Precision microbiome medicine: Identifying diagnostics and treatments

Jack A Gilbert

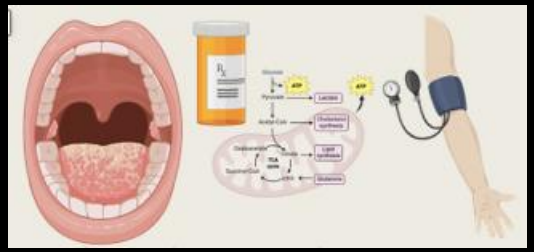
Disclosures

(1) Co-Founder & Scientific Advisor, BiomeSense
(2) Scientific Advisory Board Holobiome
(3) Scientific Advisory Board, Oath Inc.
(4) Scientific Advisor, Bened Life

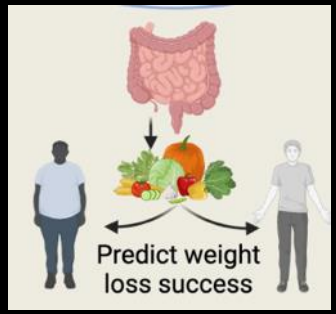
The immune system is like a National Park warden or a gardener managing the microbial ecosystem to benefit human health

Understanding clinical translation of microbiome research through the concept of mechanisms, metrics and modifiers

Mechanism – identifying how microbes interact with the body can help identify drug targets.

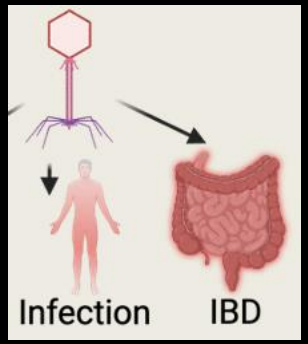


Gilbert et al., NatMed, 2025



Metrics – Identifying microbial features that are predictive of risk or response, or diagnostic of disease.

Modifiers – Proven strategies to manipulate the microbiome to treat disease or improve treatment efficacy.



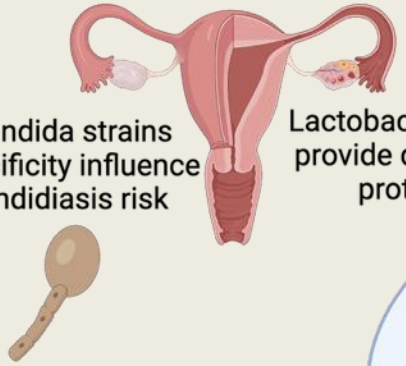
Microbiome Mechanisms

Strain specific functions

Ecological Dynamics

Microbial metabolism

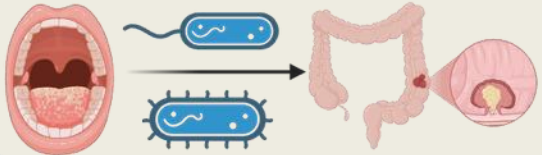
Immune System Mediation



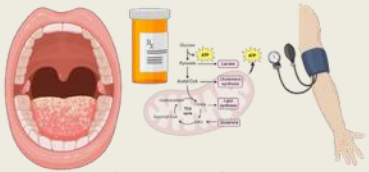
Candida strains specificity influence candidiasis risk

Lactobacillus strains provide different BV protection

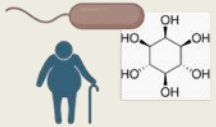
Complement and IgA in BM controls pathogens, ecological succession, and immune development



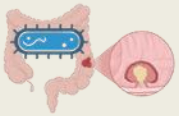
Ecological disruption in gut microbiome increases translocation of oral bacteria and subsequent CRC risk



Oral antibiotics disrupt microbial N cycling increasing blood pressure



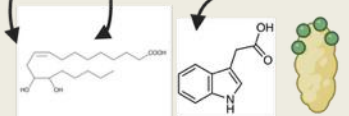
Microbial metabolism of myo-inositol promotes lipid absorption and obesity



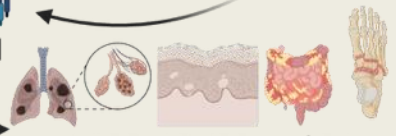
Fusobacterium stimulates CRC tumor growth through formate metabolism

Microbes mediate inflammatory diseases

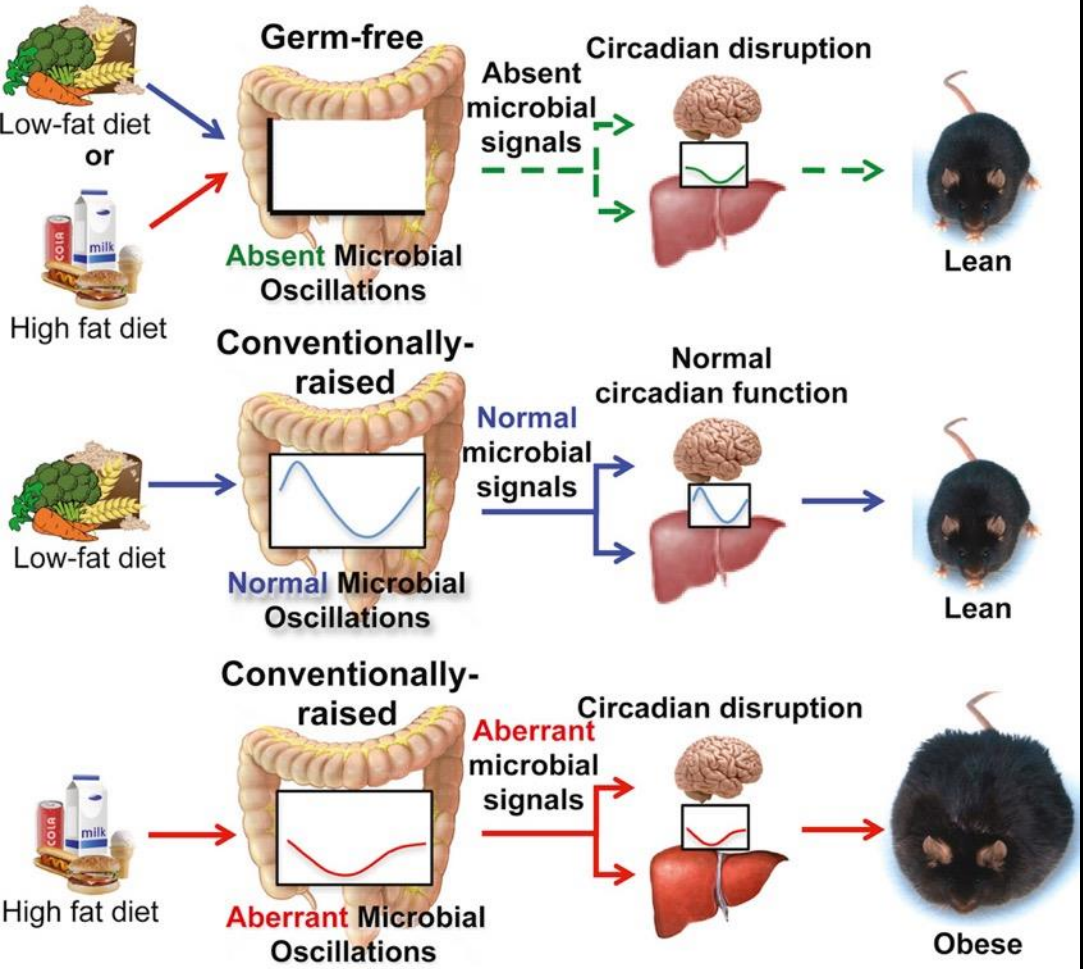
AHR1; TLR4; IFN1



12,13 DiHOME; I3AA; BA



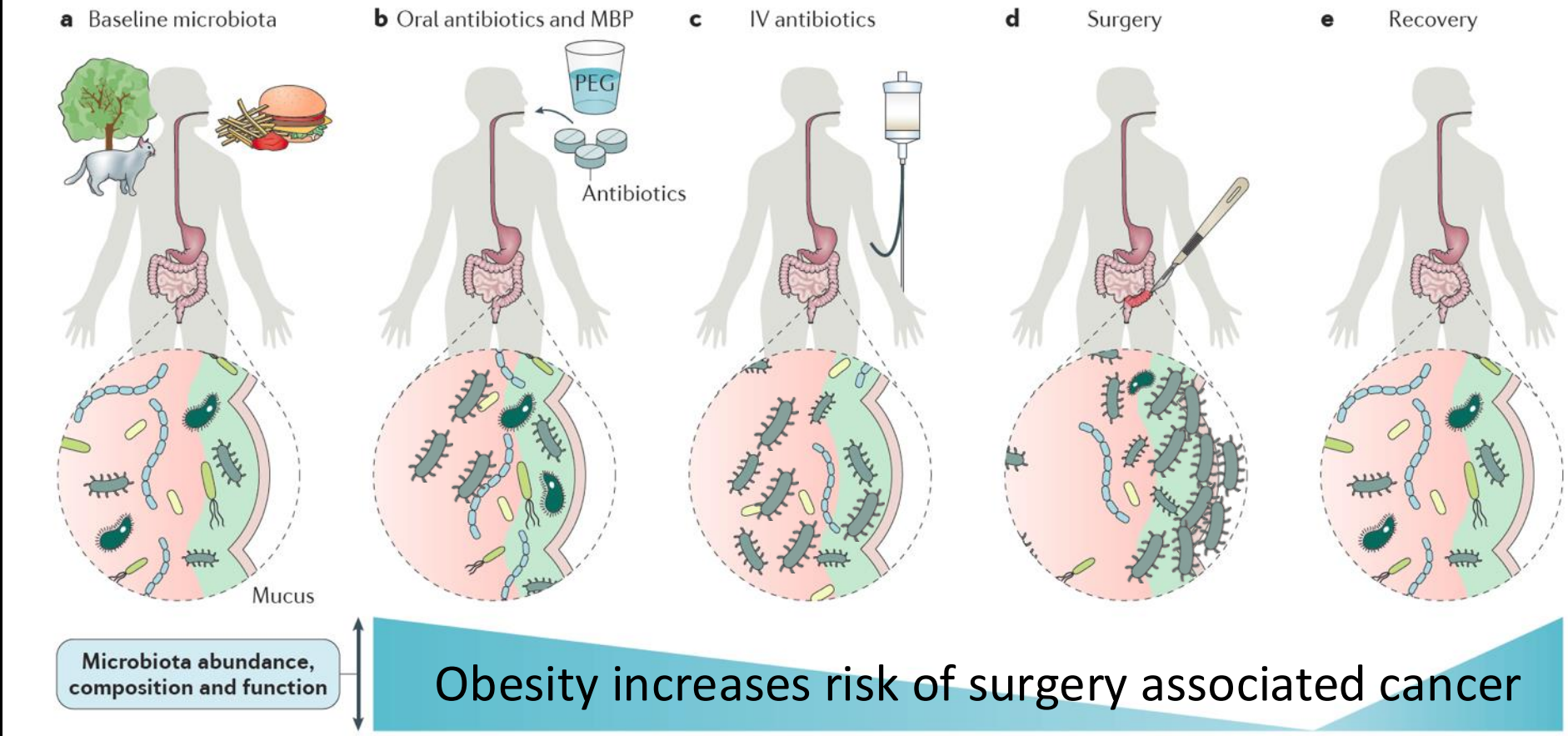
COPD, AD, IBD and RA



Food creates Dysbiosis which influences obesity

High saturated fat and sugar increases the abundance of facultative anaerobes, increasing H2S production which interferes with CLOCK gene transcription, changing hepatic hormones, adipose tissue production, and appetite

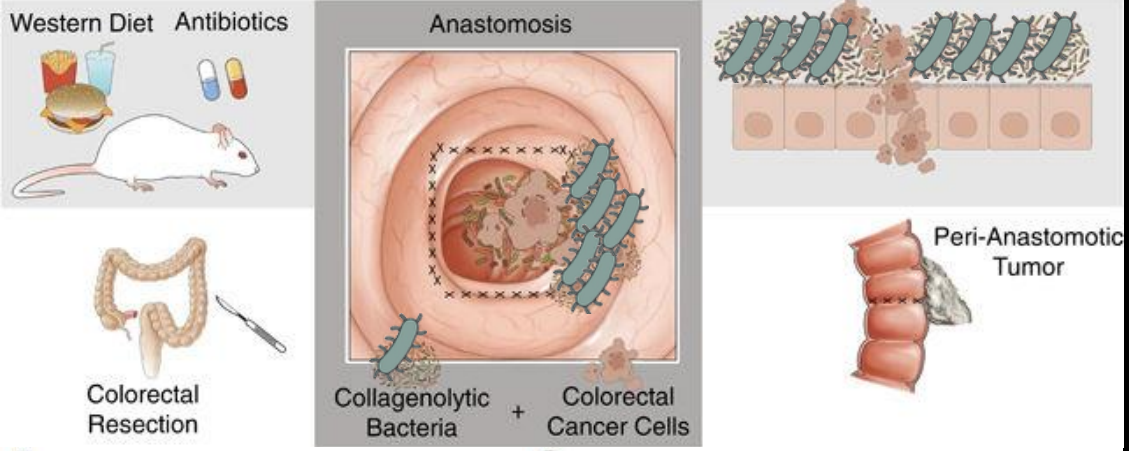
Leone et al., 2015 Cell Host Microbe

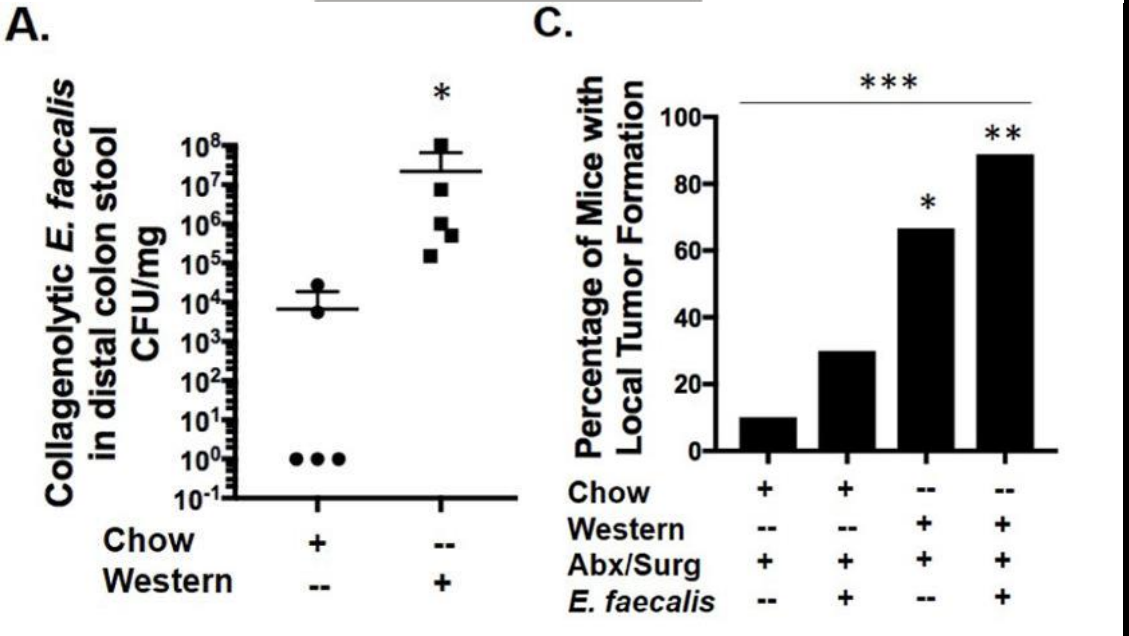


Collagenolytic Bacterium

Western Diet and obesity promotes Intestinal Colonization by Collagenolytic Microbes and Promotes Tumor Formation Following Colorectal Surgery – **Gaines et al Gastroenterology, 2019**

Obesity associated bacteria can trigger tumor formation



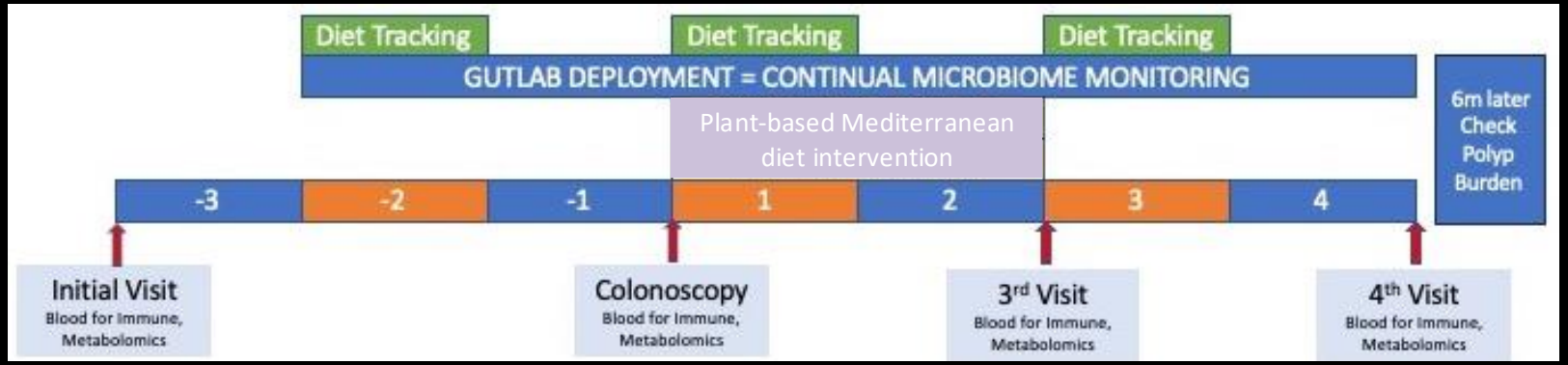


- Tumor formation is dependent upon a high-fat diet and collagenase producing bacteria at the site of intestinal surgery.
- Western Diet causes increase in collagenolytic bacteria.
- High Fiber chow reduces these bacteria and risk of tumor formation.

Gaines et al Gastroenterology, 2019

Can we remove collagenolytic bacteria with diet?

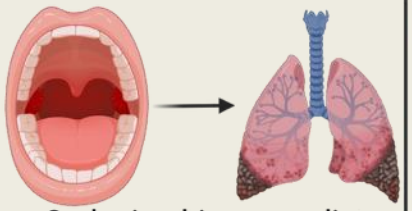
Joshua Tran



- Recruiting people with Serrated Polyposis Syndrome
- Diet Intervention with plant-based Mediterranean diet.
- Phage intervention to remove *E. Faecalis*.
- Assess immunology, metabolomics, metagenomics and polyp reemergence.

SEERAVE FOUNDATION

GBS subtypes predict infant infection risk

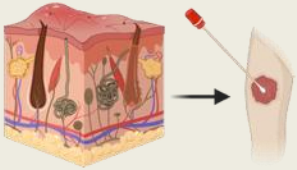


Oral microbiome predict survival and severity in IPF

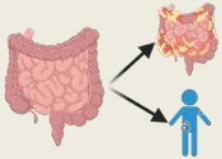
Candida strains predict VVC

Oral bacteria in gut predicts IBD and CRC

Skin microbiome predicts frailty



Skin microbiome predicts SSI



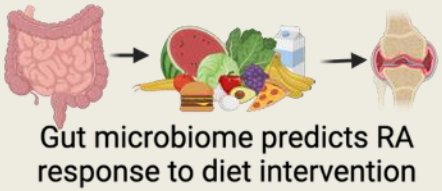
Gut microbiome predicts IBD and T2D

Predicting Disease Risk

Diagnosing Disease

Microbiome Metrics

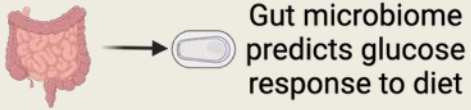
Predicting Treatment Response



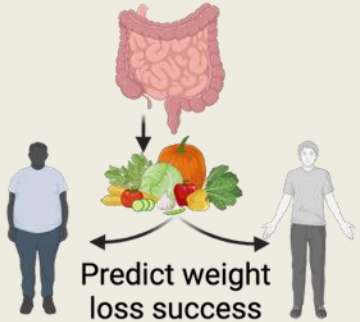
Gut microbiome predicts RA response to diet intervention

Gut microbiome predicts diet that will improve metabolic health

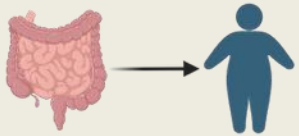
Gut microbiome predicts ICB treatment survival



Gut microbiome predicts glucose response to diet

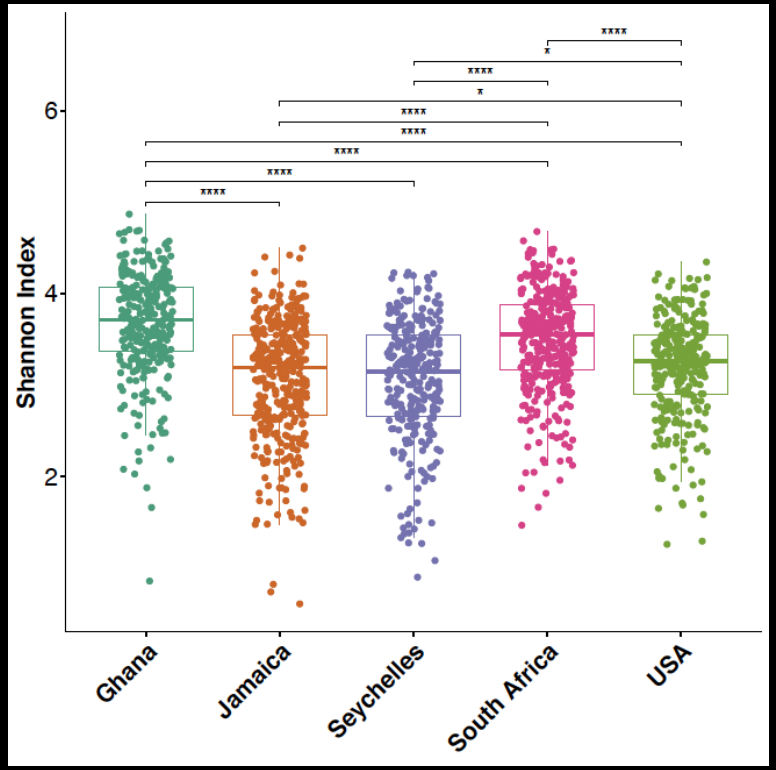


Predict weight loss success



Gut Christensenellaceae and Blastocystis predict healthy lifestyle and health outcomes.

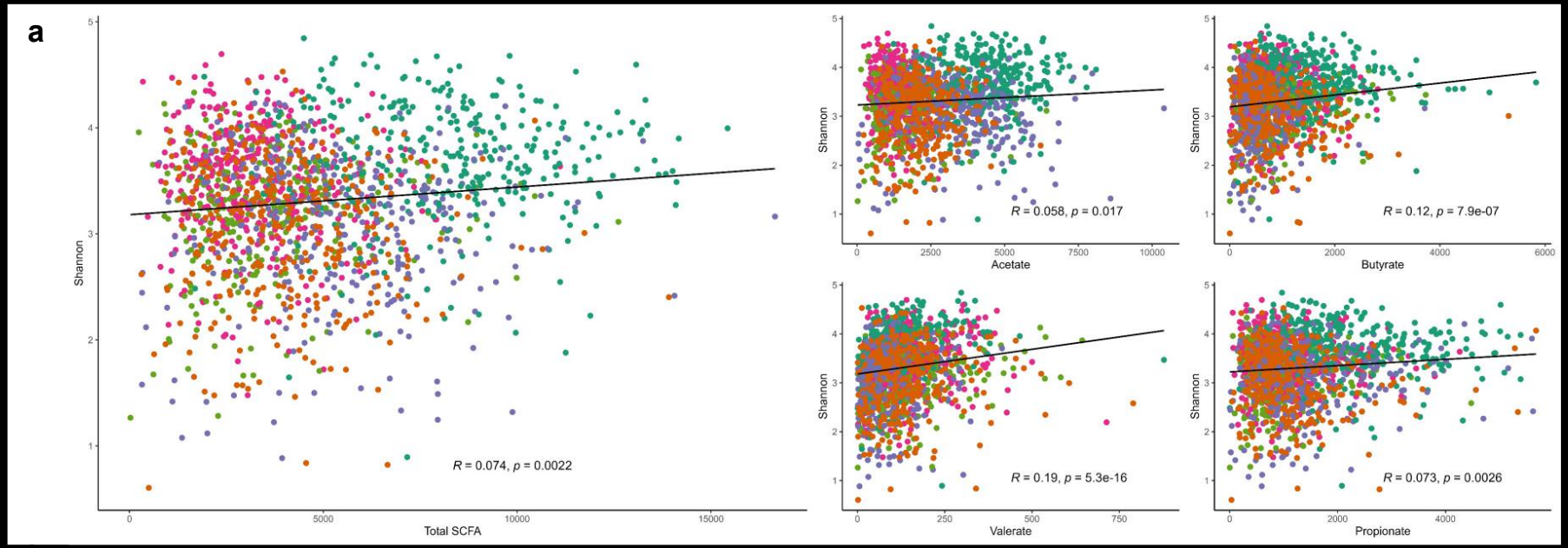
Greatest alpha diversity in Ghanaian participants, lowest in US participants



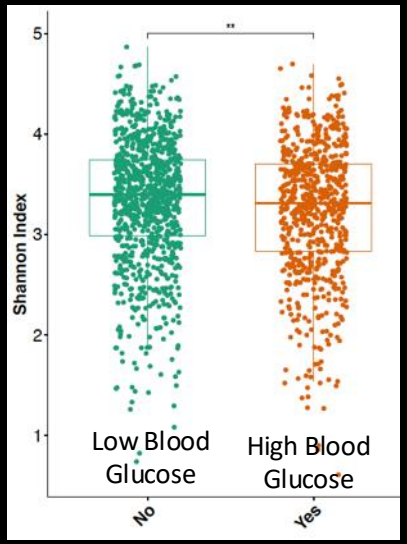
- Species richness of gut microbes shows clear signs of acculturation
- Lowest species diversity seen in Seychelles and USA
- Ghana has greatest diversity – likely resulting from high fiber content in diet

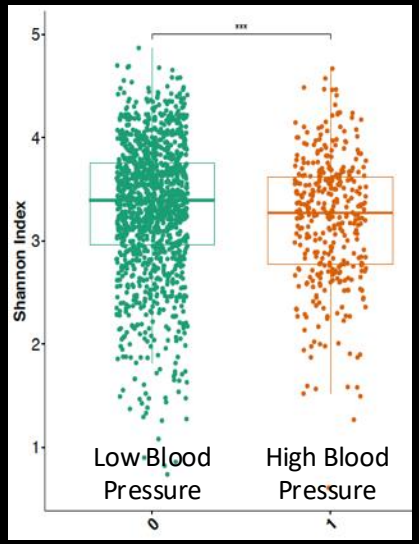
Gertrude Ecklu-Mensah

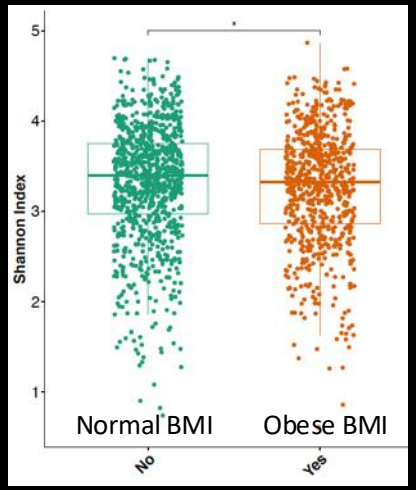
Alpha diversity positively correlates with fecal short chain fatty acid concentrations

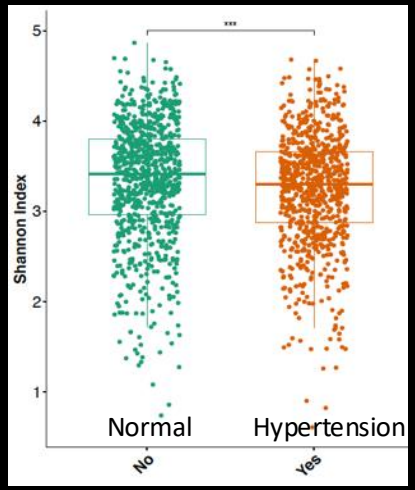


Ecklu Mensah et al Nature Communications 2023







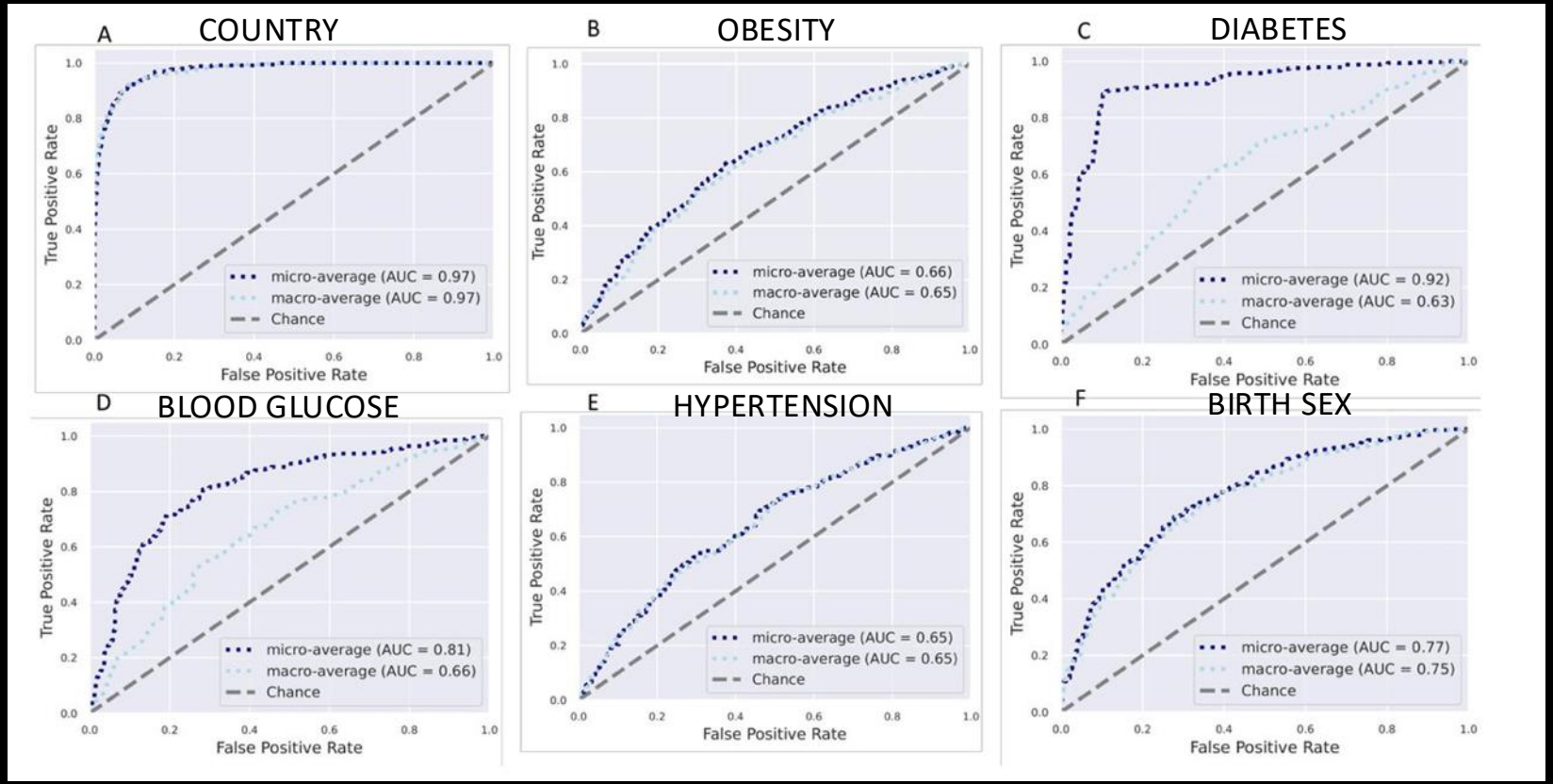


Greater alpha diversity correlates with protection from metabolic disease risks

- High microbial species diversity appears to correlate with a reduction in disease.
- While differences are varied, overall diversity is significantly lower for diabetes and cardiovascular disease risk factors.

Ecklu Mensah et al Nature Communications 2023

Microbiome can diagnose disease state



Ecklu Mensah et al Nature Communications 2023

Nutrition for Precision Health

Powered by the All of Us Research Program, part of the National Institutes of Health

The goal of the **NIH Common Fund's *Nutrition for Precision Health, powered by the All of Us Research Program***, is to develop algorithms that predict individual responses to food and dietary patterns.

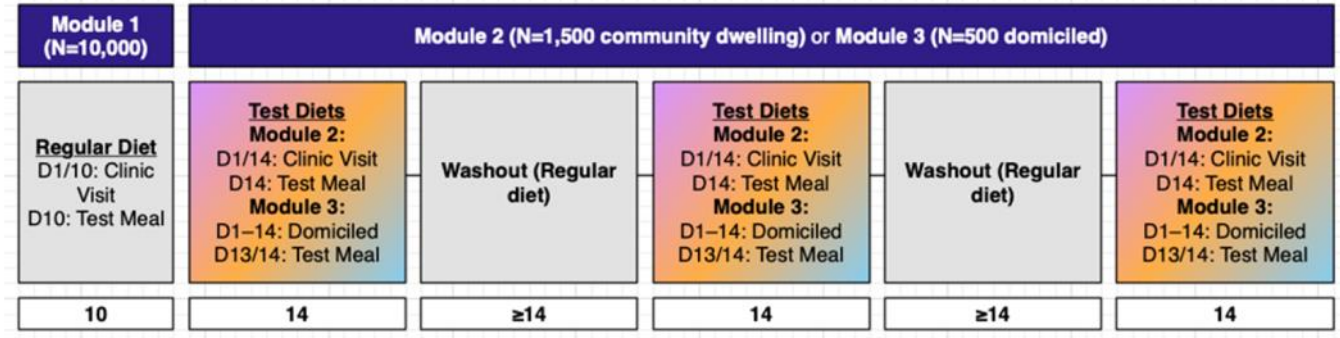
NPH Study Design

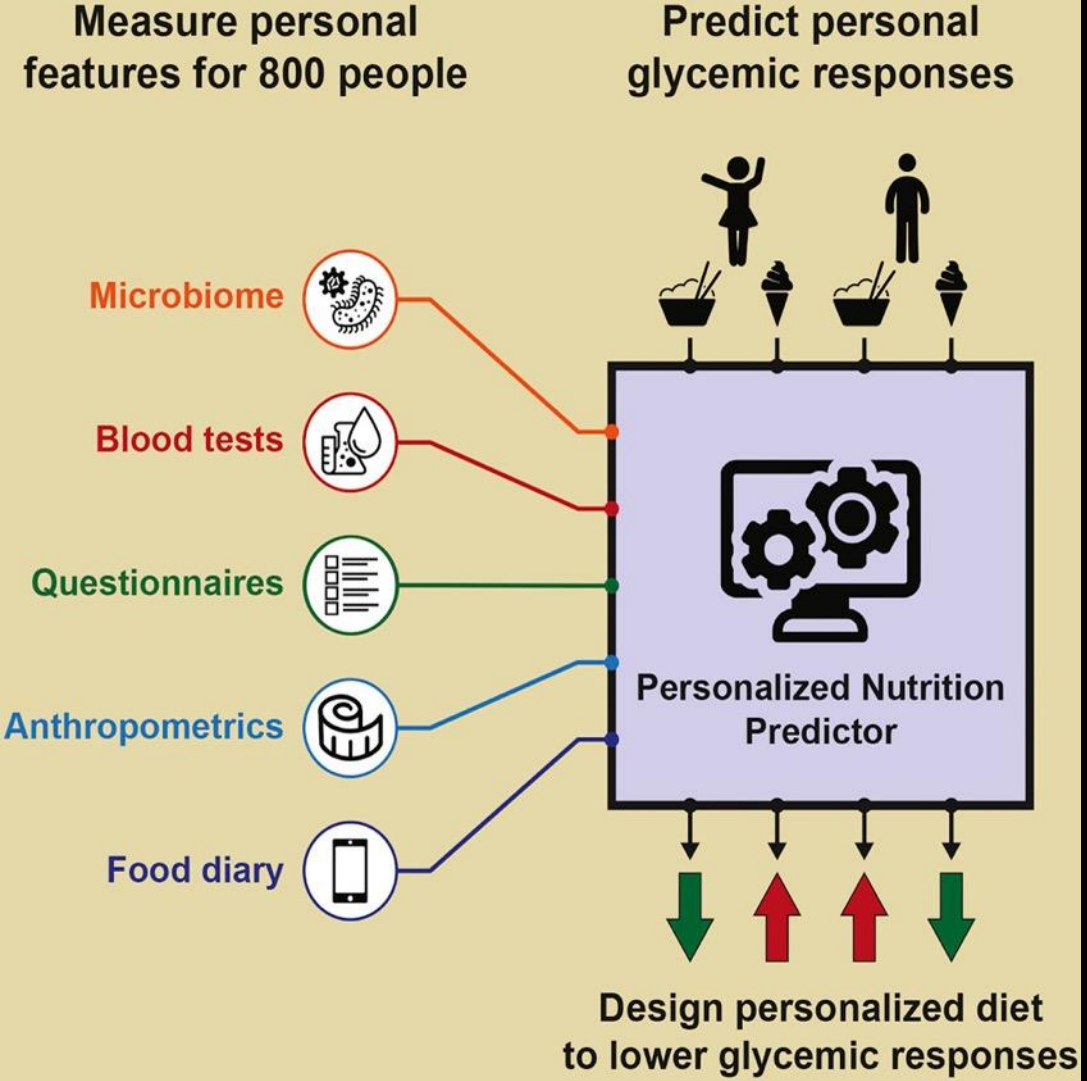
Module 1 – Detailed characterization of 10,000 people – food recall, body and performance measures, physiological, **MICROBIOME**, blood chemistry, etc. on normal diets.

Module 2 – Longitudinal analysis of 2500 people on 3 cross-over prescribed diets at home.

Module 3 – Longitudinal analysis of 500 people on 3 cross-over diets in domiciled clinical centers.

Figure 1. Participant Flow Diagram

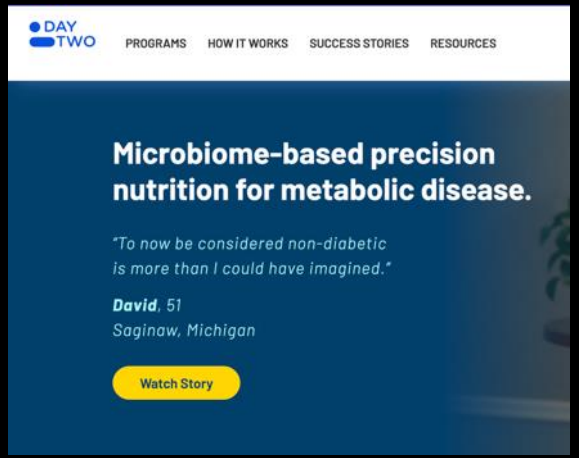




Precision Nutrition

Use stool metagenome and other tests to predict glycemic response to different foods.

Commercialized as DayTwo Inc.

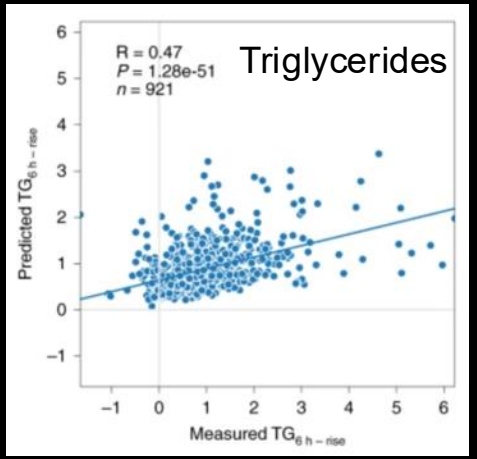


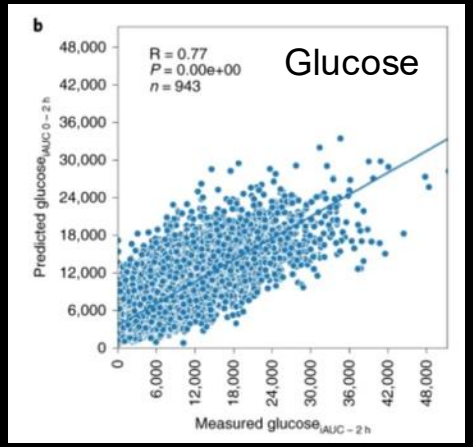
Zeevi et al., Cell 2015

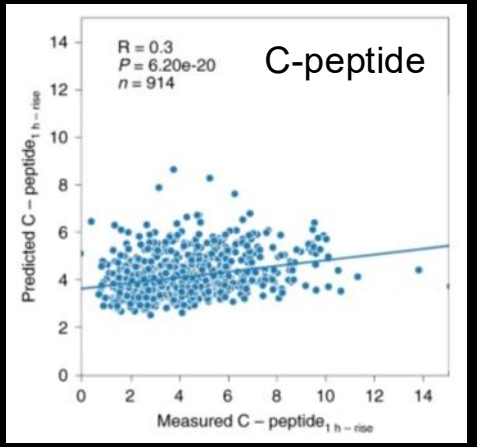
PREDICT 1 – Microbiome can predict postprandial glucose

Prevotella copri and *Blastocystis spp*. are reliable biomarkers of favorable postprandial glucose metabolism.

Overall microbiome composition was predictive of various cardiometabolic blood markers.

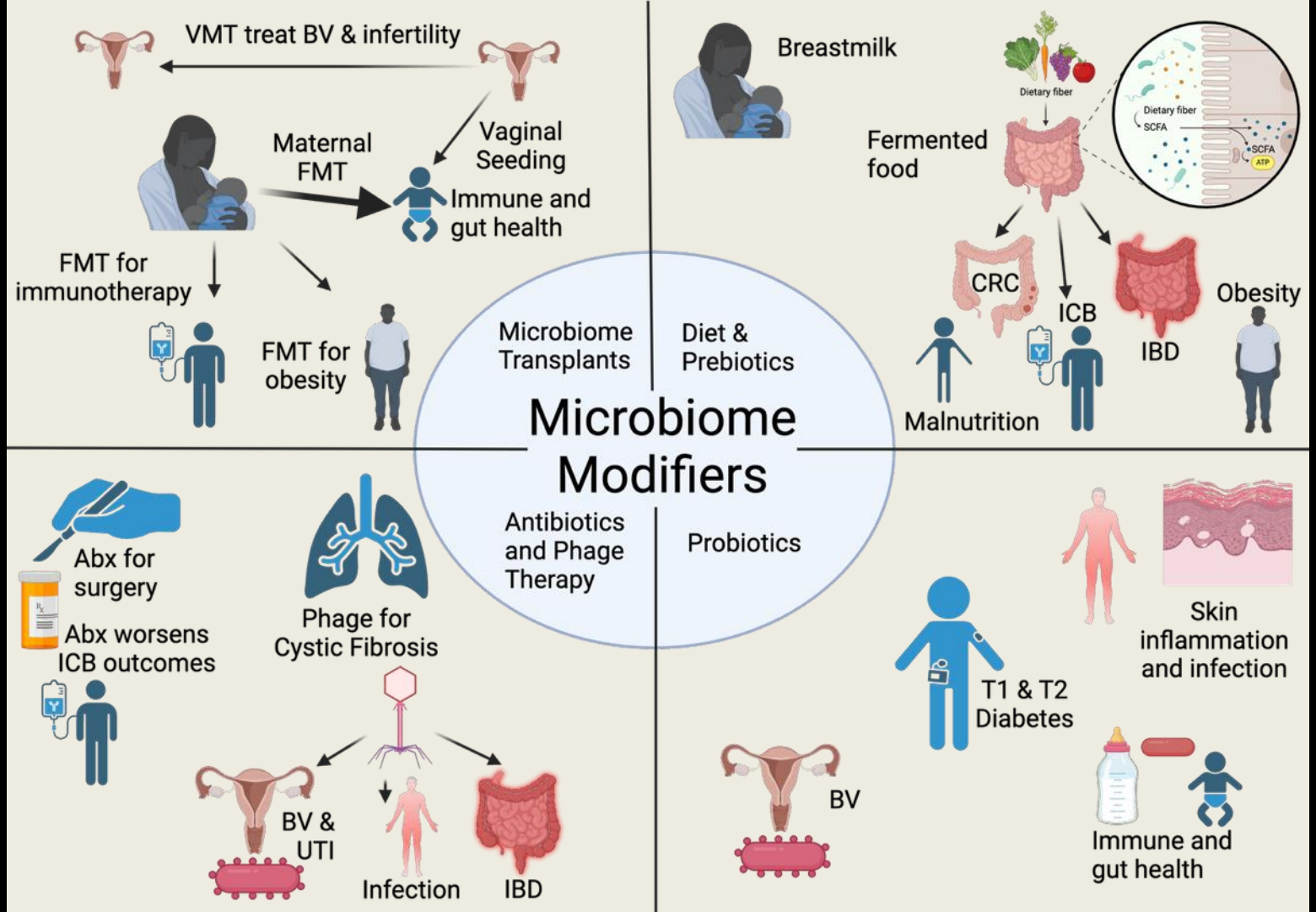






Meal composition, habitual diet, meal context, anthropometry, genetics, microbiome, clinical and biochemical parameters were used to predict postprandial triglycerides, glucose and C-peptide

Berry et al., Nature Med. 2020


VMT treat BV & infertility
Maternal FMT
Vaginal Seeding
Immune and gut health
FMT for immunotherapy
FMT for obesity
Breastmilk
Dietary fiber
Fermented food
Dietary fiber
SCFA
SCFA
ATP
CRC
ICB
IBD
Obesity
Malnutrition
Microbiome Transplants
Diet & Prebiotics
Microbiome Modifiers
Antibiotics and Phage Therapy
Probiotics
Abx for surgery
Abx worsens ICB outcomes
Phage for Cystic Fibrosis
BV & UTI
Infection
IBD
T1 & T2 Diabetes
Skin inflammation and infection
BV
Immune and gut health

Microbiome and Mental Health

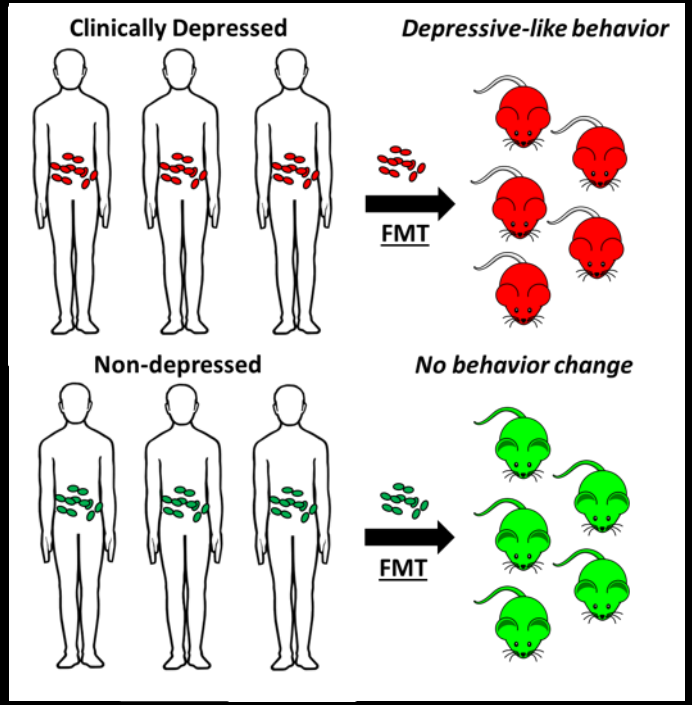
Neurological Disorders are often associated with Diarrhea or Constipation

Changes in the microbiome are associated with:

- Brain development
- Mood/behavior
- Neurodegenerative disorders

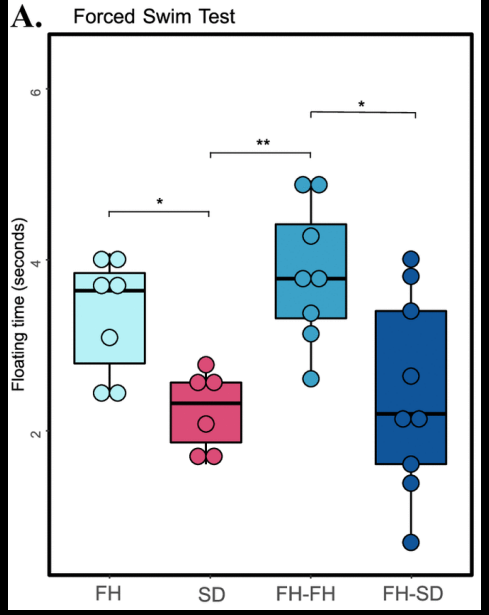
Antibiotics use linked to behavioral phenotypes (depression + anxiety)

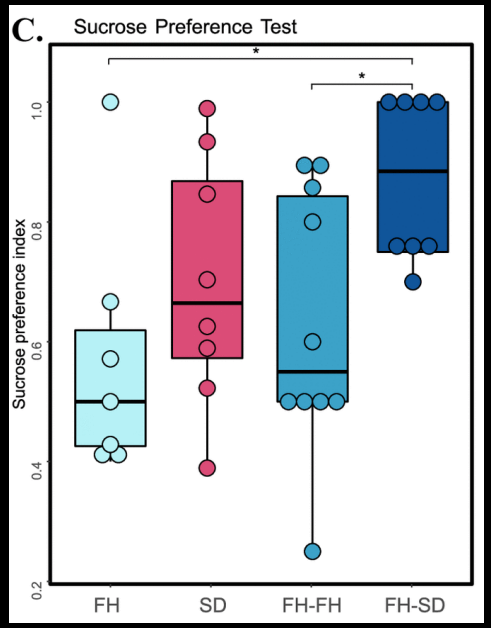
But not antivirals or antifungals



Fecal Microbiome Transplant from human to animal transmits phenotype

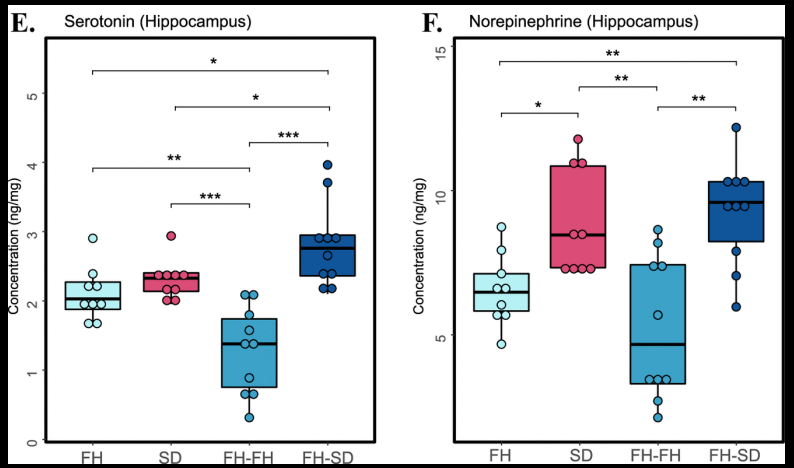
FMT from Sprague-Dawley (SD) rats ('healthy' controls) to Fawn-hooded (FH) rats (depression model)

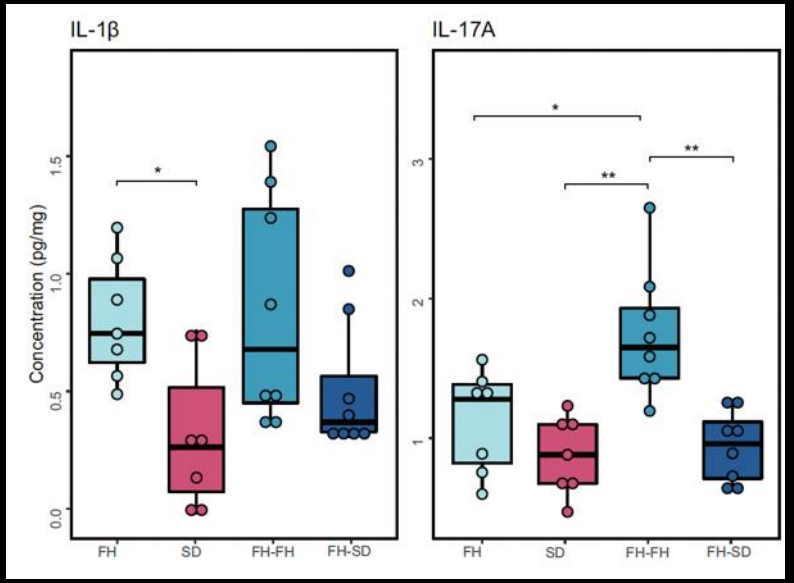




- FH rats exhibit depressive-like behaviors and distinct neurotransmitter and cytokine levels compared with SD rats.
- FH recipients receiving FH fecal microbiota (FH-FH rats) showed aggravated depressive-like behaviors.
- FH recipients receiving SD fecal microbiota (FH-SD rats) had:
  - less depressive symptoms,
  - increased hippocampal neurotransmitter concentrations,
  - Reduction in neuroinflammation.

Hu, Das et al., 2022 mSystems





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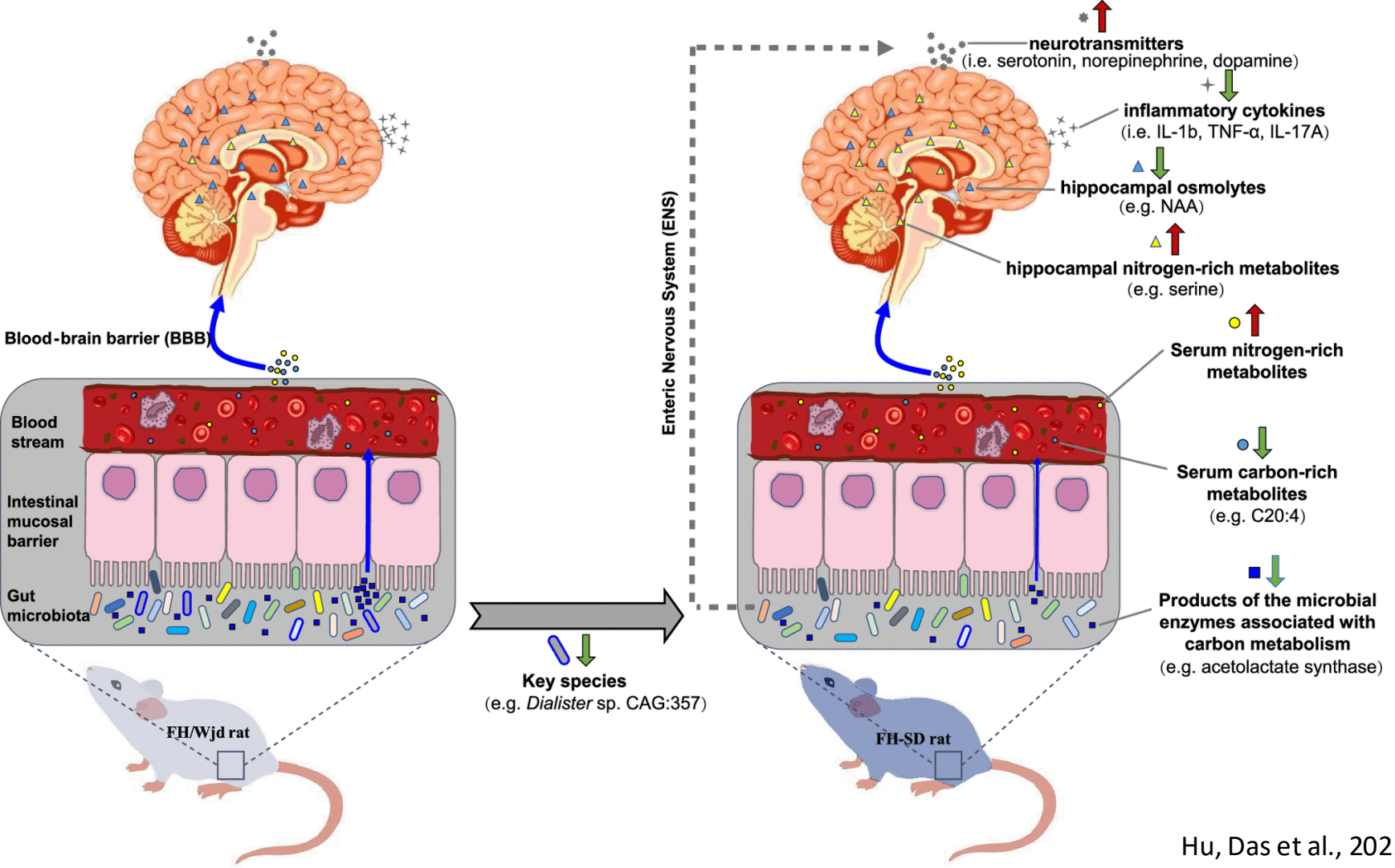
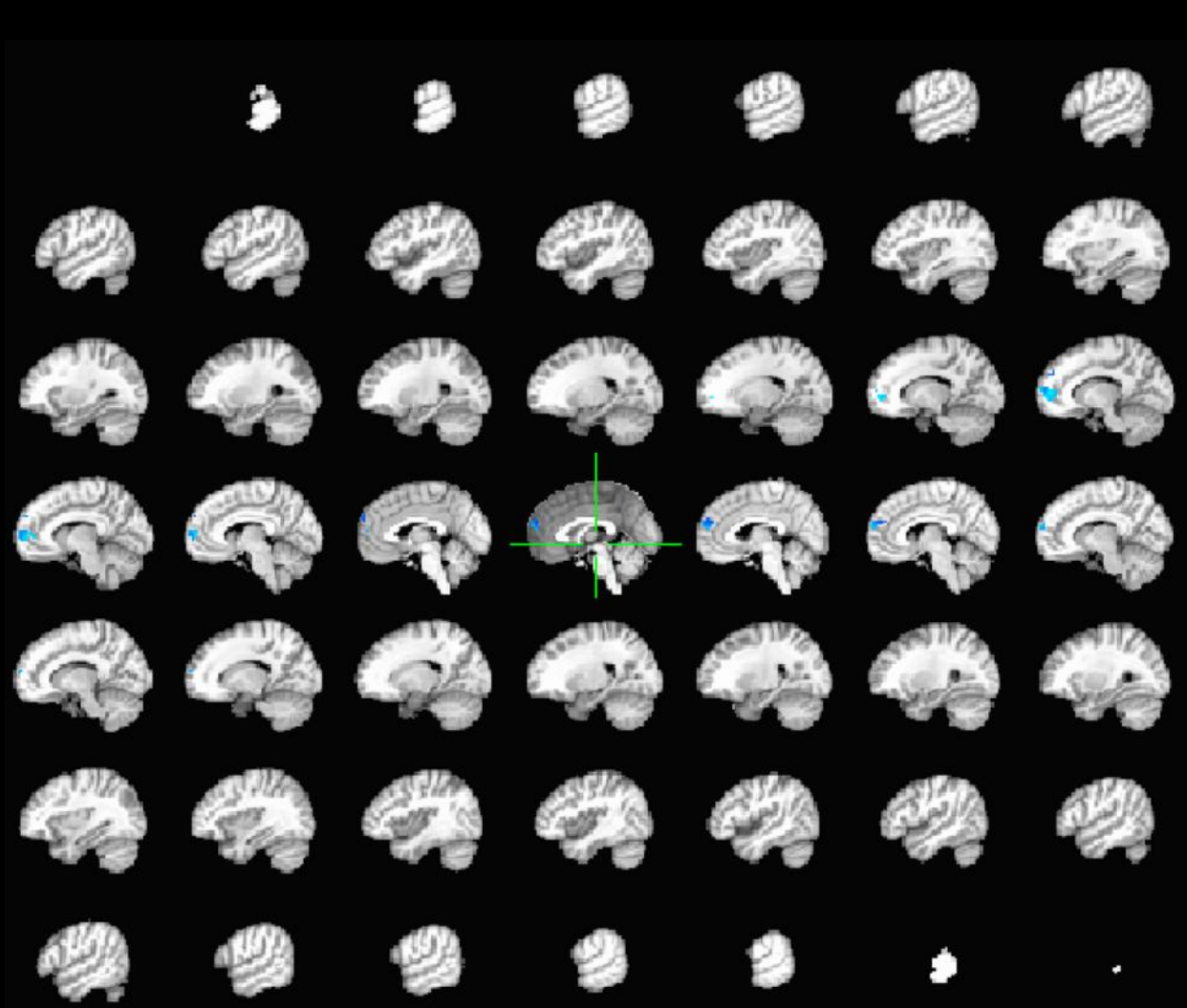
Hu, Das et al., 2022 mSystems



Hu, Das et al., 2022 mSystems



Microbiome data with functional magnetic resonance imaging in patients with major depressive disorder, a disease associated with an altered GABA-mediated response, demonstrates:

The abundance of *Bacteroides* is negatively correlated with brain signatures associated with depression.

Bacteroides were shown to synthesize GABA in the gut

Strandwitz et al Nature Microbiology 2018

Bacteroides can reverse symptoms of ‘depression’

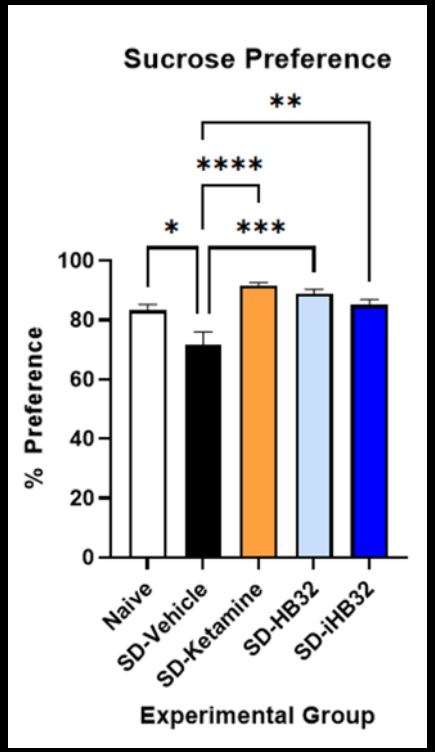
UC San Diego

Dr Promi Das

Prof. Andre Der-Avakian

Ms Marisol Dothard

A model of depression: Social defeat



TRANSLATIONAL RESEARCH INSTITUTE FOR SPACE HEALTH

Animals that experience social defeat do not crave sugar.

Ketamine can rescue the phenotype.

Bacteroides salyersiae can comparably rescue the phenotype whether alive or dead!

Holobiome

Dr. Philip Strandwitz

Dr. Katya Gavrish

Dr. Mariaelena Caboni

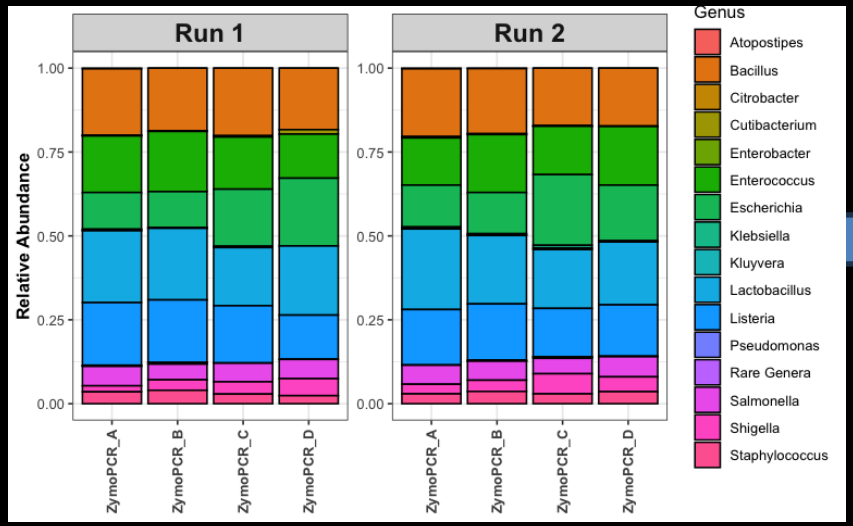
Translation to Clinical Practice

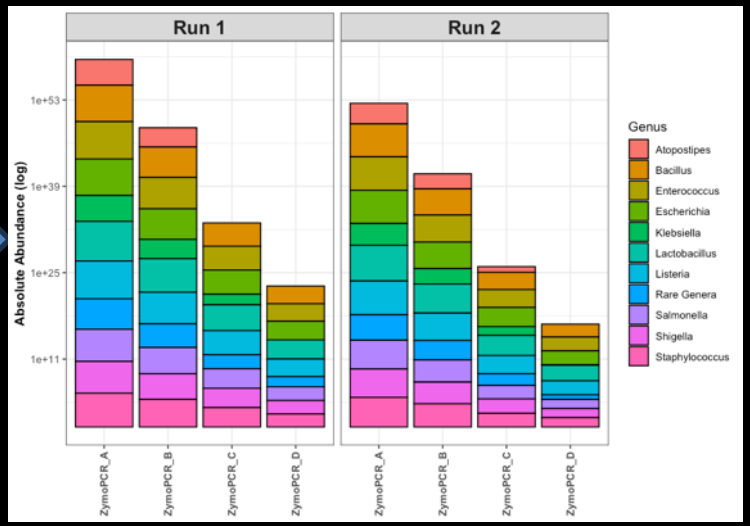
- In 2022, the FDA permitted the use of FMT to treat recurrent Cdiff infections IF the stool was obtained from a registered stool bank.
  - $1695 per dose
- In 2023, the FDA approved two microbiome therapeutics for Cdiff:
  - REBYOTA™ (Ferring Pharmaceuticals Inc.); $9629 per dose
  - VOWST™ (Seres Therapeutics, Inc.); $19543 per dose
- As of 2024 there are currently:
  - 11 clinically relevant phase 3 trials
  - 22 clinically relevant phase 2 trials

Phase	Company	Treatment	Mod0.5ality	Delivery Method	Completion Date (anticipated)	Indication	Reference
3	Mikrobiomik Healthcare	MBK-01	Pooled Lyophilized Fecal Transplant	Oral	Nov-23	Clostridium difficile (recurrent or primary)	NCT05201079
3	Infant Bacterial Therapeutics	Lactobacillus reuteri IBP-9414	Single Strain	Oral	Jul-24	Necrotizing Enterocolitis	NCT03978000
3	MaaT Pharma	MaaT013	Pooled Fecal Transplant	Enema	Sep-24	Graft Versus Host Disease (Ruxolitinib Refractory)	NCT04769895
3	Vedanta Biosciences	VE303 [undisclosed]	Defined consortium (8 strains)	Oral	Oct-27	Clostridium difficile (recurrent)	NCT06237452
3	AOBiome/Maruho	Nitrosomonas eutropha B244	Single Strain	Topical	Planned	Atopic Dermatitis	Planned
3	Ferring Pharmaceuticals	RBX2660 (REBYOTA®)	Pooled Fecal Transplant	Colonoscopic	Jan-25	Clostridium difficile (recurrent)	NCT05831189
3	RDC Clinical Pty Ltd	Maolactin	Biologic (Bioactive Proteins)	Oral	Feb-25	Gastrointestinal Dysfunction	NCT06104917
3	Mikrobiomik Healthcare	MBK-01	Pooled Lyophilized Fecal Transplant	Oral	Planned	Nonalcoholic fatty liver disease	Planned
2/3	Kibow Biotech	KT-301 [Streptococcus thermophilus (KB19), Lactobacillus	Defined consortium (3 strains)	Oral	Mar-24	Chronic Kidney Disease (Stage IV)	NCT05407389

If we want to identify mechanism and metrics, we need to change how we do microbiome science…..

Microbiome data has been compositional and that is a problem



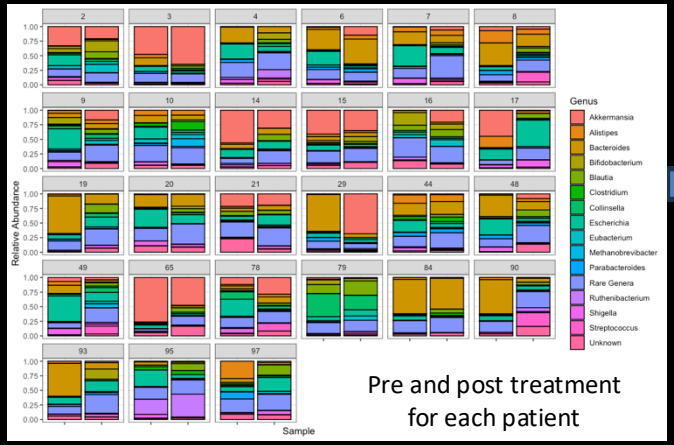


Our standard practice is to calculate the percentage of total sequencing reads associated with a microbial species or gene.

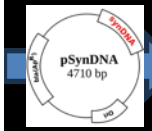
Quantification of each sequence in the metagenome as number of cells per gram of material creates a standard across all samples.

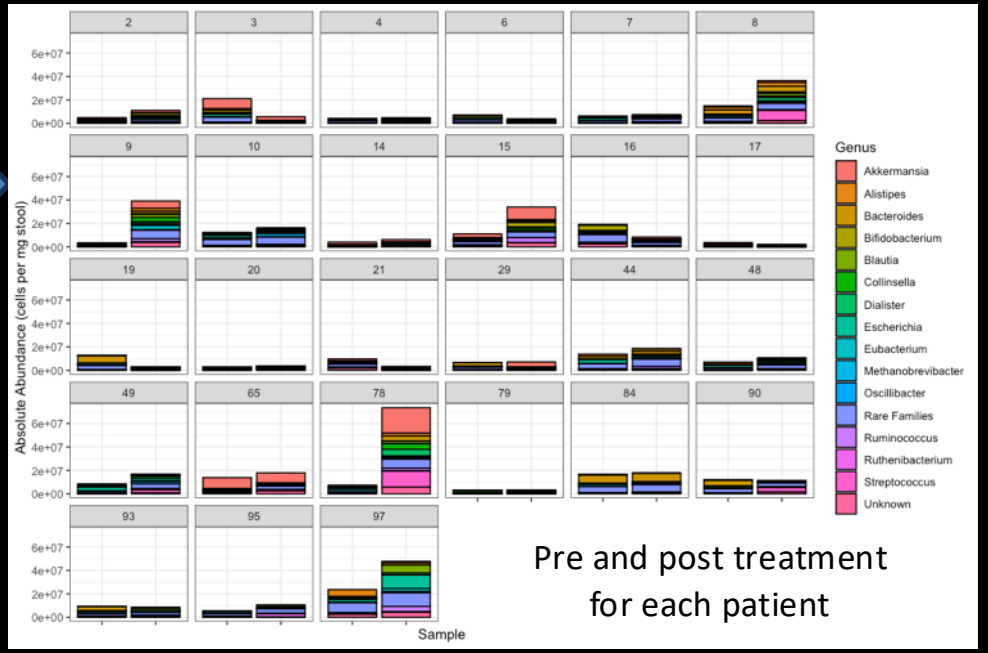
Zaramela et al., 2022, mSystems

Quantifying metagenomic data associated with lung cancer patients undergoing radiation treatment + immunotherapy combination



Pre and post treatment for each patient





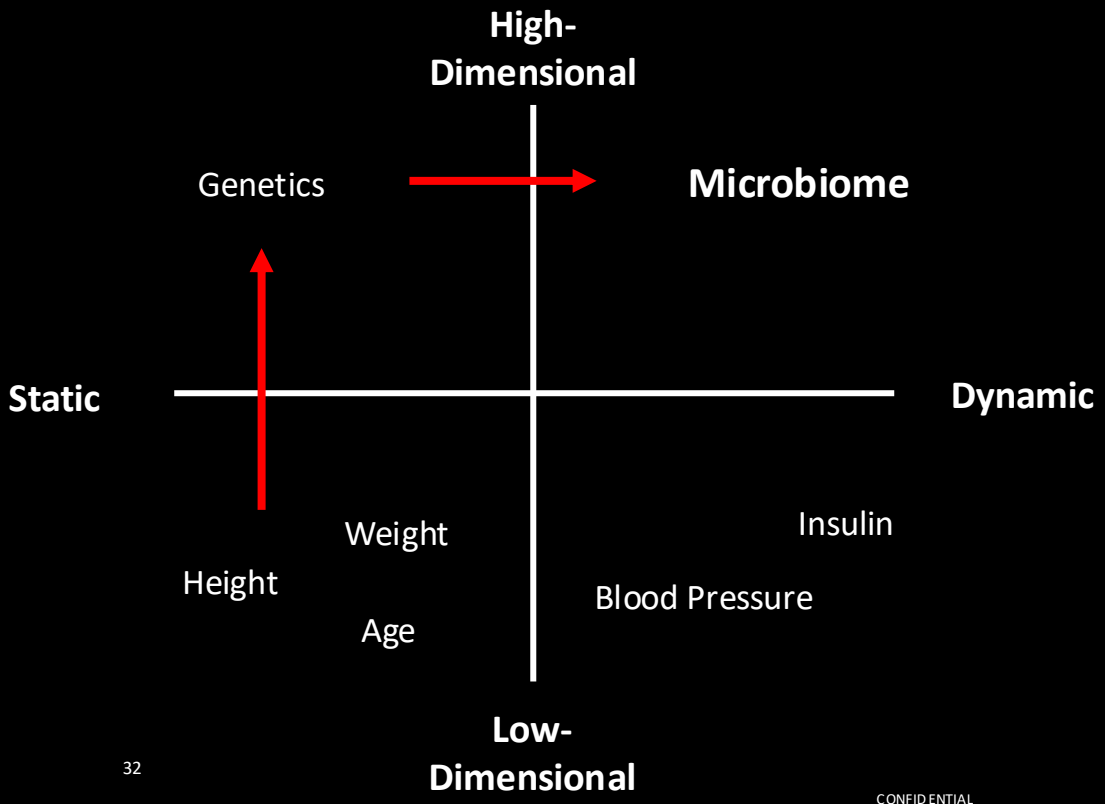
Pre and post treatment for each patient

Absolute abundance of microbial features provides a clearer picture of species burden.

Quantification also ensures a uniform metric for inter-study comparison

Kodera et al, In prep.

We don’t usually measure microbiomes over time – that is a mistake!



Effective Discovery Requires:

- Sufficient cohort size to account for high dimensionality
- Frequent sampling to account for the dynamic nature of a changing microbial ecosystem

GutLab^{tm} Automated, At-home Microbiome Tracking

- Tool for scientists to generate large, time-longitudinal datasets easily and cheaply
- Deployed into the Nutrition for Precision Health study, SeeRave Colonoscopy trail, and breast cancer trials.
- No stool interaction, no tubes, no swabs, no shipping, storage or different lab processing.
- A 90% reduction in the cost of generation and analysis of a 7M read metagenome.

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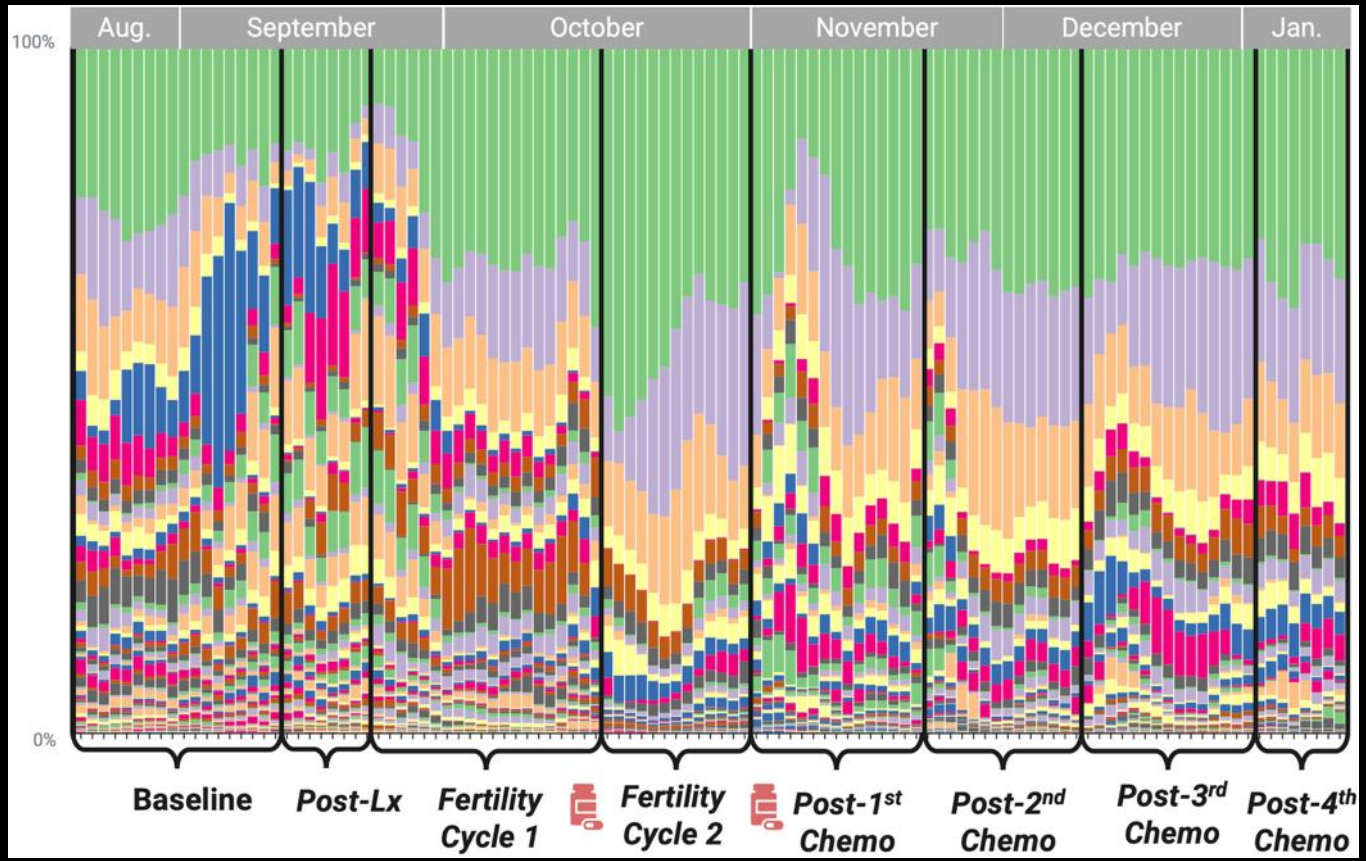
Microbiome of newly diagnosed cancer patient



Using GutLab we can now detect nuanced shifts in microbial community composition and function over time to identify new mechanisms, metrics and potential modifiers.

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80
60
40
20
0
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Your Sample
Average
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Similar BMI
Similar Age
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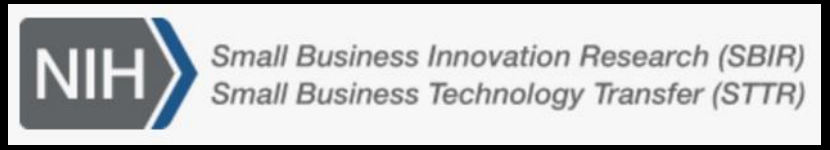
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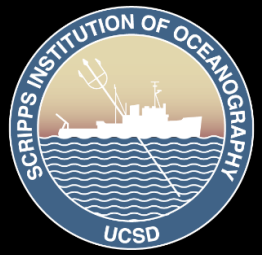
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N FILM

HACK YOUR HEALTH
THE SECRETS OF YOUR GUT

Hack Your Health: The Secrets of Your Gut

2024 | TV-14 | 1h 19m | Documentary

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