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The Gastrointestinal Microbiome

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Conflict of Interest Disclosure

- I am a pharmaceutical factory
  - The FDA has determined poop is a drug
- I do not have any conflicts

Overview

- Definitions
- Human Microbiome
- GI Microbiome
- GI Microbiome & Disease
  - Inflammatory Bowel Disease
  - Liver Disease
  - Colorectal Cancer
  - *C. difficile* Infection

Definitions

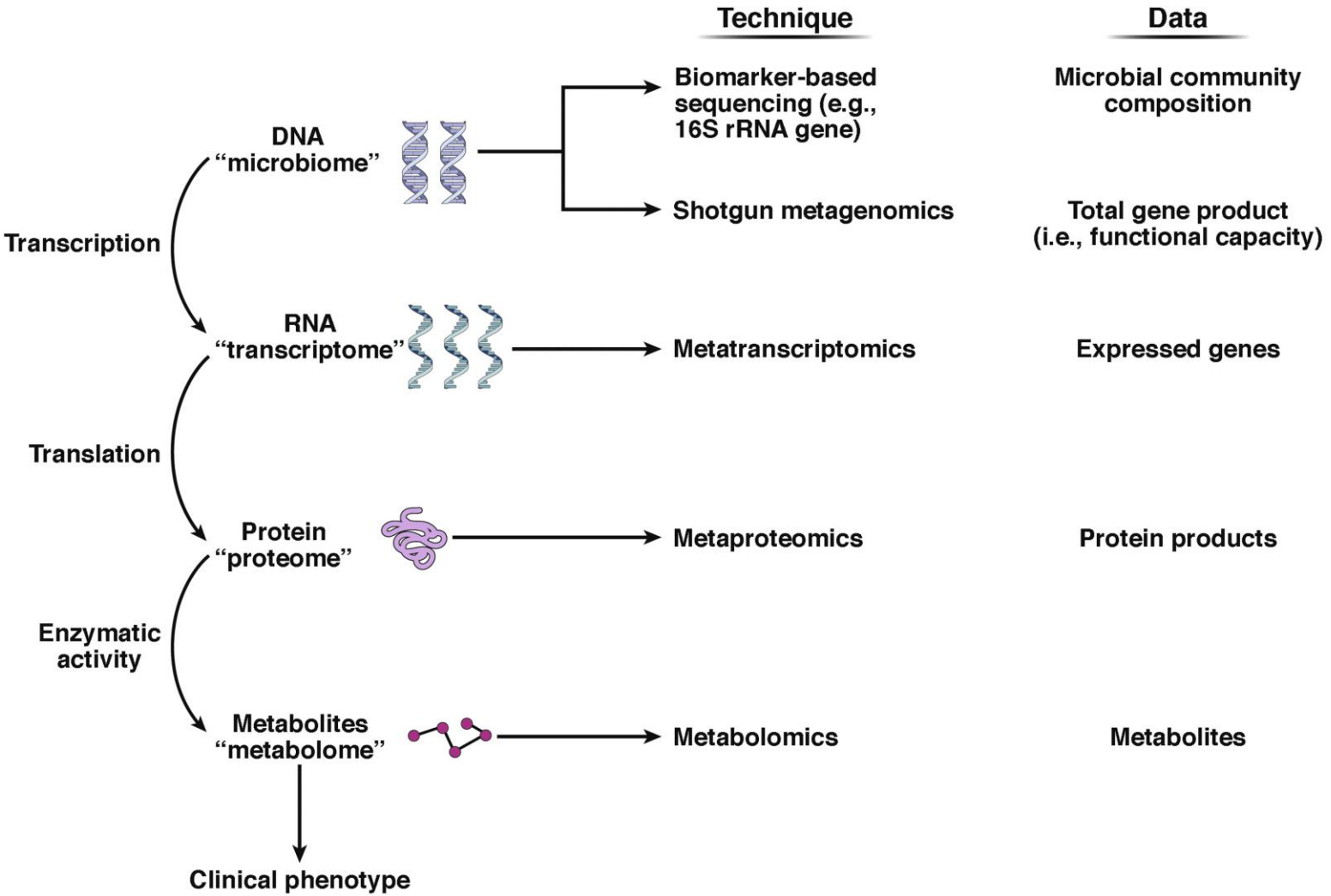
- **Microbiome:** An entire habitat, including the microorganisms, their genomes, and the surrounding environmental conditions
- **Microbiota:** The assemblage of microorganisms in a defined environment
- **Microflora:** Microscopic plants (often misused)
- **Metagenome:** The collection of genomes and genes from the members of a microbiota
- **Dysbiosis:** A disturbance in a biological system, such as changes in type/number of bacteria

Marchesi & Ravel *Microbiome* 2015
Marchesi, et al. *Gut* 2015

Genomics Definitions

- **Next-generation sequencing:** DNA sequencing that harnesses advances in miniaturization technology to simultaneously sequence multiple areas of the genome rapidly and at low cost
- **16S rRNA gene sequencing**
  - Method for determining which bacteria are present
- **Metagenomics:** The process used to characterize the metagenome
  - Sequence all DNA extracted from a sample to determine which genes are present
  - Provides information on the function of the microbiota

Feero, et al. *NEJM* 2010; Marchesi & Ravel *Microbiome* 2015



Clinical Gastroenterology and Hepatology 2019 17, 296-306DOI: (10.1016/j.cgh.2018.08.065)

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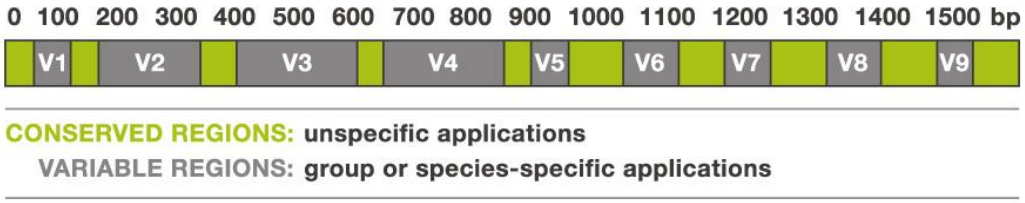
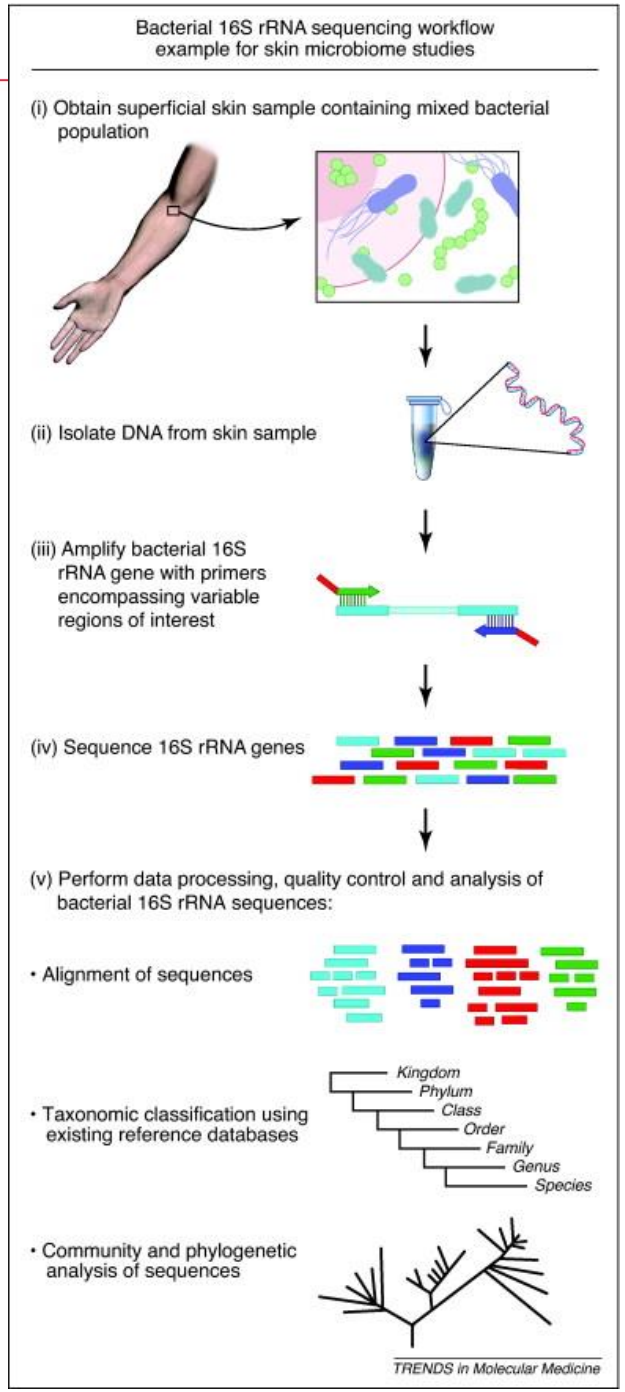
16S rRNA gene sequencing





1) http://www.alimetrics.net/en/index.php/dna-sequence-analysis
2) Kong HH, Trends in Molecular Medicine, 2011

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The Human Microbiome

- The sum of the microbiomes in all parts of the human body
- The Human Microbiome Project – launched 2008
- "Bacteria cells outnumber human cells by ~10-fold"
  - Or do they?
- Co-evolution/Mutualism
  - Human benefits:
    - Nutrition
    - Immune system education
    - Colonization resistance
  - Microbe benefits:
    - A happy place - warm/moist/nutrients

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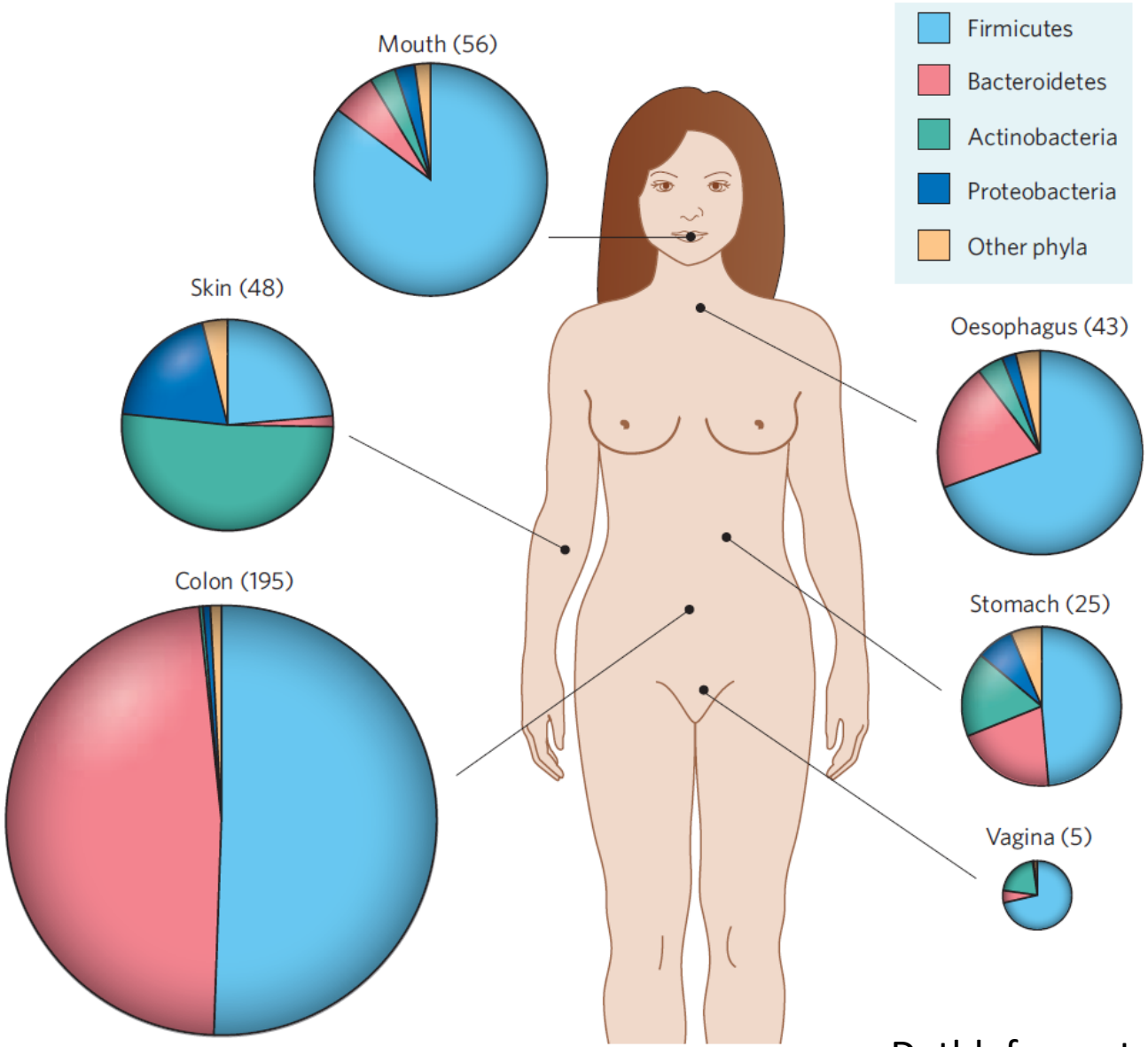
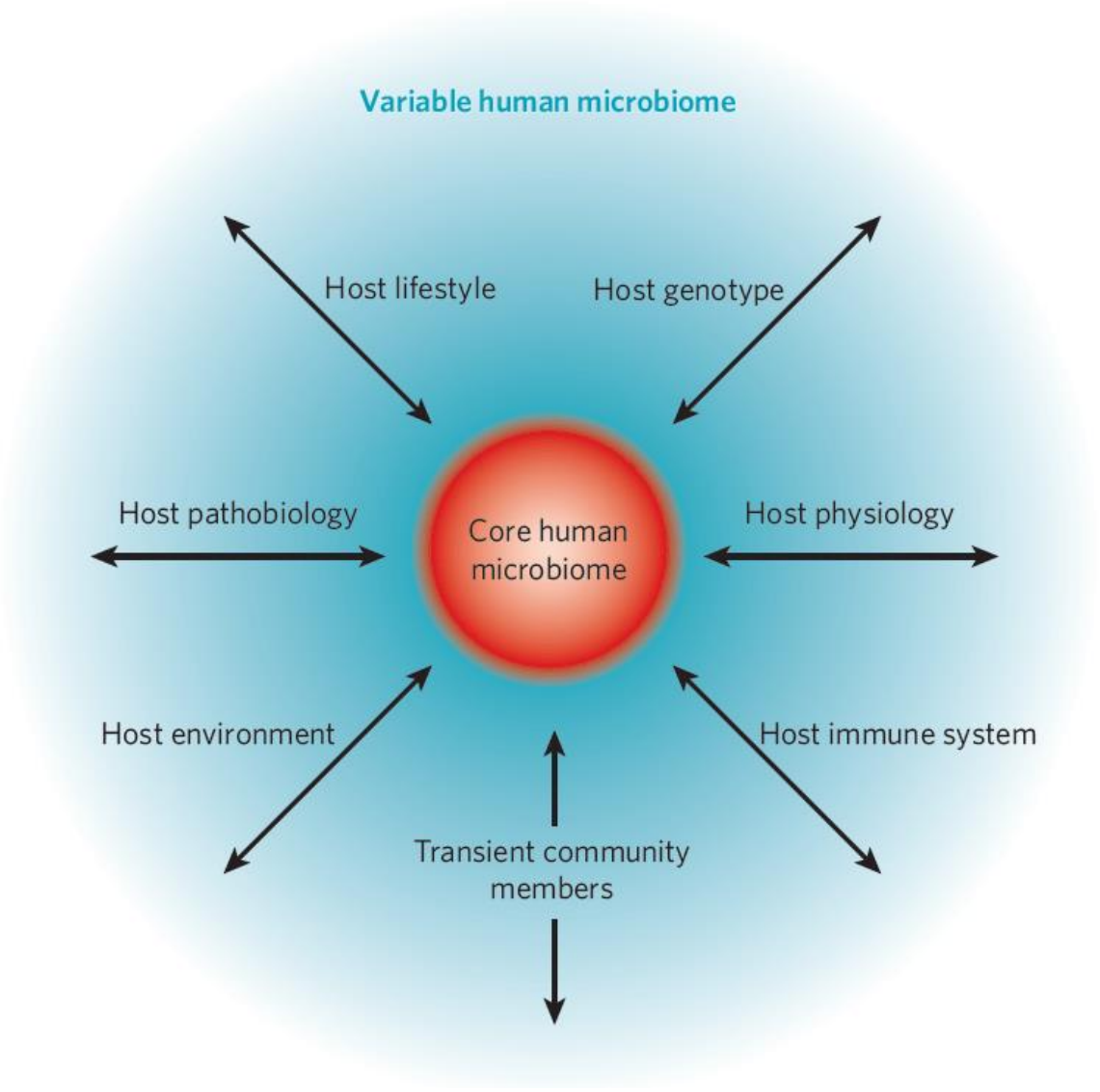
Microbial Members of the Human Microbiome

- Bacteria
- Archea – single-celled organisms without nuclei
- Fungi – primarily yeasts
- Microbial eukaryotes (e.g. *Blastocystis*)
- Viruses
- Phages

Clinical Gastroenterology and Hepatology 2019 17, 218-230 DOI: 10.1016/j.cgh.2018.09.017



Dethlefsen, et al. *Nature* 2007

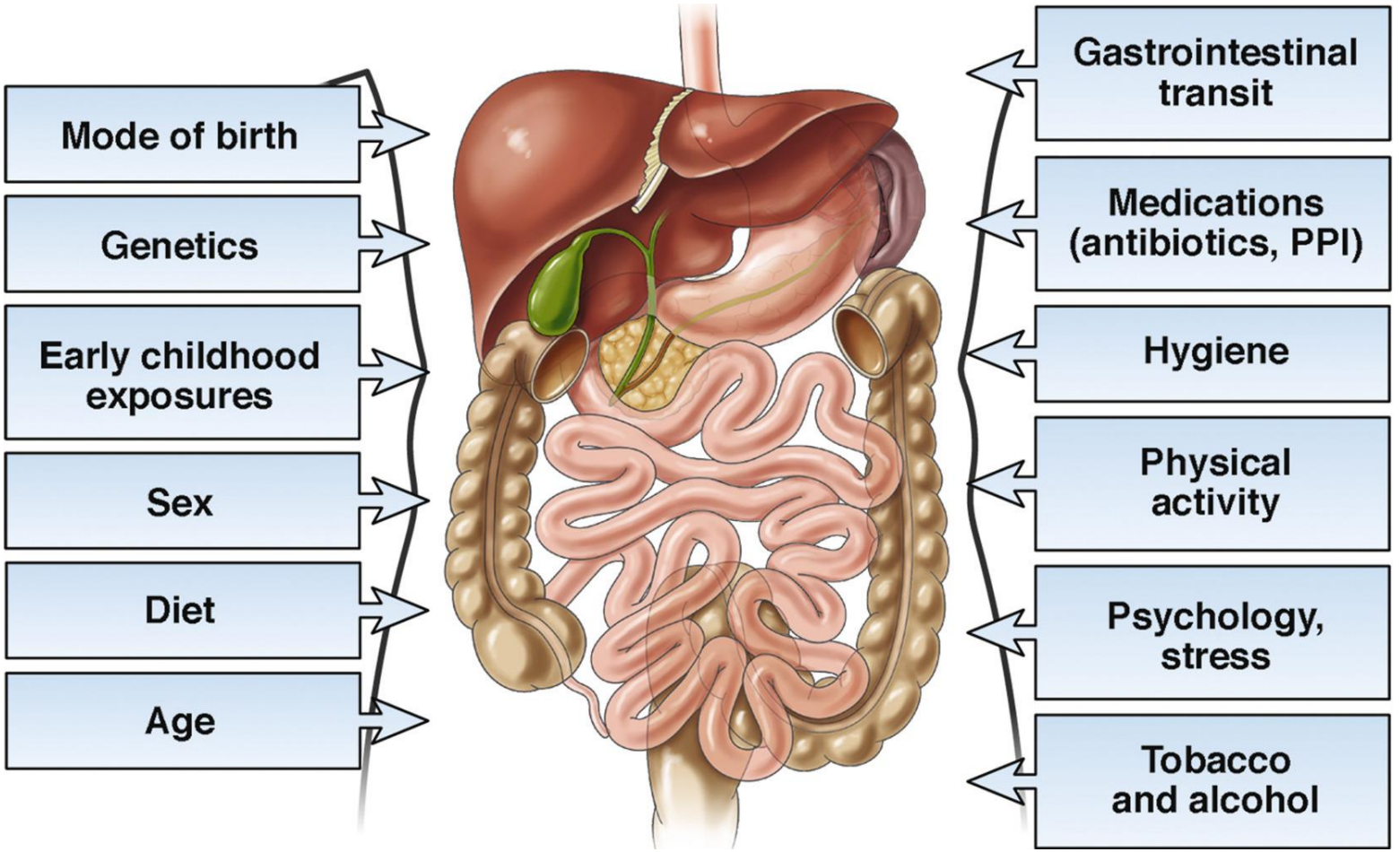


Turnbaugh, et al. *Nature* 2007

The Human GI Microbiome

- Approximately 100 trillion microorganisms
- Most reside in the colon
- Large increase in microbial density across ICV
- >90% belong to two phyla (Firmicutes and Bacteroidetes)
- ~90% have never been cultured
- Metabolic, immune system, and pathogen resistance functions

Wu & Lewis, *CGH* 2013



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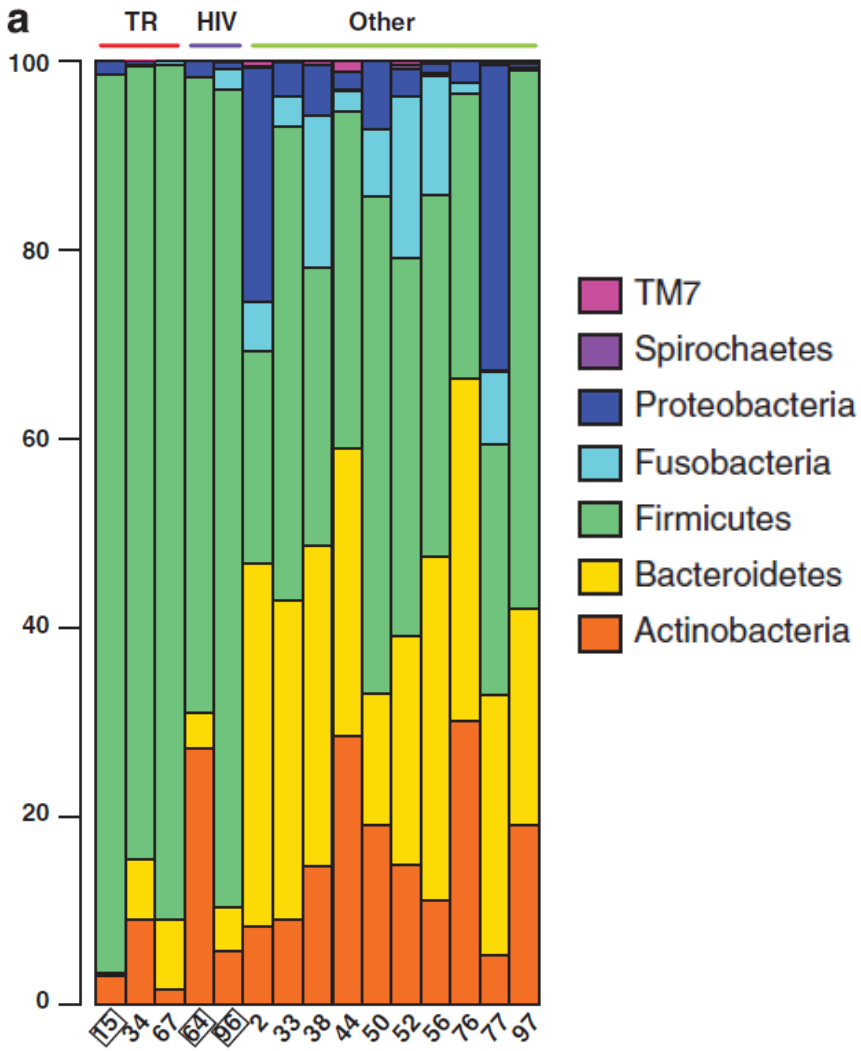
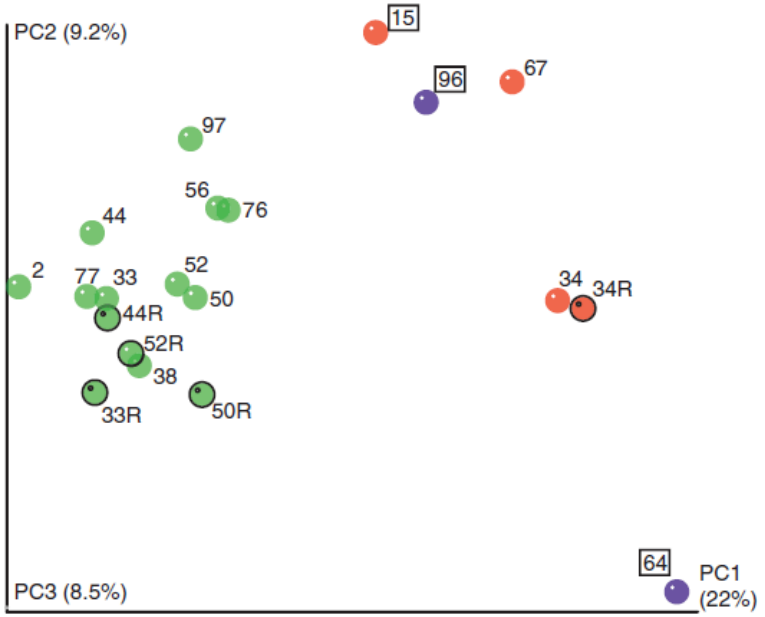
Gastric Fluid Microbiota



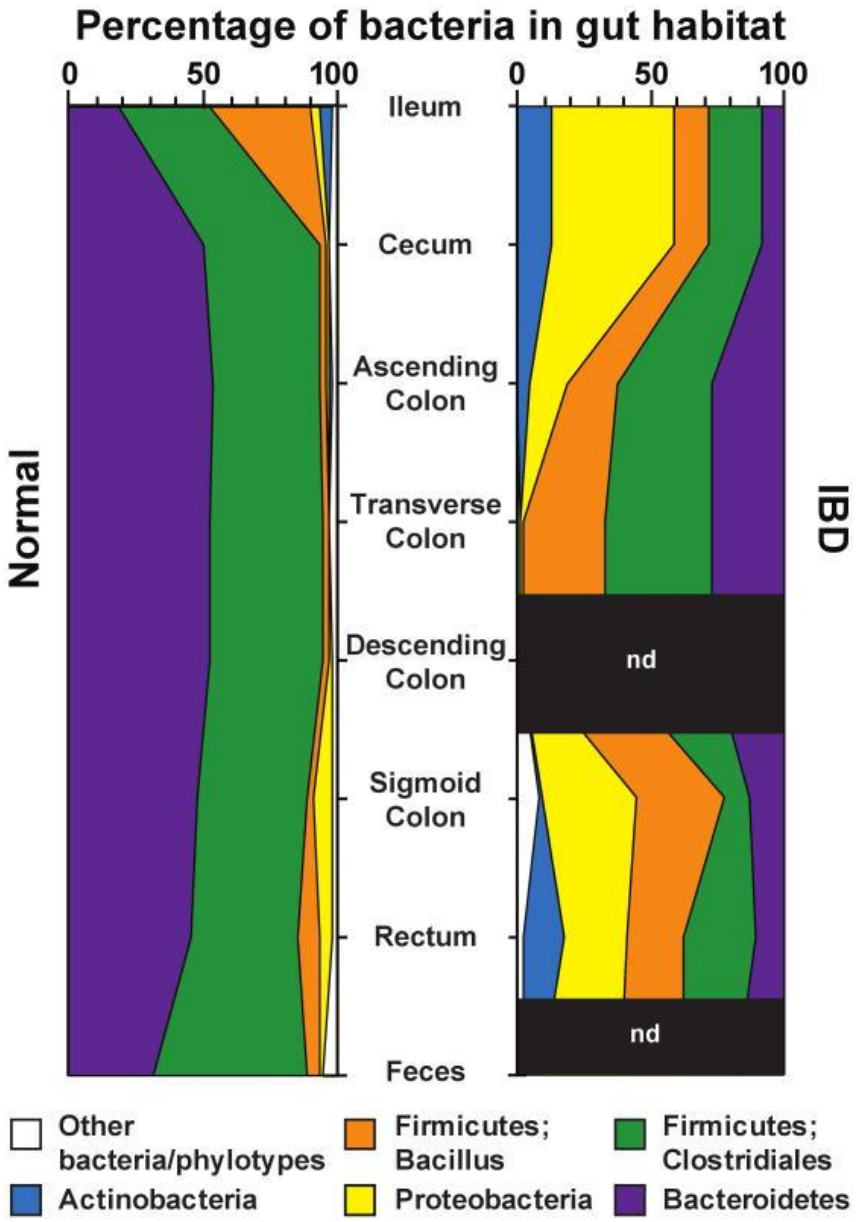


von Rosenvinge, et al. *ISME J* 2013

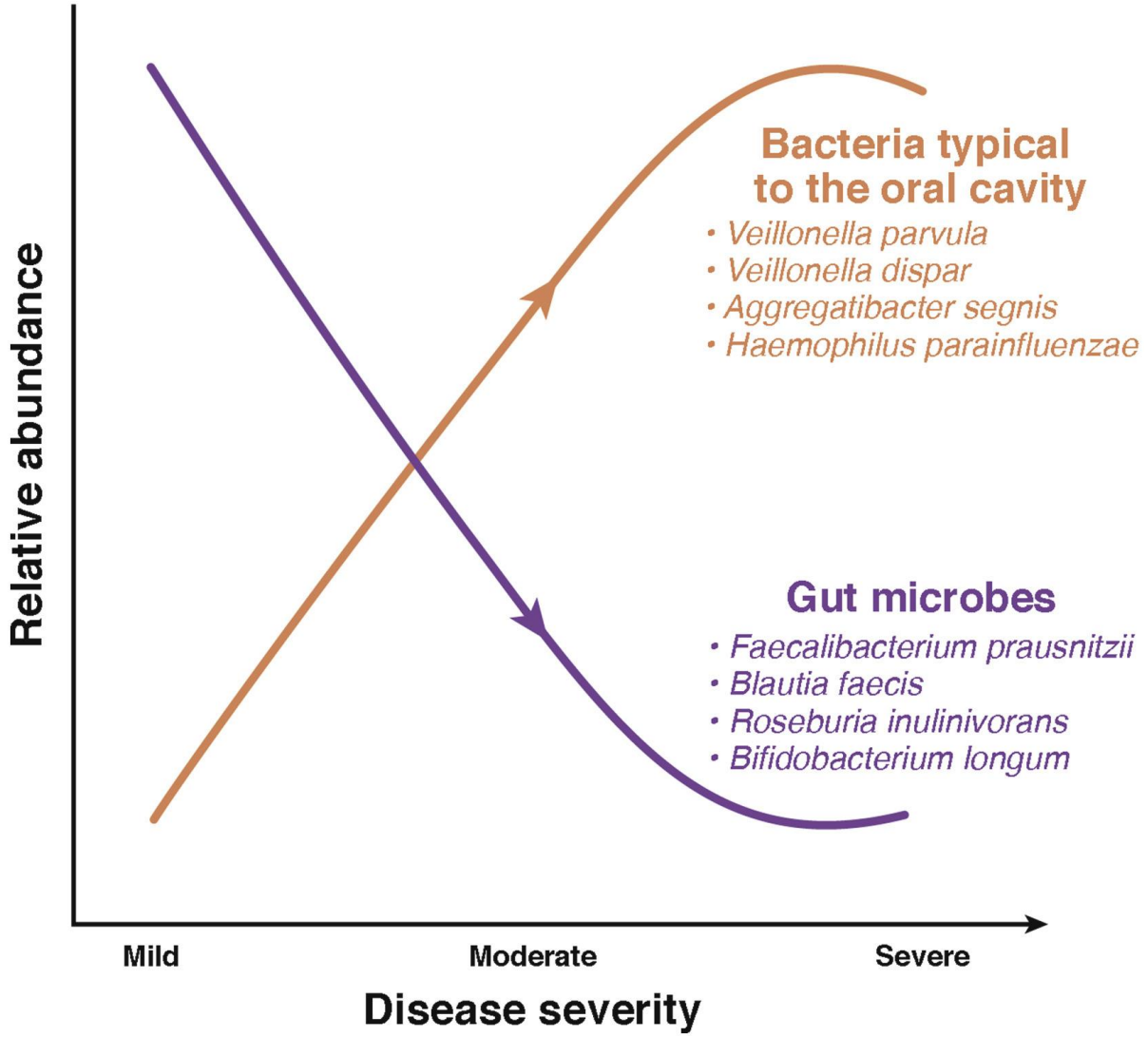
Inflammatory Bowel Disease

- An inappropriate and persistent inflammatory response to commensal gut microbiota in genetically susceptible people
- In Crohn's disease:
  - The phylum Firmicutes is commonly reduced
  - The family Enterobacteriaceae are commonly increased

Chehoud, et al. *IBD* 2015



Peterson, et al.
Cell Host Microbe 2008



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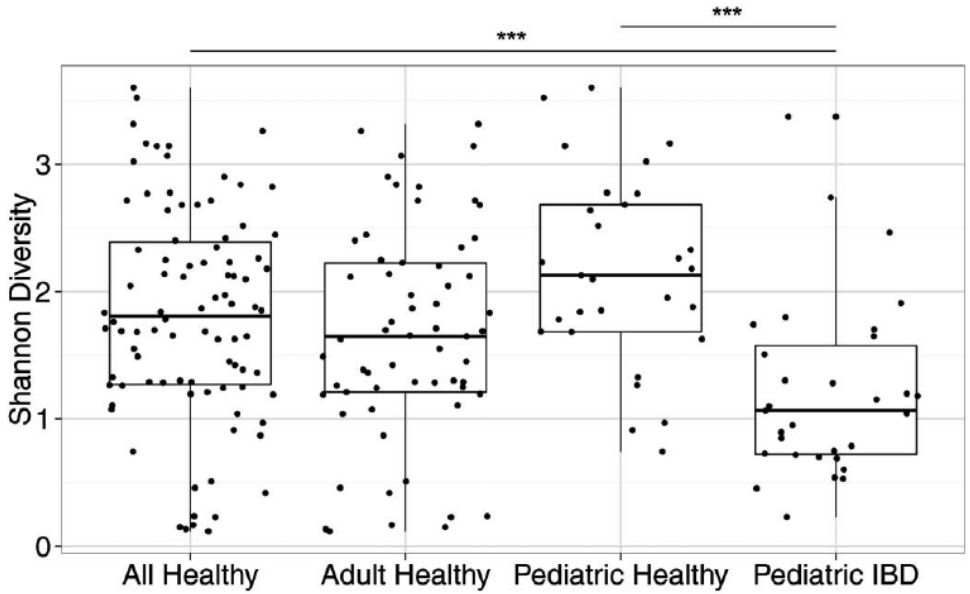
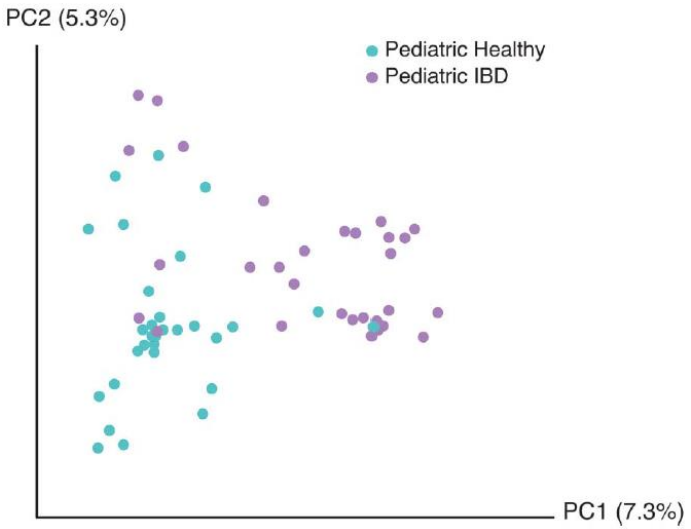
Fungal Signatures in IBD





Chehoud, et al. *IBD* 2015

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Fecal Microbiota Transplantation for Ulcerative Colitis: Not Just Yet

Table 1. Comparison of the 2 Studies

Characteristic	Moayyedi et al[5]	Rossen et al[6]
Study design	Double-blind, randomized (1:1), controlled	Double-blind, randomized (1:1), controlled
Study population	Adult patients with mild to moderate UC	Adult patients with mild to moderate UC
Sample size calculation	130	80
Subjects randomized (n)	75	50
Completing therapy (n)	70	37
Anti-TNF permitted?	Yes, at stable doses for ≥12 weeks	No
Route of FMT delivery	Retention enema	Nasoduodenal tube
Placebo	Water	Autologous FMT
Donor stool	6 volunteers, fresh or frozen	15 donors, fresh
Dose schedule	Weekly for 6 weeks	2 doses (0 and 3 weeks)
Primary endpoint	Remission (Mayo score ≤2 with an endoscopic score of 0) at week 7.	Remission (simple clinical colitis activity score ≤2) combined with ≥1-point decrease in Mayo endoscopic score at week 12
Subjects who achieved the primary endpoint	9/38 (24%) treated with FMT vs 2/37 (5%) controls ($P = .03$)	7/23 (30.4%) treated with FMT vs 5/25 (20%) controls ($P = .51$)
Microbiome analyses	Yes; increased diversity in FMT treated subjects compared with the control group.	Yes; increased diversity of responders in both groups. FMT treated group developed similar microbiota profile to respective donor.

FMT, fecal microbiota transplantation; TNF, tumor necrosis factor; UC, ulcerative colitis.

Grinspan & Kelly *Gastroenterology* 2015

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Grinspan & Kelly *Gastroenterology* 2015

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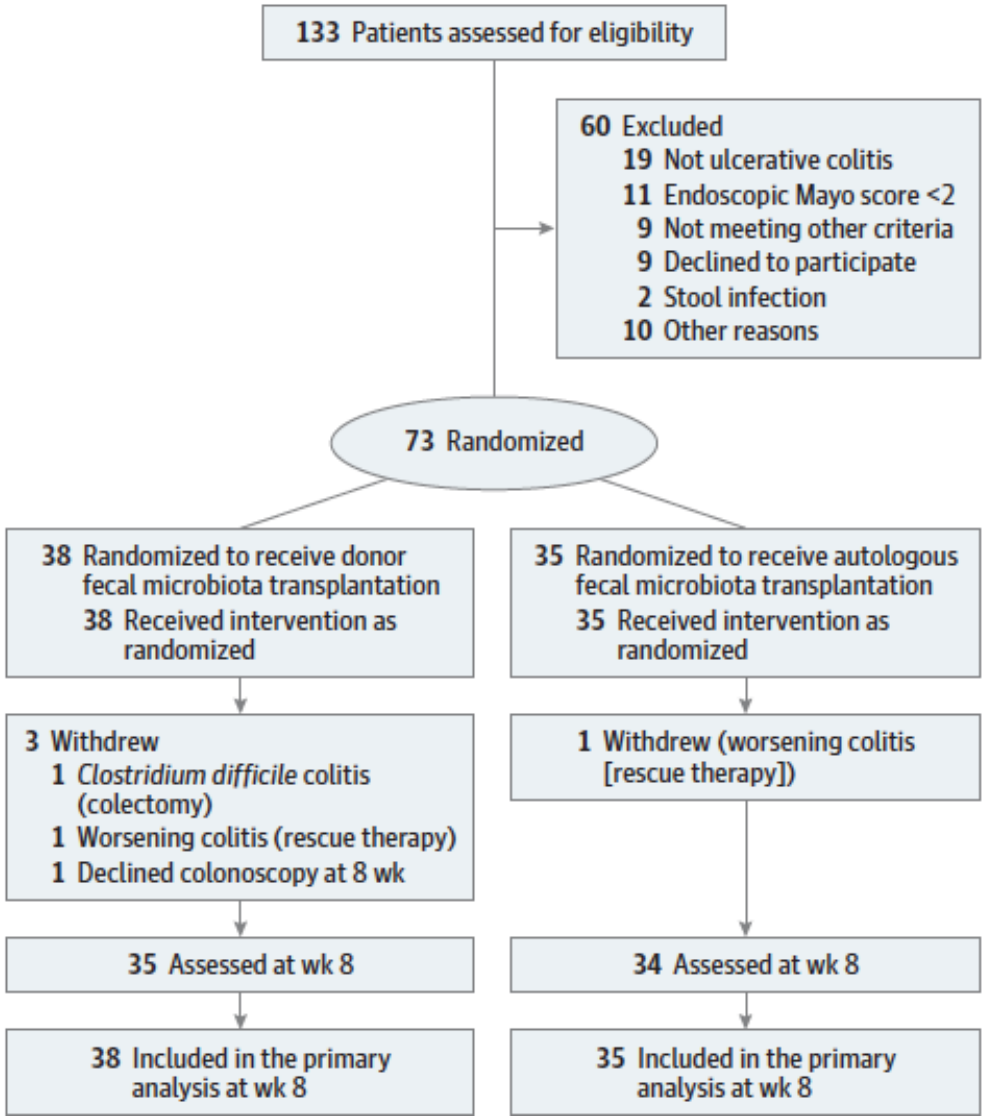
JAMA | Preliminary Communication

Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis



Costello, et al. JAMA January 2019

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Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis

Table 2. Outcome Measures Comparing Donor Fecal Microbiota Transplantation (FMT) With Autologous FMT at Week 8

Outcome	No./Total No. (%)		Absolute Percentage Gain Over Autologous FMT, % (95% CI)[a]	Mixed-Effect Odds Ratio (95% CI)	*P* Value[b]
	Donor FMT (n = 38)	Autologous FMT (n = 35)			
Primary Outcome[c]					
Steroid-free remission of ulcerative colitis at wk 8[d]	12/38 (32)	3/35 (9)	23 (4 to 42)	5.0 (1.2 to 20.1)	.03
Secondary Outcomes[c]					
Clinical response[e]	21/38 (55)	8/35 (23)	32 (10 to 54)	4.3 (1.5 to 11.9)	.007
Clinical remission[f]	18/38 (47)	6/35 (17)	30 (7 to 51)	4.5 (1.5 to 13.5)	.01
Endoscopic remission[g]	4/38 (11)	0/35 (0)	11 (−1 to 27)	NA[h]	.12
Other Outcomes					
Mean change in total Mayo score from wk 0 to wk 8 (SD)	−1.2 (2.1)	−3.5 (2.5)	−33 (−48 to −17)	−2.4 (−3.5 to −1.2)	<.001

Costello, et al. JAMA January 2019

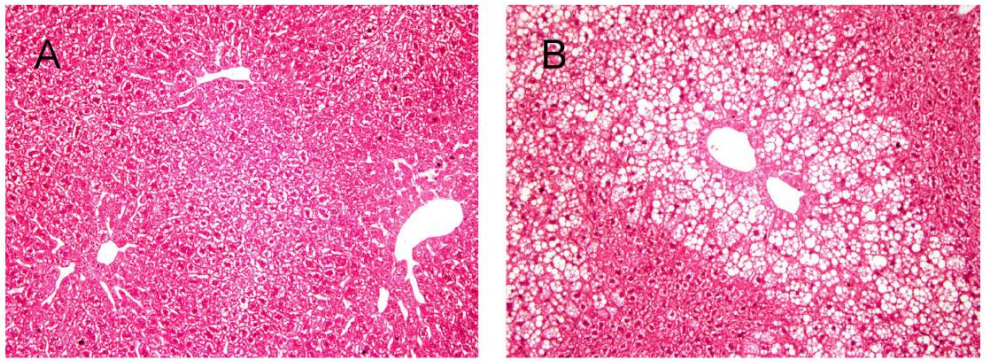
Liver Disease and the GI Microbiome

- 70% of the liver's blood supply comes from the intestine via the portal vein
  - Continuously exposed to bacterial components
    - Endotoxins, peptidoglycans
    - Multiple liver cell types express innate immune receptors that respond to microbial-derived products
- Dysbiosis, integrity of the gut barrier, and hepatic immune responses govern effects

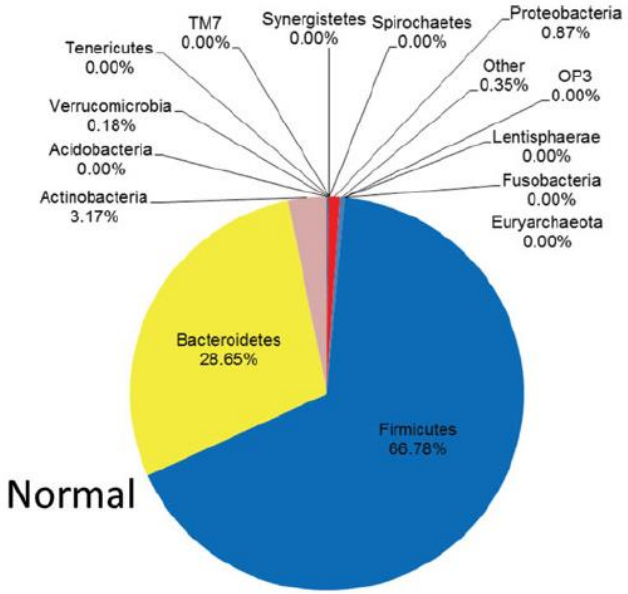
Marchesi, et al. *Gut* 2015

NAFLD

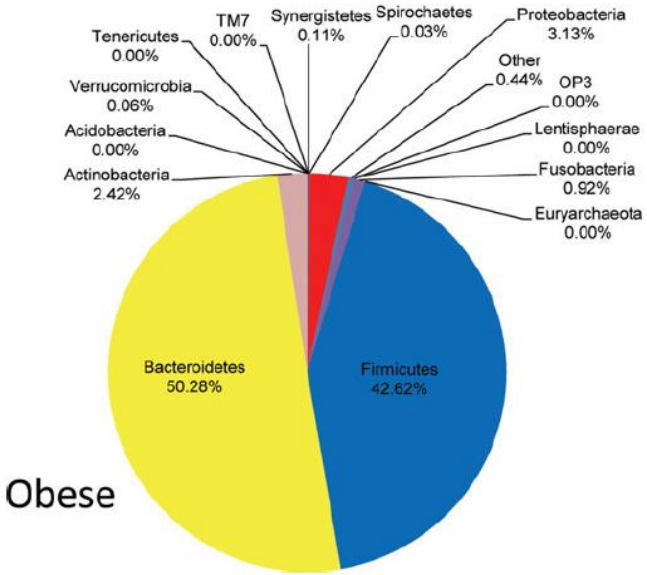
- GF mice colonized with stool from obese mice with NAFLD and fed a HFD develop obesity and NAFLD
- GF mice colonized with stool from obese mice without NAFLD and fed a HFD develop comparable obesity but not NAFLD

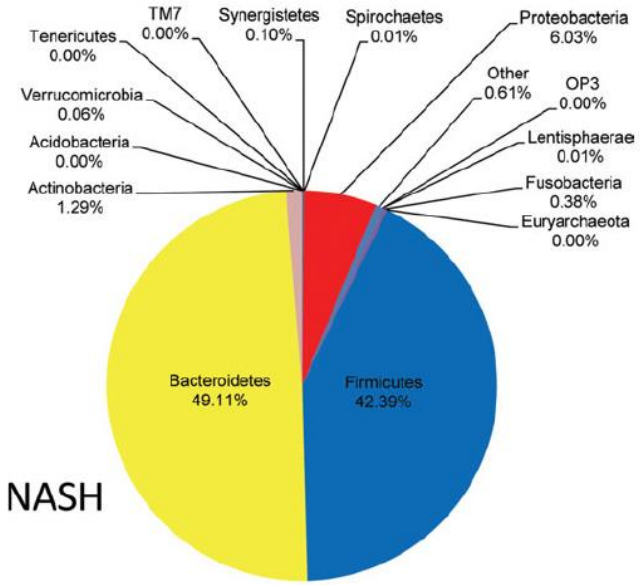


Le Roy, et al. *Gut* 2013

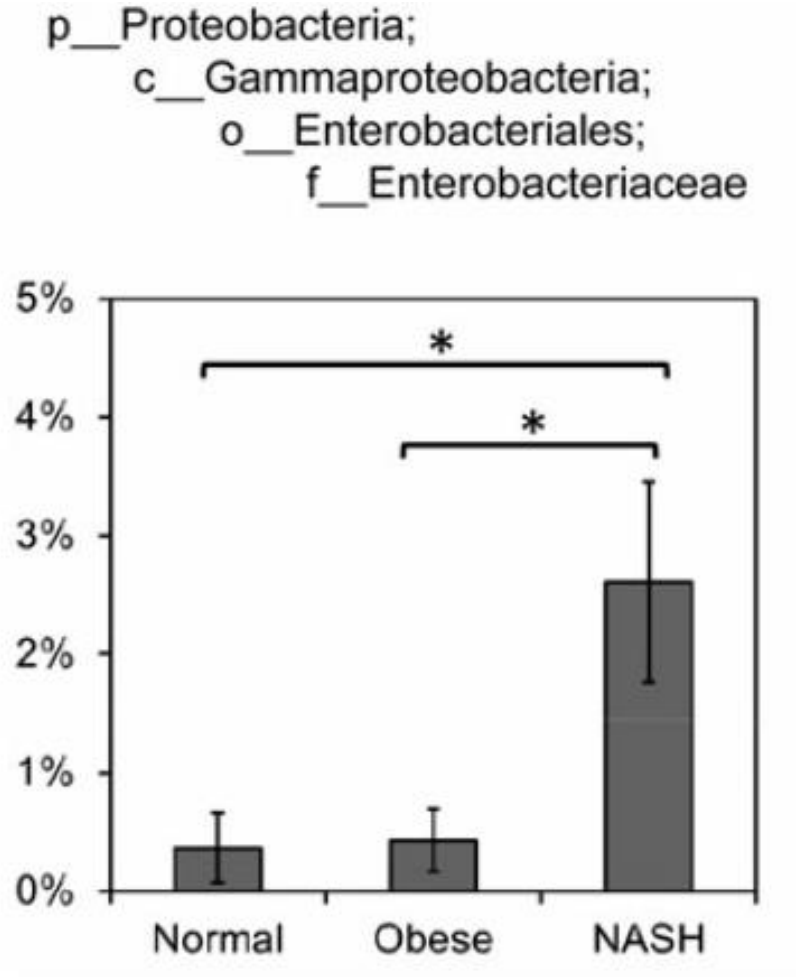


All Children and Adolescents





Zhu, et al. *Hepatology* 2013



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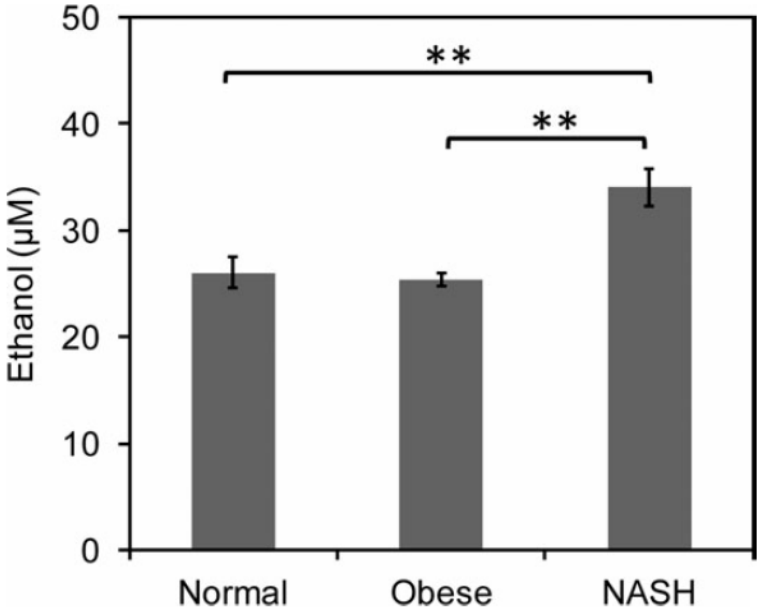

Zhu, et al. *Hepatology* 2013

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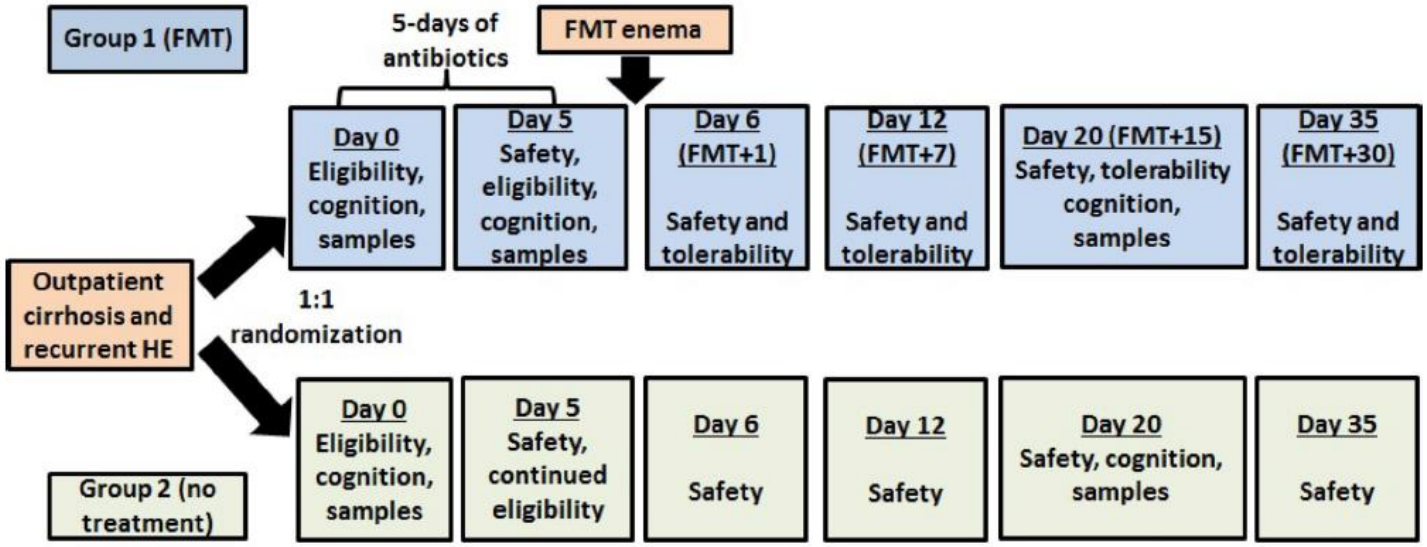
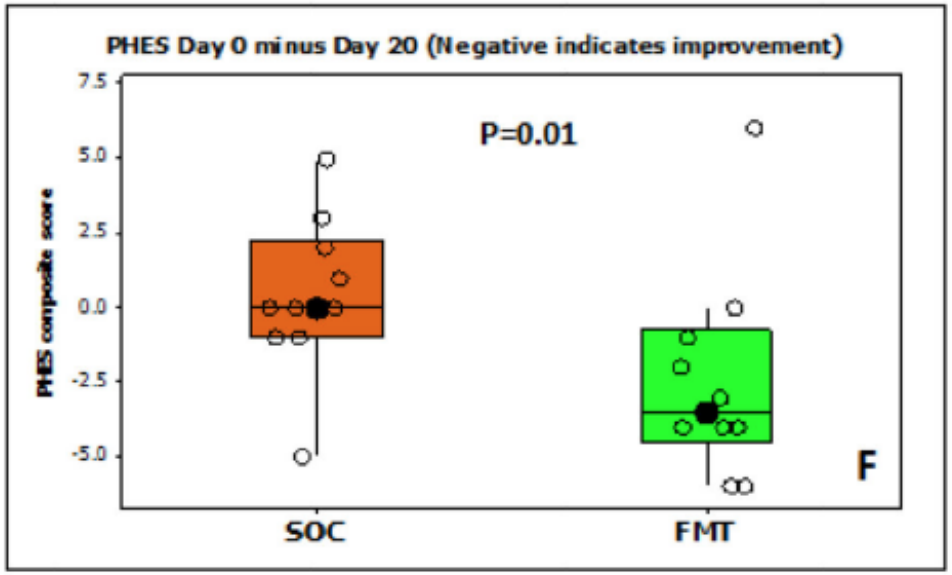
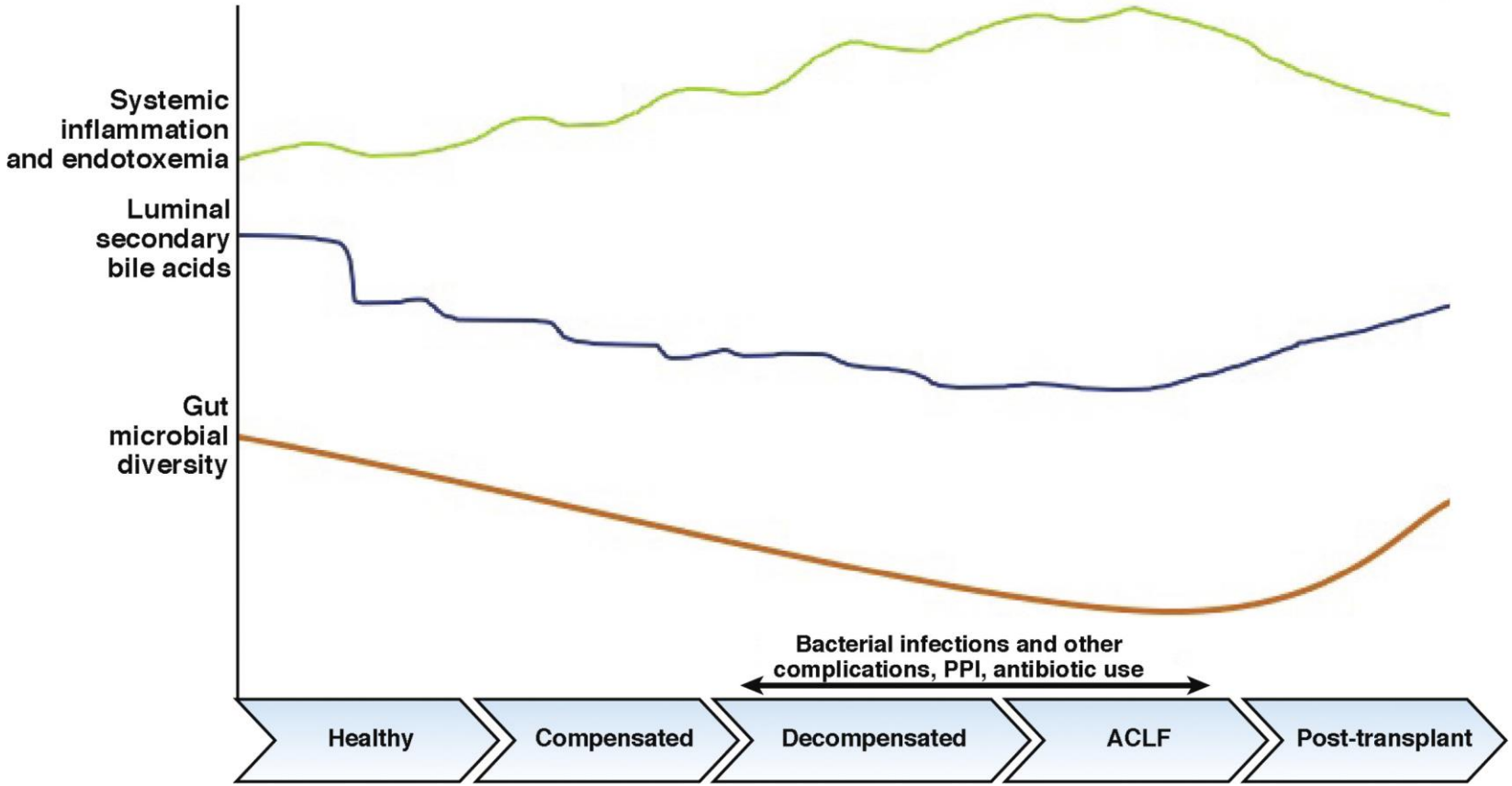
FMT for Hepatic Encephalopathy

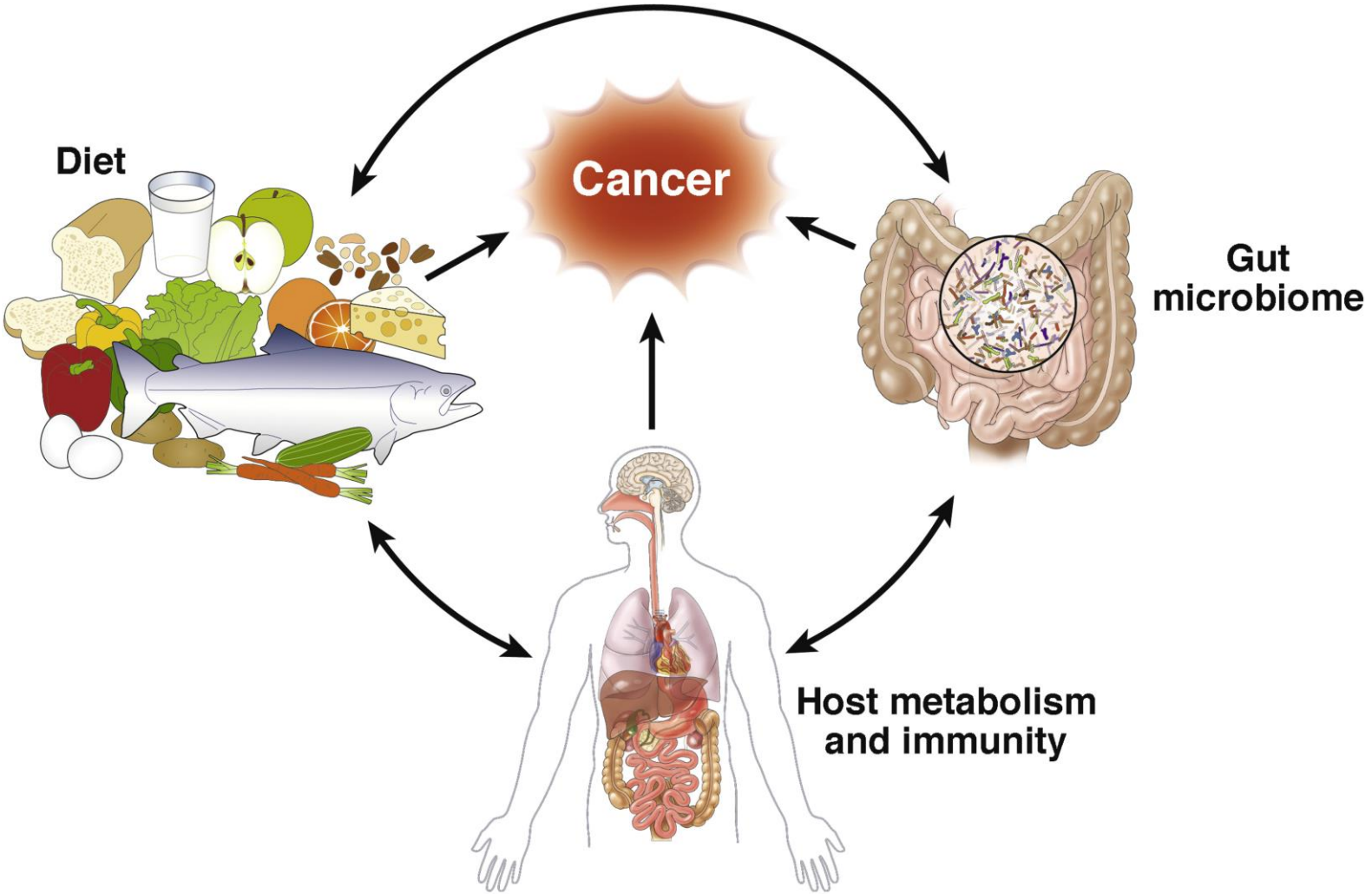




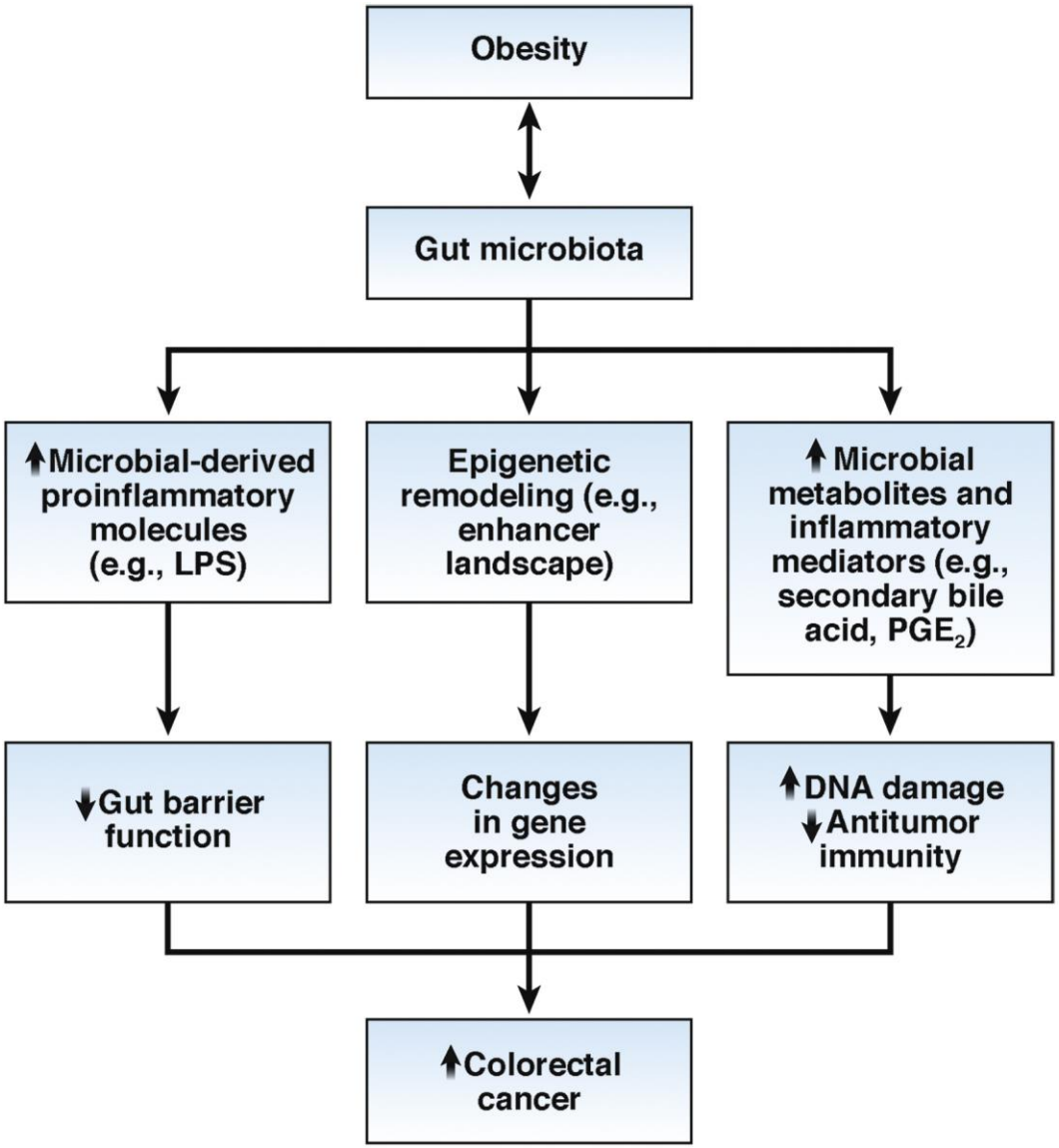
Bajaj, et al. Hepatology 2017



Clinical Gastroenterology and Hepatology 2019 17, 307-321DOI: (10.1016/j.cgh.2018.08.008)



Clinical Gastroenterology and Hepatology 2019 17, 275-289DOI: (10.1016/j.cgh.2018.07.012)



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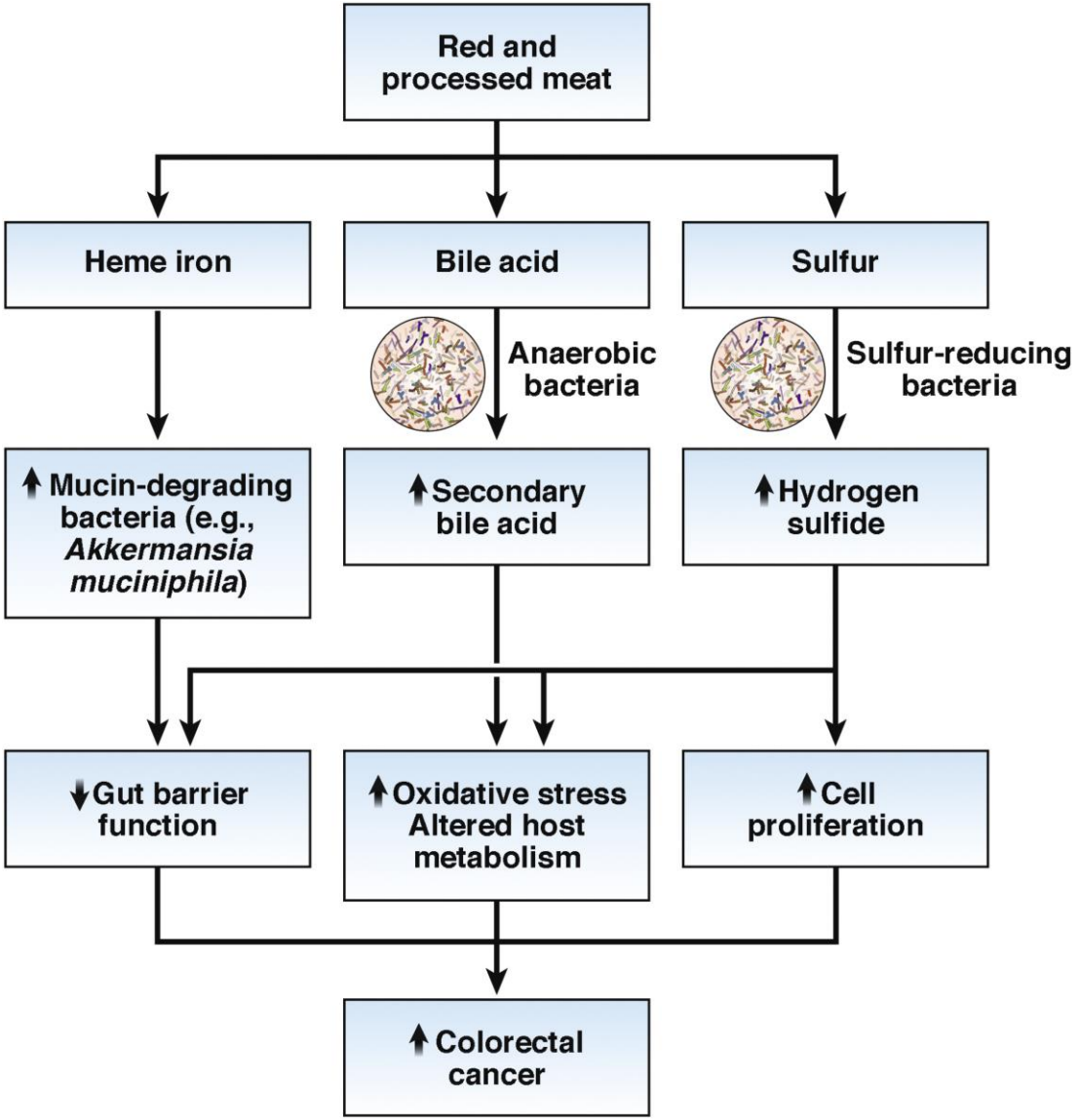

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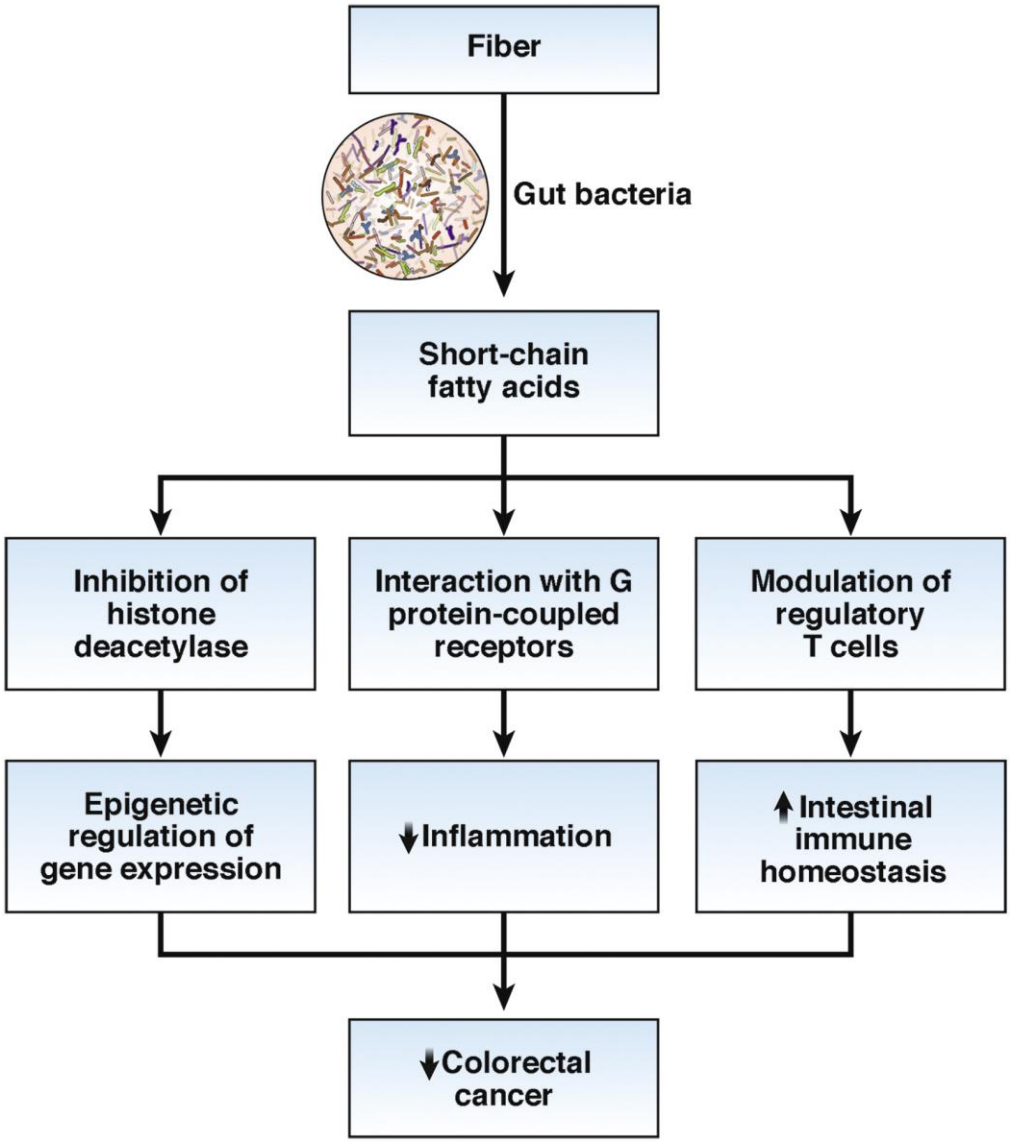


Clinical Gastroenterology and Hepatology 2019 17, 275-289DOI: (10.1016/j.cgh.2018.07.012)

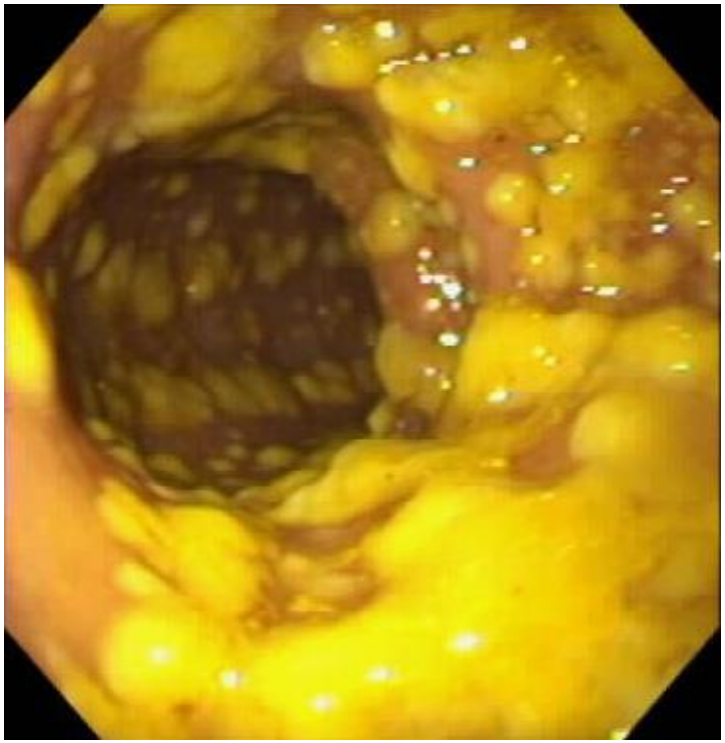
Clostridium difficile

- Gram-positive, anaerobic, spore-forming bacillus
- *C. difficile* infection (CDI):
  - Toxin mediated
  - Associated with alterations in the GI microbiota
  - Responsible for ~half a million infections and associated with ~29,000 deaths per year in the US[1]
  - Rates have surpassed MRSA making CDI the most common HAI[2]
- Traditional risk factors are antibiotic use, hospitalization, advanced age, and co-morbidities

1) Lessa FC, et al. NEJM 2015; 2) Miller BA, et al. ICHE 2011

Clinical Presentation

- Asymptomatic carriage
- Non-severe -diarrhea
- Severe
  - Elevated WBC count
  - Renal dysfunction
  - Abdominal pain/distention
  - Fever
  - Pseudomembranous colitis



Clinical Presentation

- Fulminant
  - Hypotension
  - Shock
  - Ileus
  - Toxic megacolon
  - Death
- Recurrent disease
  - 20 ➔40➔60% rule

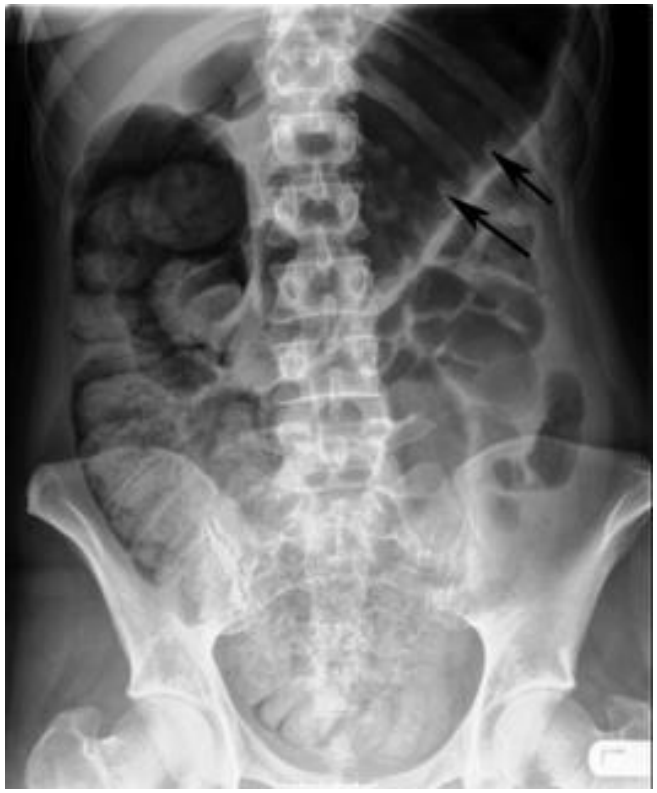


Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

Fecal Microbiota Transplantation

- The process of taking stool from a healthy donor and placing it into the GI tract of a patient
- Goal is to restore the healthy gut microbiota by replenishing the intestinal ecosystem of the patient with the microbiota of the healthy donor
- Increasingly popular in the clinical arena and the public media
- Introduction of detrimental microbes during fecal transplantation is a concern

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First Fecal Transplant at UMMC – February 2013

Fecal Transplant - Technique

- Healthy donor screened for infectious pathogens and diseases that may be linked to the GI microbiota
- Donor stool processed into a liquid slurry
  - Added to saline, water, or milk
  - Blended or mixed
  - Strained through sieve, gauze, or coffee filter
- Stool solution administered to patient
  - NG or NE tube
  - Upper endoscopy
  - Colonoscopy
  - Enema


NSF
HIGH FIVE
HIGH FIVE

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OPENBIOME

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Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

- 317 patients from 27 case series and reports
- Resolution in 92% (89% after single treatment)
- Factors that appeared to predict success:
  - Related donor
  - Instillation via colonoscopy or enema
  - Use of > 50g donor stool

Gough E, et al. CID 2011

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

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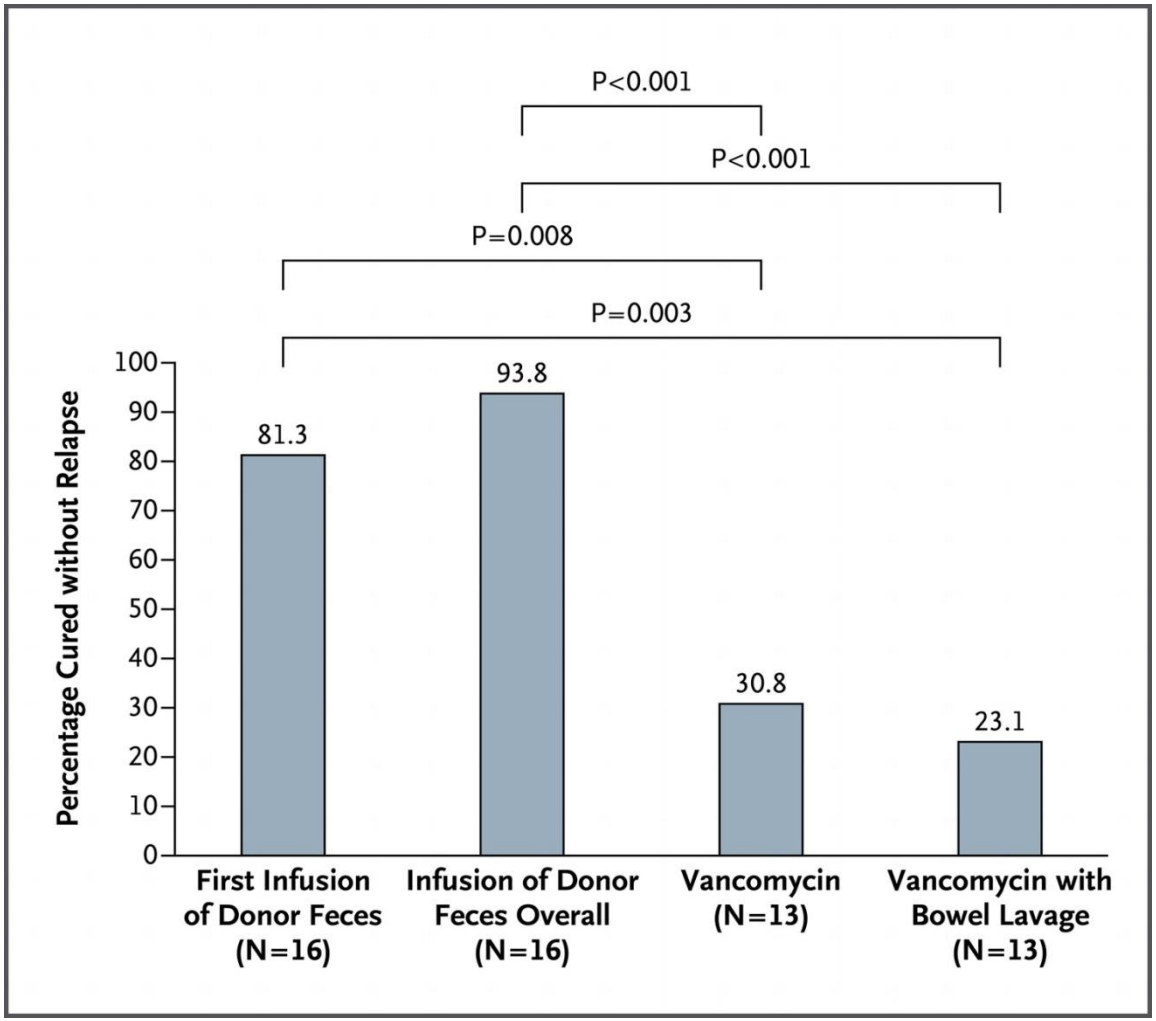
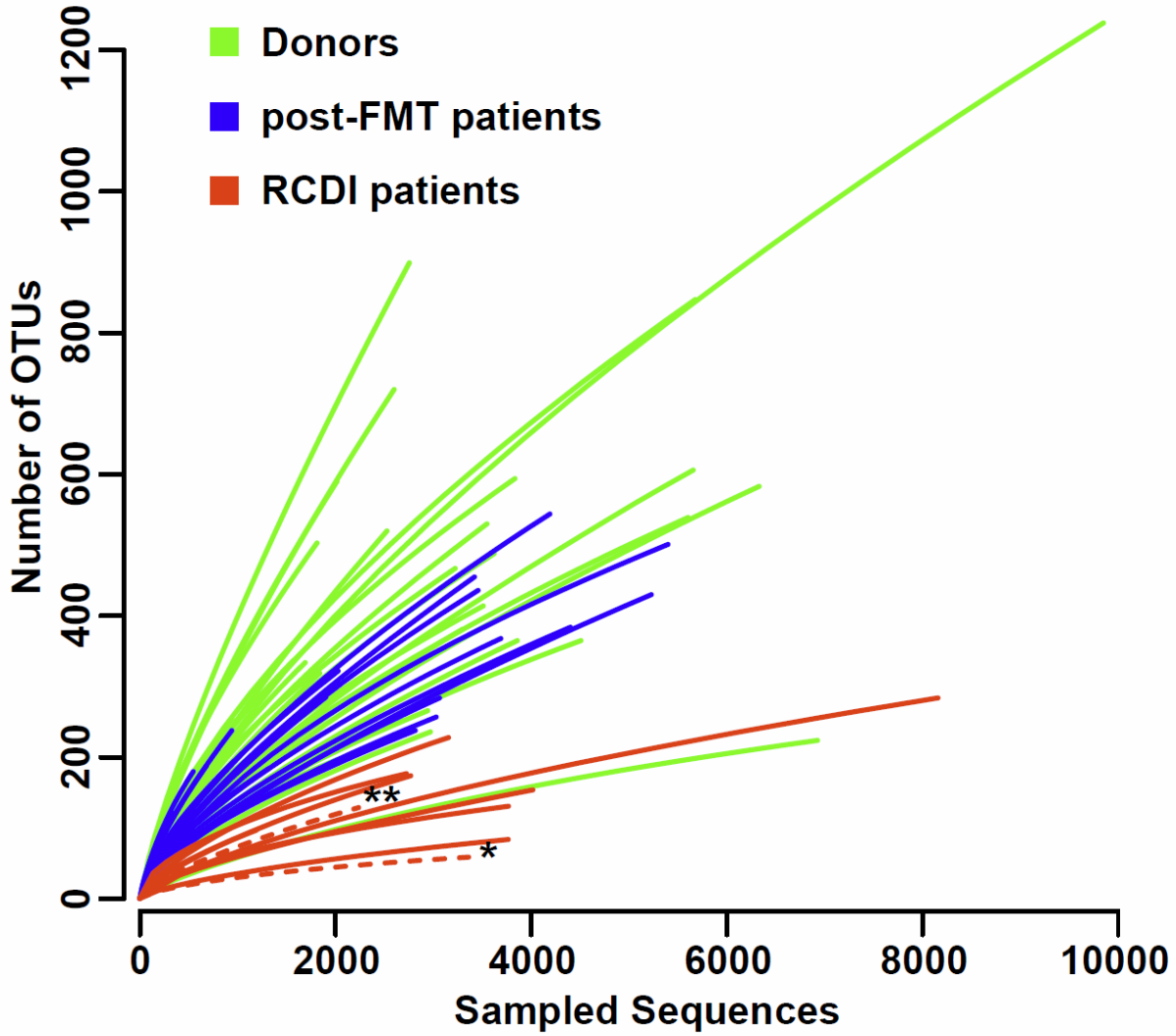
Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.



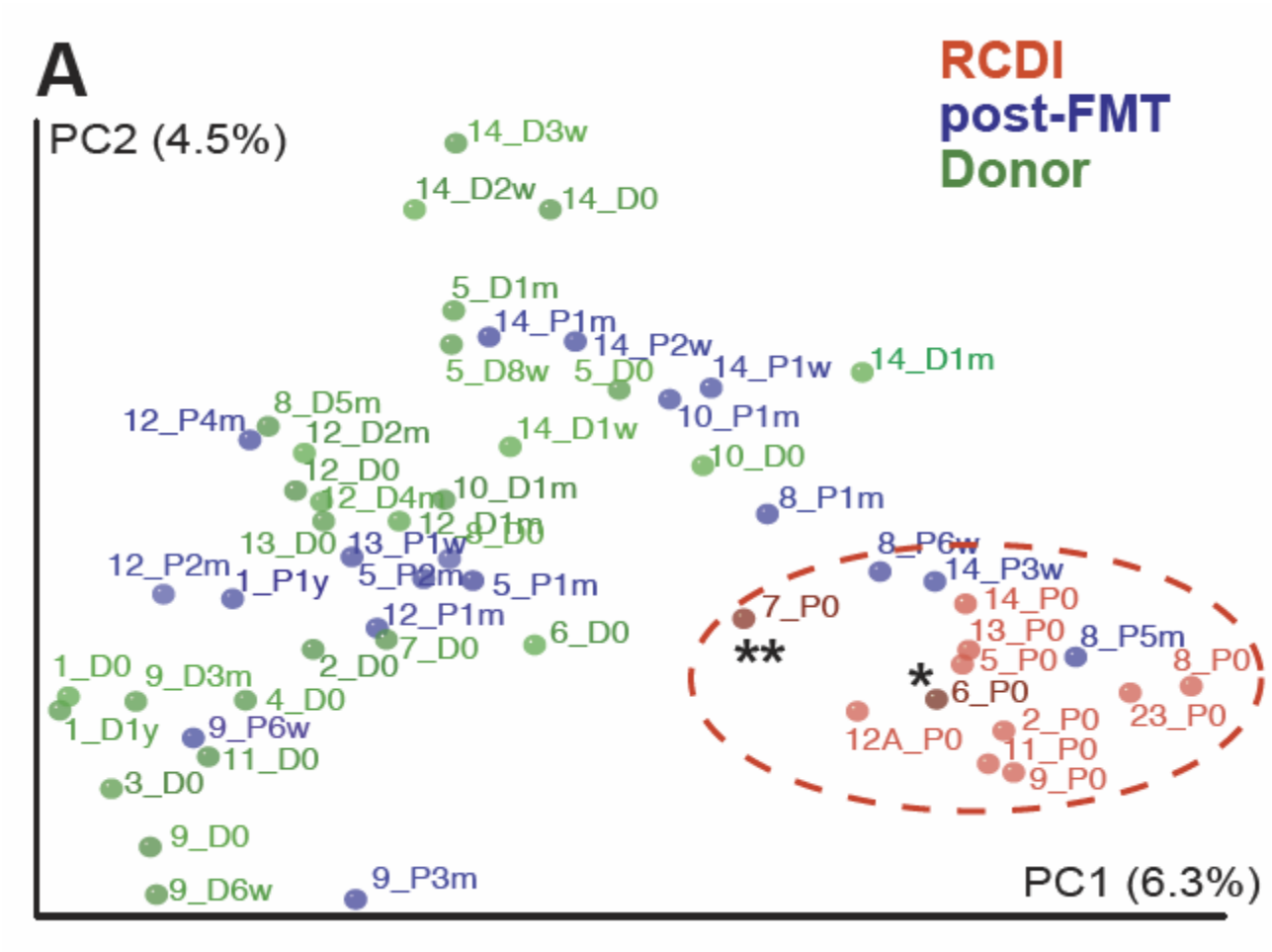
van Nood E et al. N Engl J Med 2013;368:407-415.

How do fecal transplants really work?

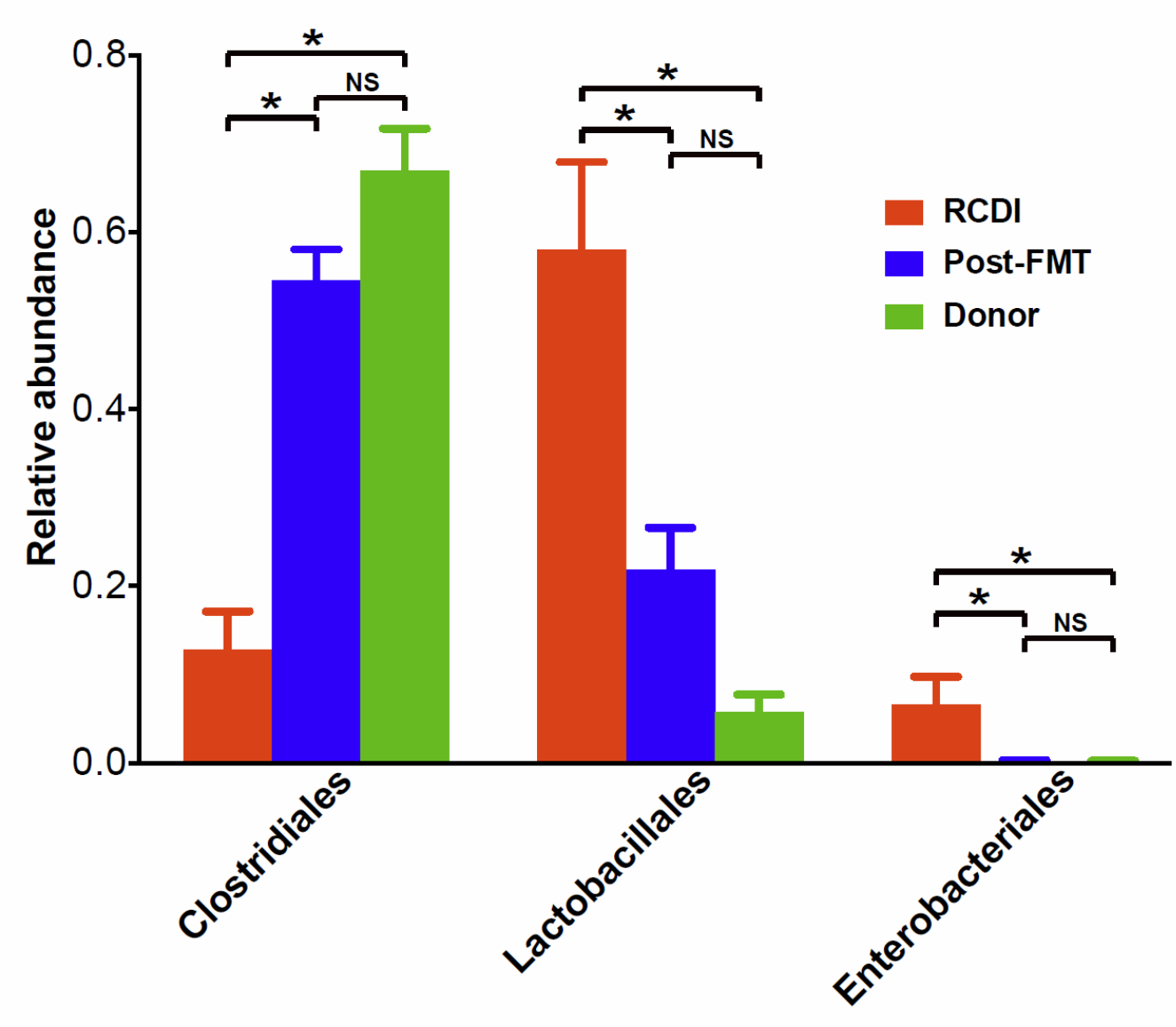
- Which bacteria are beneficial?
- Which bacteria are detrimental?
- Can you create a “synthetic stool” using a subset of fecal bacteria?
- What changes in the microbiota occur during a fecal transplant?



Song Y, et al. PLOS ONE 2014



Song Y, et al. PLOS ONE 2014



Song Y, et al. PLOS ONE 2014

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Current FDA Policy

(Effective July 18, 2013)

Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies

We, FDA, are informing members of the medical and scientific community, and other interested persons that we intend to exercise enforcement discretion regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat *Clostridium difficile* (*C. difficile*) infection not responding to standard therapies. FDA intends to exercise this discretion provided that the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. Informed consent should include, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its potential risks. FDA intends to exercise this discretion on an interim basis while the agency develops appropriate policies for the study and use of FMT products under IND.

Future of FMT?

- Multiple companies studying FMT products
- The end of enforcement discretion?
- The end of stool banks?
- Still the future is bright!
- >150 trials of FMT registered on clinicaltrials.gov

Questions?

Fecal Microbiota Transplantation Working Group (Indications)

- Recurrent or relapsing CDI
  - At least 3 episodes of mild to moderate CDI and failure of a 6- to 8-week taper with vancomycin
  - At least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity
- Moderate CDI not responding to standard therapy for at least a week
- Severe (and perhaps fulminant CDI) with no response to standard therapy after 48 hours

Bakken, JS, et al. *Clin Gastroenterol H*. 2011