Microbe-Aware
Precision Medicine

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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

- Inflamed Gut
- Joint Pain
- Sequencing
- Human DNA RNA Protein
- Genetic Biomarker
Microbe Abundance Fails as a Disease Biomarker
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- 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

Stool metagenomes from 2 people
Find shared species
For each species, compare genes

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

Data: Healthy individuals from 8 studies, downloaded from SRA
Nayfach & Pollard (2015)
Idea: Study Microbes at the Level of Genetic Mutations, Just Like Human DNA
Precision Medicine 2.0

- Inflamed Gut
- Joint Pain
- Sequencing
- Human DNA
- RNA
- Protein
- Microbe Genome
- Genetic Biomarker
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?

Data: Backhead et al. (2015)
Nayfach et. al (2016)
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

Data: Backhead et al. (2015)
Nayfach et. al (2016)
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