The Human Microbiome
What We Know About It and How We Can Manipulate It

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Disclosures

None

*Companies in Microbiome Space, no financial relationship
Historic Context

1796: Edward Jenner

1860: Louis Pasteur

1928: Sir Alexander Fleming discovers *Penicillium*.

1942: Manufacturing process for Penicillin
The Age of Antibiotics: Killing Bad Bugs is Good

WHO, 2015

The top 10 causes of death in low-income economies 2015

- Lower respiratory diseases: 3.1 million
- Diarrhoeal diseases: 2 million
- Stroke: 1.5 million
- Ischaemic heart disease: 2 million
- HIV/AIDS: 3.1 million
- Tuberculosis: 2 million
- Malaria: 1.5 million
- Preterm birth: 2 million
- Birth asphyxia: 1.5 million
- Road injury: 2 million

The top 10 causes of death in high-income economies 2015

- Ischaemic heart disease: 30
- Stroke: 30
- Alzheimer disease: 20
- Trachea, bronchus, and lung: 20
- Chronic obstructive pulmonary disease: 20
- Lower respiratory: 20
- Colon and rectum: 10
- Diabetes mellitus: 10
- Kidney disease: 10
- Breast cancer: 10

Deaths per 100,000 population

WHO, 2015
The Human Microbiome: an Innocent Bystander?

- Antibiotics are generally broad spectrum
- Americans receive, on average, ~18 rounds of antibiotics by age 20.
- Regional variation in antibiotic usage suggest cultural practices as opposed to medical necessity

CDC, 2015
Unintended Consequences?

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Joussen et al.12 In Panel B, data on immune disorders are derived from Swarbrick et al.,10 Dubois et al.,11 Tuomilehto et al.,14 and Pugliatti et al.15

Bach. New England J. of Medicine 2002
Ancient Relationships
The Human Microbiome

Human body is composed of 30 trillion cells

It harbors $2-10 \times$ as many microorganisms

- 3 lb of bacteria
- Genetic material outnumbers that of human genome 150:1
- “Second Genome” - One that we can shape and cultivate

The Human as an Ecosystem

- **Microbiota** - community of microorganisms
- **Metagenome** - collection of genes contained by entire microbiota
- **Microbiome** - microbiota + host
Why Now?.....
Modern Genomic Technology
Normal Development of the Human Microbiome

- Neonatal period is generally sterile*
- Birth and colonization
  - Mode of delivery
  - Breast Feeding
- Volatility and increasing diversity (0-2 yrs)
- Stability and resilience (2 yrs-adulthood)
- Decreasing diversity and return of volatility (elderly)
- Each individual is unique
  - *personalized medicine

*personalized medicine

Wopereis, 2014
The Rhythms and Environmental Niches of the Human Microbiome

Host Physiology and the Microbiome

Phys Rev 2010 Sekirov et al.
Disruption of the Human Microbiome: Dysbiosis

Dysbiosis: Cause or Effect?

The microbiome and rheumatoid arthritis

Jose U. Scher and Steven B. Abramson

Subgingival microbiota dysbiosis in systemic lupus erythematosus: association with periodontal status

Joice Dias Corrêa, Débora Cegueira Calderaro, Gilda Aparecida Femeira, Santuza Maria Souza Mendonça, Gabriel R. Fernandes, E. Xian, Antônio Lúcio Taixeira, Eugene J. Leys, Dana T. Graves, and Tarcília Aparecida Silva

Interactions between Gut Microbiota, Host Genetics and Diet Modulate the Predisposition to Obesity and Metabolic Syndrome

Siegfried Ussar, Nicholas W. Griffin, Olivier Bezy, Shiho Fujisaka, Sara Vienberg, Samir Sofic, Luxue Deng, Lynn Bry, Jeffrey I. Gordon, and C. Ronald Kahn

Gastrointestinal Malignancy and the Microbiome

Maria T. Abreu and Richard M. Peek, Jr.

Tumour-associated and non-tumour-associated microbiota in colorectal cancer

Burkhardt Pfeiffer, Denise B Lynch, Jillian M R Brown, Ian B Jeffery, Feargal J Ryan, Marcus J Claesson, Micheal O'Riordan, Fergus Shanahan, and Paul W O'Toole
Correlation ≠ Causation

"Do you think all these film crews brought on global warming or did global warming bring on all these film crews?"

Cable
The Human Microbiome: What is Normal?

HMP. Nature 2012
Evolution of the Human Gut Microbiome

The Modern Gut Microbiome

- Urbanization, housing
- Sanitation
- Modern Medicine
  - Antibiotics
- Diet
  - Easy access to historically rare foods (sweet, salty)
  - Processed Foods
  - Dietary fiber: average American 15 g/ ADA 30 g/ Hadza 300 g
Diet: Major Influence Shaping the Gut Microbiome
Diet and the Gut Microbiome

• “Enterotypes”
  • Meat vs Plant-based diet

• Controlled feeding interventions
  • Shift within days of dietary change

• Immigration studies

• Japanese and seaweed

Prebiotics vs Probiotics

**Prebiotics**: Food for your gut bacteria
- Microbiota-accessible carbohydrates (MACs)
  - Dietary: Fermentable fiber
  - Host-derived: mucosal glycans

**Probiotic**: Live organisms consumed for a health benefit.
Dietary Fiber
Breast Milk: The First Probiotic + Prebiotic

• Breast Milk
  • Cytokines, Immunoglobulins, Growth factors, Lysozymes, Lactoferrin, and...

• Microbiota
  • Bacteria, archaea, viruses, fungi, and protozoa

• 21%: Oligosaccharides (complex carbohydrates)
  - Selects for bacteria (i.e. *Bifidobacterium longum*) to begin cultivation of the baby’s gut.

*Raul Cabrera-Rubio et al. 2012*
Probiotics: Challenges

• The bug
  • Aerobic manufacturing (vs anaerobic gut)
  • Storage and preservation (heat killed, temperature)
  • FDA regulation

• The host
  • “Drop in the bucket”
  • Colonization niches (pass on through vs. fill an unfilled niche and last)
Effects of the Modern Western Diet on the Gut Microbiome

**Decreased complex fiber**
- “Hungry” bugs metabolize host glycans (mucus layer) instead
- Thinning of the protective mucus layer => Microbes closer to the epithelium => Immune activation

**Artificial Sweeteners (sucralose and saccharin)**
- Metabolized by microbes instead of host
- Results in microbial shifts
- Associated with metabolic changes in mice

**Emulsifiers**
- Thin host mucus layer in mouse models
Is the Modern Gut Microbiome the (or Part of the) Link?

Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

In Panel A, data concerning infectious diseases are derived from reports of the Centers for Disease Control and Prevention, except for the data on hepatitis A, which are derived from Jousselmet et al. In Panel B, data on immune disorders are derived from Swarbrick et al., Dubois et al., Tuomilehto et al., and Pugliatti et al.
The Gut Microbiome and Immune Education

~70% Immune System

Gut Microbiota
The Gut Microbiome and Immune Education

Prospective, birth cohort

Primary outcomes: Multi-sensitized atopy at 2 yo; Asthma at 4 yo

R. Valladares. Mol. TriCon. 2018

Fujimura 2016
The Gut Microbiome and Immune Education

- Exposure of immune cells to sterile fecal water of “high risk” neonates =>
  - T cell activation (increased IL-4) and
  - Decreased immune regulatory cells.
Using the Gut Microbiome to Prevent Disease: Asthma

Siolta Therapeutics

<table>
<thead>
<tr>
<th>IMMUNE ACTIVATION</th>
<th>INFLAMMATORY SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allergic Inflammation</strong></td>
<td></td>
</tr>
<tr>
<td>Allergen Exposure</td>
<td>Antibody Production IgE</td>
</tr>
<tr>
<td>Immune Cell Activation</td>
<td>Inflammation</td>
</tr>
</tbody>
</table>

**Current Standard Of Care**

**Siolta Therapeutics**

**Prevention**
- Reduces IgE levels
- Reduces Th2-associated response
- Reduces airway inflammation

**Alleviate Symptoms**
- Biologics
- Steroids
- Immunomodulators
Using the Gut Microbiome to Treat Disease: Fecal Microbiota Transplant
**Clostridium difficile Colitis**

- *C. difficile* colitis is characterized by profuse, watery diarrhea, abd pain, fever
  - Incidence ~ 500,000
  - Mortality ~ 14,000
  - Morbidity includes drug toxicity ➔ Abx use, toxic megacolon, total colectomy

- Deaths linked to *C. diff* increased fivefold between 1999 and 2007.

- Risks for developing colitis include antibiotic use, increasing age, long term care facility

- Recurrent *C. difficile* colitis (rCDI)
  - 1st reoccurrence: ~25% of patients,
  - Of those, 35-65% will suffer multiple episodes
Fecal Microbiota Transplant: *C. difficile* Colitis

**Prospective, randomized, controlled trial**

1) **FMT**: Short-course of vancomycin (500 mg orally q6 x 4d) =>FMT

2) **Standard vancomycin**: 500 mg orally q6 x 14 days

3) **Vancomycin with bowel lavage**: Bowel lavage performed on d 4

Fecal Microbiota Transplant: *C. difficile* colitis

- The **study was stopped** after an interim analysis.
  - 13/16 (81%) resolved with 1 FMT, 2 of 3 remaining patients resolved after 2nd FMT.

- Recurrence rate 5 weeks following treatment:
  - 62% in vancomycin alone
  - 54% in vancomycin + bowel lavage
  - 1 patient (6%) in FMT

- Average cure rate: 93%

- No serious adverse events to date have been reported.
Fecal Microbiota Transplant: Delivery
Fecal Microbiota Transplant: Donor

- Neurological conditions
- Psychiatric conditions
- Atopic and autoimmune conditions
- Chronic pain syndromes
- Medications, including antibiotics, antivirals, antifungals
- HIV or viral hepatitis exposures
- Gastrointestinal conditions
- Metabolic conditions
- BMI & waist circumference
- Travel history to regions with high risk of acquiring infectious pathogens
- Current communicable diseases
- High risk sexual behaviors, use of illicit drugs, incarceration, or recent tattoos
- Age (18-50)

Microbiome Characterization
16S rRNA microbiome characterization to evaluate diversity & representation from critical phylogenetic groups

Serologic Testing
- HIV antibody, type 1 and 2
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Treponema pallidum
- HTLV 1 and 2
- CBC with differential
- Hepatic function panel

Stool Testing
- Common enteric pathogens (e.g., Salmonella, Shigella, Campylobacter, Vibrio, E. coli, Shiga toxin)
- Clostridium difficile
- Helicobacter pylori
- Ova and parasites
- Cryptosporidium
- Giardia lamblia
- Microsporidia
- Coccidiosis
- Adenovirus
- Norovirus
- Rotavirus
- VRE
Fecal Microbiota Transplant in the Treatment of Ulcerative Colitis

• Clinical Trial #NCT02390726
• Principal Investigator: Peter L Moses, MD
• Multidisciplinary
• Study Design: Randomized Control Trial
• Intervention Model: Parallel Assignment
• Masking: Double Blind (Subject, Investigator)
Using the Microbiome to Treat Disease: Fecal Microbiota Transplant in Inflammatory Bowel Disease (IBD)

- Includes both Crohn’s Disease & Ulcerative Colitis
- US incidence ~ 1.6 million
- Peak age of onset ~ 2nd-3rd decades
IBD: Crohn’s vs Ulcerative Colitis
Gut Microbiomes of IBD patients vs. healthy individuals

Halfvarson. 2017

IBD: Evidence for Microbial Pathogenesis

• IBD patients display aberrant T-cell activation, high levels of mucosal IgG, AB cytokine responses to intestinal bacteria

• Risk increased by agents suspected of disrupting mucosal barrier and normal microbiota composition.
  • Antibiotics, enteropathogenic exposures

• IBD pts have decreased mucus layer and increased number of bacteria directly adjacent to epithelial surface.

• Effective treatments include: Diversion of fecal stream, Antibiotics
Fecal Microbiota Transplant in the Treatment of Ulcerative Colitis

**Antibiotic pretreatment** (Both Arms)
- ciprofloxacin 250mg PO q12 and metronidazole 500mg PO q8 x7 days

**Treatment Arm:**
- FMT Induction by colonoscopy plus microbial maintenance plus standard therapy

**Control Arm:**
- Sham FMT and Sham Microbial Maintenance plus standard therapy
Study Design

**Research Locations**
- Subject recruitment and sampling: UC patients @ UVM MC
- Healthy controls @ MIT

**T cell sorting:**
- Blood and biopsy samples sorted @ UVM MC

**T cell receptor sequencing:**
- All samples @ Juno Therapeutics

**Plasma metabolomics:**
- All samples @ the Broad Institute

**Whole-shotgun metagenomics:**
- @ the Broad Institute

**16s rRNA sequencing:**
- @ the Broad Institute

**Data analysis:**
- @ MIT and UVM MC

**Sample analyses**
- Whole-shotgun metagenomics
- Plasma metabolomics
- T cell sorting (Th1, Th17, Treg)
- T cell receptor sequencing
Patient Groups are Similar at Baseline

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Age</th>
<th>Sex</th>
<th>Initials</th>
<th>Primary Donor</th>
<th>Group</th>
<th>Variable</th>
<th>Base</th>
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<th>P value</th>
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<td>44</td>
<td>M</td>
<td>KDZ</td>
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<td>7</td>
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<td>46</td>
<td>F</td>
<td>JHR</td>
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<td>Age</td>
<td>39 (15)</td>
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<td>10</td>
<td>38</td>
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<td>AMR</td>
<td>A</td>
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<td>Sex</td>
<td>4 (57%)</td>
<td>4 (50%)</td>
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<tr>
<td>14</td>
<td>20</td>
<td>M</td>
<td>AJS</td>
<td>A</td>
<td></td>
<td>Race</td>
<td>6 (86%)</td>
<td>7 (88%)</td>
<td>1.00</td>
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<tr>
<td>3</td>
<td>22</td>
<td>F</td>
<td>ECT</td>
<td>B SCREEN FAIL</td>
<td></td>
<td>BMI</td>
<td>25 (3)</td>
<td>29 (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>F</td>
<td>JCJ</td>
<td>B</td>
<td></td>
<td>CRP</td>
<td>2 (29%)</td>
<td>3 (38%)</td>
<td>1.00</td>
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<tr>
<td>11</td>
<td>65</td>
<td>F</td>
<td>JFE</td>
<td>B</td>
<td></td>
<td>Fecal calprotectin</td>
<td>513 (607)</td>
<td>306 (301)</td>
<td>0.47</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fecal lactoferrin</td>
<td>7 (100%)</td>
<td>6 (75%)</td>
<td>0.47</td>
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<tr>
<td>2</td>
<td>27</td>
<td>F</td>
<td>BAE</td>
<td>SCREEN FAIL</td>
<td></td>
<td>Endo UCEIS score</td>
<td>6.6 (2.0)</td>
<td>7.4 (2.6)</td>
<td>0.51</td>
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<tr>
<td>4</td>
<td>65</td>
<td>M</td>
<td>AZN</td>
<td></td>
<td></td>
<td>Endo Mayo score</td>
<td>1.4 (0.8)</td>
<td>1.8 (1.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>M</td>
<td>MCT</td>
<td></td>
<td></td>
<td>Mayo symptom score</td>
<td>4.6 (1.8)</td>
<td>4.4 (1.1)</td>
<td>0.80</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>F</td>
<td>CLR</td>
<td></td>
<td></td>
<td>IBDQ bowel system</td>
<td>4.4 (0.7)</td>
<td>4.2 (0.8)</td>
<td>0.67</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>F</td>
<td>LEH</td>
<td></td>
<td></td>
<td>IBDQ emotional health</td>
<td>4.6 (1.0)</td>
<td>4.7 (1.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>F</td>
<td>LLM</td>
<td>DROPPED OUT</td>
<td></td>
<td>IBDQ systemic systems</td>
<td>4.5 (1.1)</td>
<td>4.2 (1.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>13</td>
<td>58</td>
<td>M</td>
<td>GLF</td>
<td></td>
<td></td>
<td>IBDQ social function</td>
<td>5.1 (0.5)</td>
<td>4.9 (1.2)</td>
<td>0.60</td>
</tr>
<tr>
<td>15</td>
<td>57</td>
<td>M</td>
<td>CSE</td>
<td>SCREEN FAIL</td>
<td></td>
<td>IBDQ total score</td>
<td>147.3 (19.3)</td>
<td>144.1 (25.1)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

ITT n = 15
Adverse Events: No difference between groups

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cases</th>
<th>Relatedness</th>
<th>Severity</th>
<th>Group Designation</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>2</td>
<td>Not Related, Possibly Related</td>
<td>1</td>
<td>Active, Active</td>
</tr>
<tr>
<td>Worsening Disease</td>
<td>2</td>
<td>Possibly Related</td>
<td>1</td>
<td>Active, Placebo</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>Not Related</td>
<td>1</td>
<td>Active (not treated)</td>
</tr>
<tr>
<td>Epitaxis</td>
<td>1</td>
<td>Not Related</td>
<td>1</td>
<td>Placebo</td>
</tr>
<tr>
<td>URI</td>
<td>1</td>
<td>Not Related</td>
<td>1</td>
<td>Placebo</td>
</tr>
<tr>
<td>Head Cold</td>
<td>1</td>
<td>Not Related</td>
<td>1</td>
<td>Active</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>Probably related</td>
<td>1</td>
<td>Placebo</td>
</tr>
<tr>
<td>Post-Anesthesia Myocolonic Jerks</td>
<td>1</td>
<td>Probably Related</td>
<td>3</td>
<td>Active (not treated)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>1</td>
<td>Not Related</td>
<td>1</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

6/7 vs 5/8  \( p = 1.0 \) fischer’s exact test
Primary Clinical Outcomes

Clinical Remission: 29% vs 0% (p=0.20)

Clinical Response: 43% vs. 0% (p=0.08)

Endoscopic Remission: 43% vs 0% (p=0.08)

Endoscopic Response: 43% vs. 0% (p=0.08)

*Either Endoscopic Remission or Response: 57% vs 0% (p=0.03)
FMT patients reported enhanced bowel health

- **IBDQ** (Inflammatory Bowel Disease Questionnaire)
  - Validated
  - Disease-specific
FMT patients have a decrease in stool markers of inflammation (fecal calprotectin and lactoferrin)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Screen or Procedure</th>
<th>4 week</th>
<th>12 week</th>
<th>18 week</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>Active</td>
<td>Adjusted %</td>
<td>27%</td>
<td>30%</td>
<td>79%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>Adjusted %</td>
<td>31%</td>
<td>37%</td>
<td>71%</td>
<td>7%</td>
</tr>
<tr>
<td>Fecal calprotectin</td>
<td>Active</td>
<td>Adjusted mean (SE)</td>
<td>447 (39)</td>
<td>184 (43)</td>
<td></td>
<td>0.03</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>Adjusted mean (SE)</td>
<td>417 (34)</td>
<td>396 (41)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Screen or Procedure</th>
<th>Visit</th>
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<tbody>
<tr>
<td>Fecal lactoferrin</td>
<td>Active</td>
<td>#(% positive)</td>
<td>Screen</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>#(% positive)</td>
<td>0.47</td>
</tr>
<tr>
<td>P value</td>
<td>0.47</td>
<td>1.00</td>
<td>0.45</td>
</tr>
</tbody>
</table>

C-Reactive Protein:
Nonspecific, acute phase reactant
Method: Immunoturbidimetric Assay
Ref Range: <10mg/L

Fecal Calprotectin:
Heterodimer of S100A8 and S100A9. Member of the calcium-binding protein family. Primarily expressed by neutrophils
Method: ELISA
Ref Range:
< or =50.0 mcg/g (Normal)
50.1-120.0 mcg/g (Borderline)
or =120.1 mcg/g (Abnormal)

Fecal Lactoferrin:
Fe+ binding protein.
Antibacterial.
Secreted by neutrophils
Method: ELISA
Ref Range: negative
FMT patients trend toward decreasing histologic evidence of inflammation
## Global Assessment:
The Super Responders and Non Responders

### Global Response:

3/6 (50%) vs 2/6 (33%)

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Age</th>
<th>Sex</th>
<th>Extent of Disease</th>
<th>Duration of Disease (yrs)</th>
<th>BMI</th>
<th>Primary Donor</th>
<th>Total Mayo B</th>
<th>Change in Total Mayo</th>
<th>UCCEIS B</th>
<th>Change in UCCEIS</th>
<th>Mayo B</th>
<th>Change in Mayo</th>
<th>Geboes B</th>
<th>Change in Geboes Score</th>
<th>Fecal Lactoferrin</th>
<th>Fecal Calprotectin</th>
<th>Escalation of Therapy</th>
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<tbody>
<tr>
<td>7</td>
<td>46</td>
<td>F</td>
<td>pan-colitis</td>
<td>5.5</td>
<td>20.9</td>
<td>A</td>
<td>1</td>
<td>-7</td>
<td>4</td>
<td>-2</td>
<td>1</td>
<td>0</td>
<td>0.1</td>
<td>-3</td>
<td>PNNN</td>
<td>285=0</td>
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<td>8</td>
<td>35</td>
<td>F</td>
<td>pan-colitis</td>
<td>7.5</td>
<td>27.8</td>
<td>B</td>
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<td>-3</td>
<td>5</td>
<td>-1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>-1.3</td>
<td>PPPP</td>
<td>336=&gt;447</td>
<td></td>
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<tr>
<td>14</td>
<td>20</td>
<td>M</td>
<td>pan-colitis</td>
<td>3.8</td>
<td>25</td>
<td>A</td>
<td>4</td>
<td>-1</td>
<td>4</td>
<td>-1</td>
<td>1</td>
<td>0</td>
<td>1.1</td>
<td>2</td>
<td>PPPP</td>
<td>385=&gt;221</td>
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<td>11</td>
<td>65</td>
<td>F</td>
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Changes in the Gut microbiome of FMT patients
Immunologic Investigation of FMT: Mechanism of Action
Patient Stratification

CD45

CD4

CD8

CD25 (T-reg)

MR1 (MAIT tetramer)

TCRγδ

IFNγ
Th1
Inflammatory

IL-17
Th17
Neutrophil recruitment

IL-10
T-reg
anti-inflammatory reparative

CD14/CD13 (monos/macs)
While we work out the Science...

Eat and live like your ancestors (when appropriate)

Honor your ancient relationship with your microbes