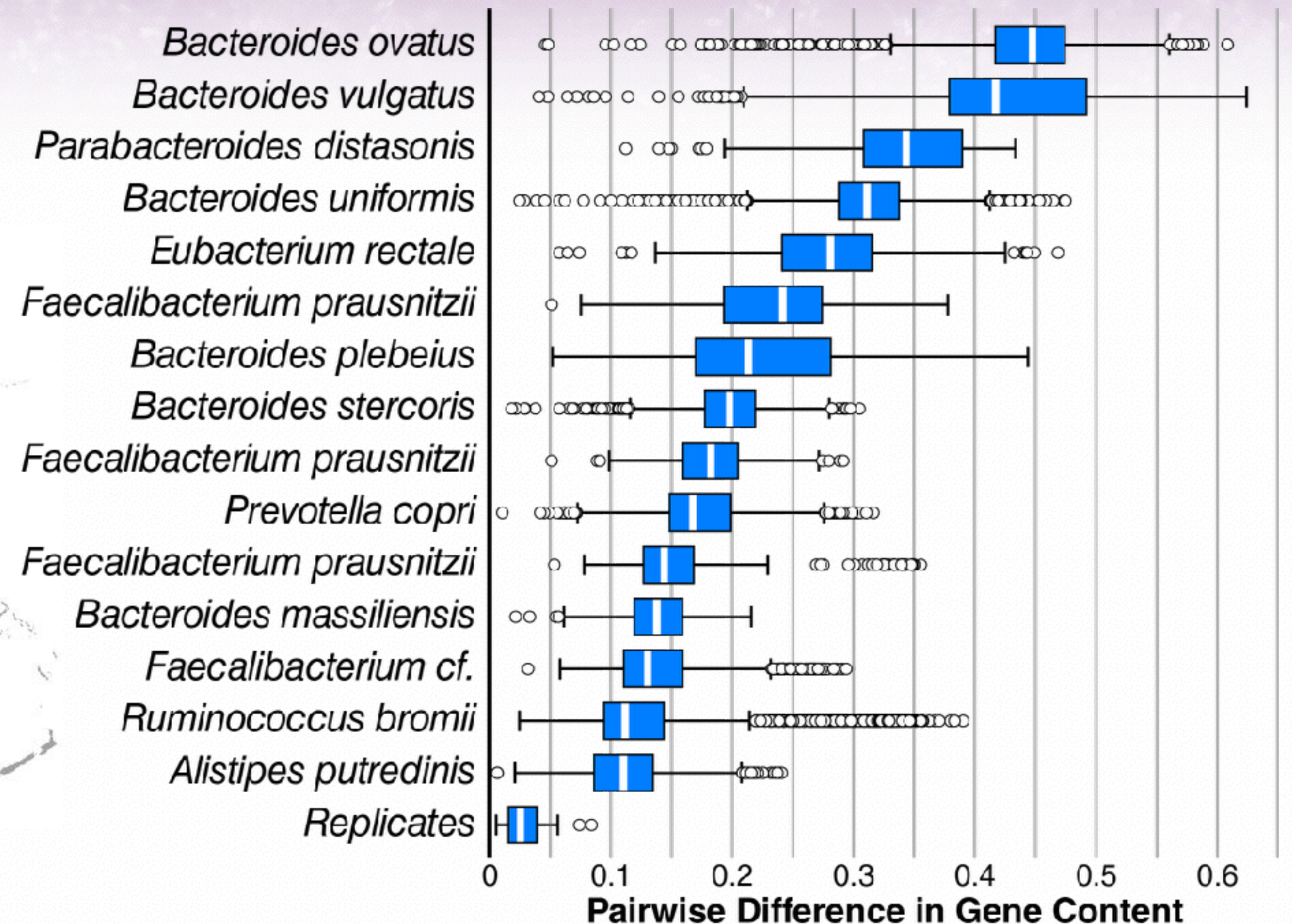
Find shared species

For each species, compare genes



**Data: Healthy individuals from 8 studies,
downloaded from SRA**

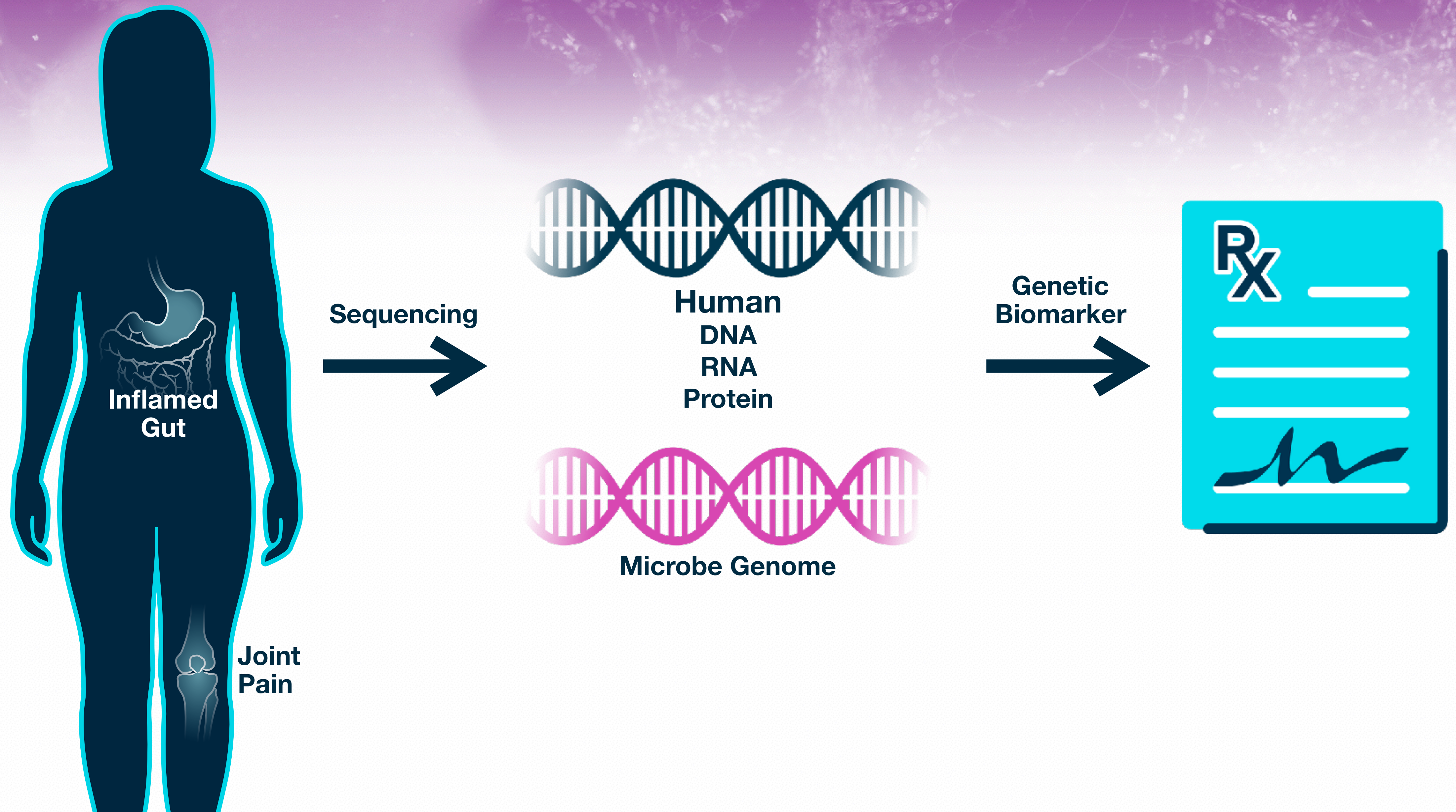
Nayfach & Pollard (2015)



The background of the slide is a microscopic image of cells, likely from a tissue sample, showing various cellular structures and nuclei. The image is in grayscale and has a slightly blurred, high-magnification appearance.

**Idea: Study Microbes
at the Level of Genetic
Mutations, Just Like
Human DNA**

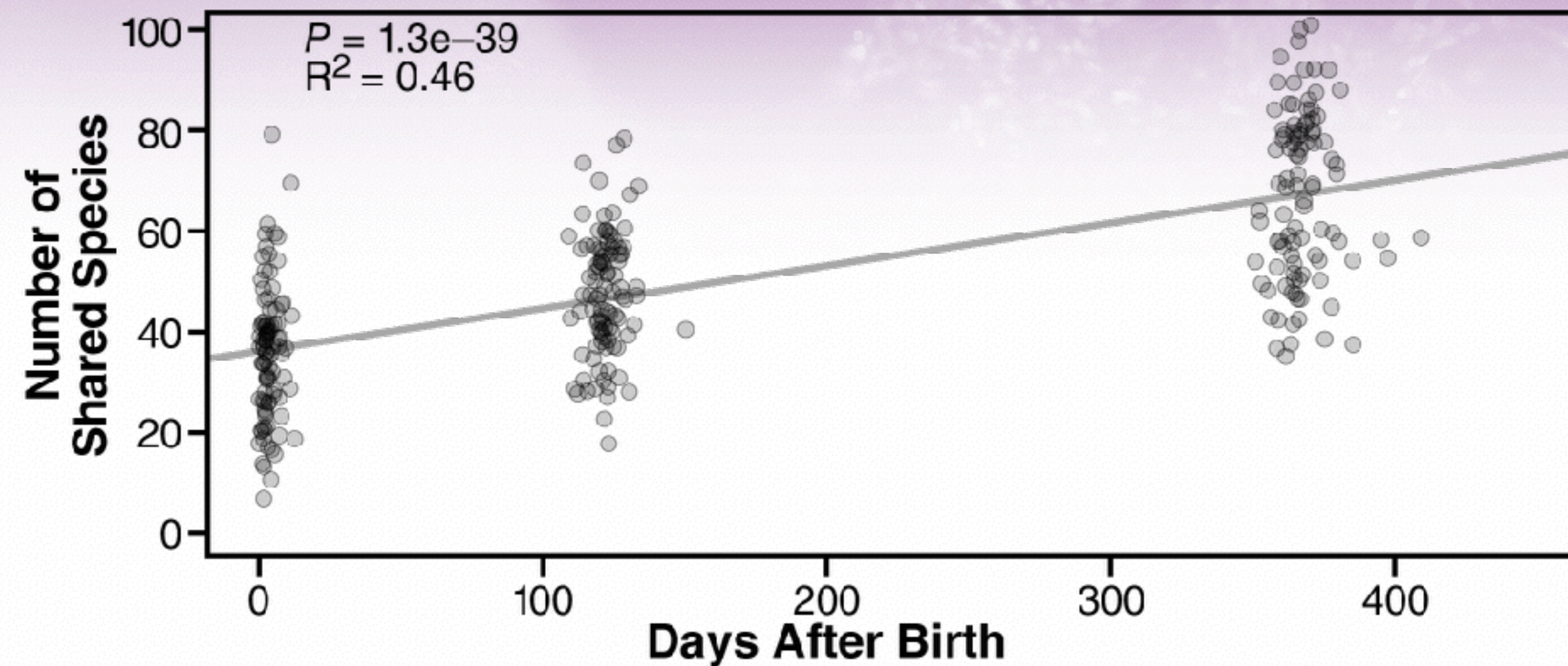
Precision Medicine 2.0



The background of the slide features a purple-to-white gradient. The top portion is a solid purple, while the bottom portion is white. A faint, intricate network of thin, light-purple lines, resembling a microbial or genetic structure, is visible across the entire background.

How Can We Use Microbiome Genetic Data?

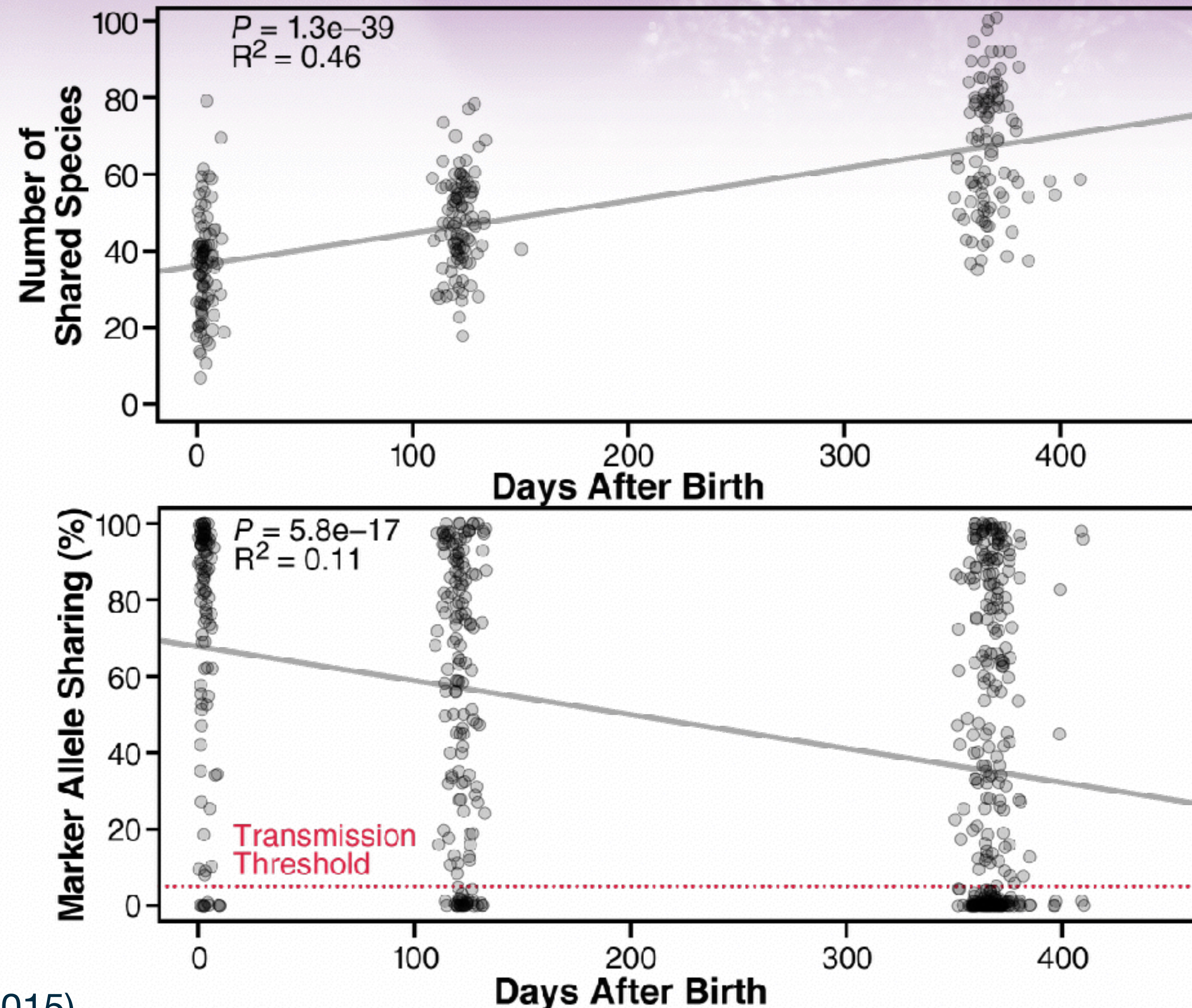
Study Example: Infant Gut Strains Not From Mom



- Species more similar over time
- Same trend with unrelated mothers

Idea: Track strains with “private” mutations in each mom. Are they in her baby?

Study Example: Infant Gut Strains Not From Mom



- Species more similar over time

- Strains less similar over time

Conclude: Infant likely colonized by sources other than mom

What Have We Learned?

- Human microbiomes encode cryptic functional variation that is missed unless you investigate individual strains and genes.
- Microbiome diversity is massive compared to what is in current databases, especially in natural environments, lab mice, and humans outside North America/Europe.
- Bioinformatics and metagenomics enable individual strains and genes to be tracked. Examples: transmission, antibiotic resistance.
- Microbe genetic variation correlates with traits such as ability to colonize humans and host disease.

The Future of Microbiome Science & Medicine

- Unlocking biomedical problems that can't be solved by studying human cells alone.
- Genetic testing for human **and** microbial cells in our bodies.
- Challenges for **microbiome precision medicine**:
 - Complexity of microbial communities and their evolution
 - Sensitivity for rare microbes/genes: could be important!
 - Microbial “dark matter”: what do mutations mean?
 - Processing and learning on terabytes of data
 - Communicating this complexity to patients/consumers/readers

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