

# Fecal Microbiota Transplantation

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# What & Why?

What & Why?

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Applications  
in Oncology

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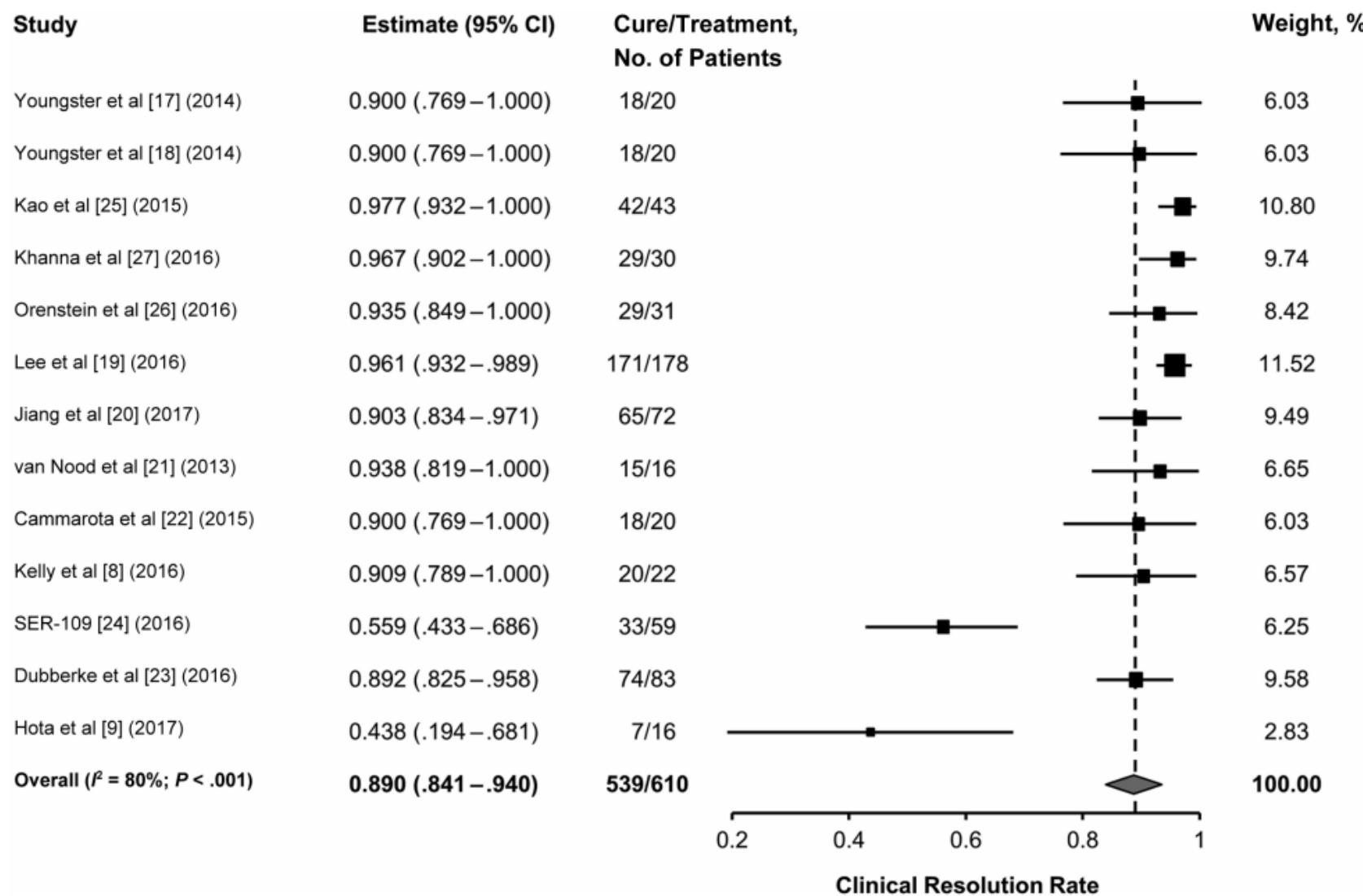
Applications  
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# Fecal Microbiota Transplantation (FMT)

- Transplant fecal microbiota from healthy donor to colon of recipient
- Methods: frozen oral capsules, solution via enteric tube, enema, colonoscopy
- Indications:
  - *C. difficile* infection (CDI) = driving force behind development
  - MDRO colonization
  - inflammatory bowel disease (IBD)
  - oncology: auto-FMT post allo-SCT; immune checkpoint inhibitors; GVHD

# *Clostridiooides difficile* Infection

- Infectious colitis that occurs after antibiotic treatment ("antibiotic-associated")
- Depletion of protective taxa (abx & PPI) → altered bile acid metabolism → germination of resident or recently ingested *C. difficile* spores → expansion of vegetative *C. difficile* → toxin production → colonic inflammation → CDI
- Treatment with anti-CDI antibiotics (vancomycin, fidaxomicin) contributes to persistent depletion of protective taxa → risk for recurrent CDI
- **FMT restores colonization resistance by restoring protective taxa**
- Note: treatment with anti-CDI antibiotics is prerequisite



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

Clinical Definition	Supportive Clinical Data	Recommended Treatment <sup>a</sup>	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of $\leq 15\,000$ cells/mL and a serum creati- nine level $< 1.5$ mg/dL	<ul style="list-style-type: none"><li>VAN 125 mg given 4 times daily for 10 days, OR</li><li>FDX 200 mg given twice daily for 10 days</li><li>Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days</li></ul>	Strong/High Strong/High Weak/High
Initial episode, severe <sup>b</sup>	Leukocytosis with a white blood cell count of $\geq 15\,000$ cells/mL or a serum creati- nine level $> 1.5$ mg/dL	<ul style="list-style-type: none"><li>VAN, 125 mg 4 times per day by mouth for 10 days, OR</li><li>FDX 200 mg given twice daily for 10 days</li></ul>	Strong/High Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	<ul style="list-style-type: none"><li>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.</li></ul>	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intrave- nous metronidazole)
First recurrence	...	<ul style="list-style-type: none"><li>VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR</li><li>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</li><li>FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode</li></ul>	Weak/Low Weak/Low Weak/Moderate
Second or subsequent recurrence	...	<ul style="list-style-type: none"><li>VAN in a tapered and pulsed regimen, OR</li><li>VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR</li><li>FDX 200 mg given twice daily for 10 days, OR</li><li>Fecal microbiota transplantation<sup>c</sup></li></ul>	Weak/Low Weak/Low Weak/Low Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

IDSA/SHEA Guidelines: McDonald LC et al *Clin Inf Dis* 2018

# Efficacy Despite Product Heterogeneity?

- FMT contains multitudes:
  - bacteria, fungi, archaea... bacteriophage, eukaryotic viruses (e.g., TTVs) ...
  - ... human colonocytes, metabolites
- Causal models for efficacy versus *C. difficile* infection:
  - Direct bacterial interaction? Bile acid metabolism-mediated interaction?
  - Bile acid metabolism & Th17 regulatory cells?
- **We do it because it works, but we don't know why!**

Bojanova & Bordenstein *PLoS Biology* 2016; Ott et al *Gastroenterology* 2017; Hang et al *Nature* 2019

# FMT Regulation & Commercial Alternatives

- Guideline-recommended for CDI but NO FDA-approved product:
  - IND required for non-CDI indications
  - for CDI, FDA exercises "enforcement discretion"
  - concern that product availability (e.g., OpenBiome) limiting RCT enrollment
- Multiple companies with "ecobiotic" FMT alternatives in phase 2/3 trials:
  - Finch, Rebiotix, Seres, Vedanta
  - May 2020: "Rebiotix and Ferring are the first to announce positive preliminary results on primary efficacy endpoint from ongoing pivotal Phase 3 clinical trial"

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# FMT Program Development at Penn

- 2014-2016: ID Division Stool Bank
  - FDA enforcement discretion (no IND)
  - 67 FMTs: 82% aggregate cure rate
- 2016-2018: OpenBiome partnership
- 2019-present: "Penn Microbiome Therapy (PMT)"
  - IND for 3 products: capsule, upper GI liquid, enema
  - 3 protocols: R-CDI, SC-CDI, postpartum incontinence (OB-GYN: Uduak Andy, PI)  
(compassionate use for MDRO colonization)

# Impact of COVID-19 on FMT at Penn

- **FDA partial hold:** all doses manufactured after December 1, 2019
- Adequate donor/dose screening:
  - challenges with stool testing for SARS-CoV-2 (high LOD)
  - donor screening with serology? NP NAAT?
- Ongoing COVID-19 activity slows (already slow) clinical trial enrollment
- **Recent resumption of enrollment for all protocols**

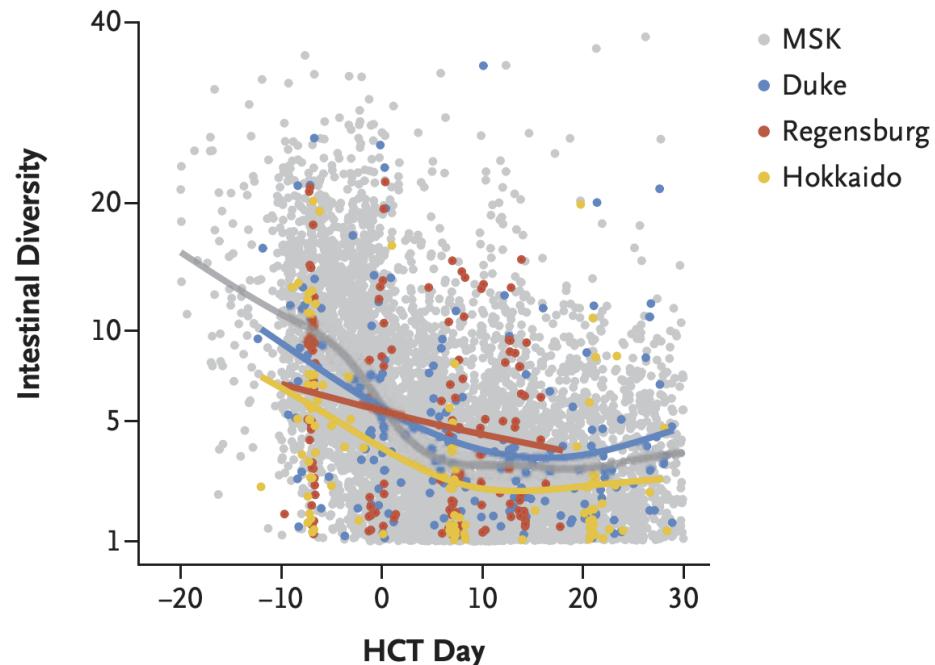
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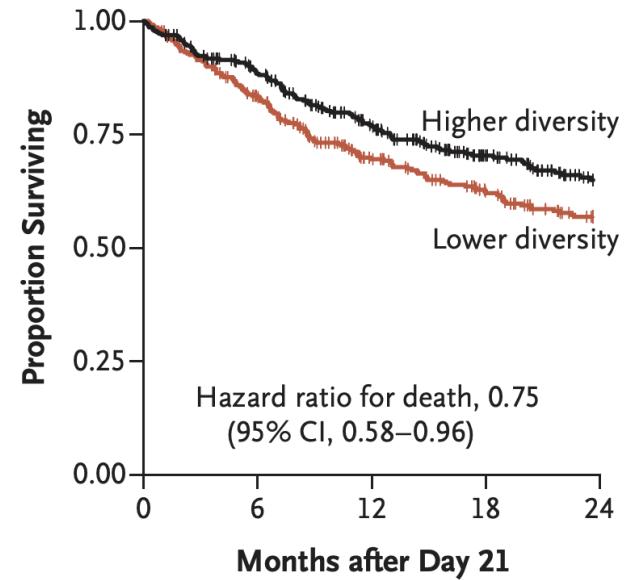
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# Dysbiosis & Death

A Change in Diversity of Intestinal Microbiota during HCT Period



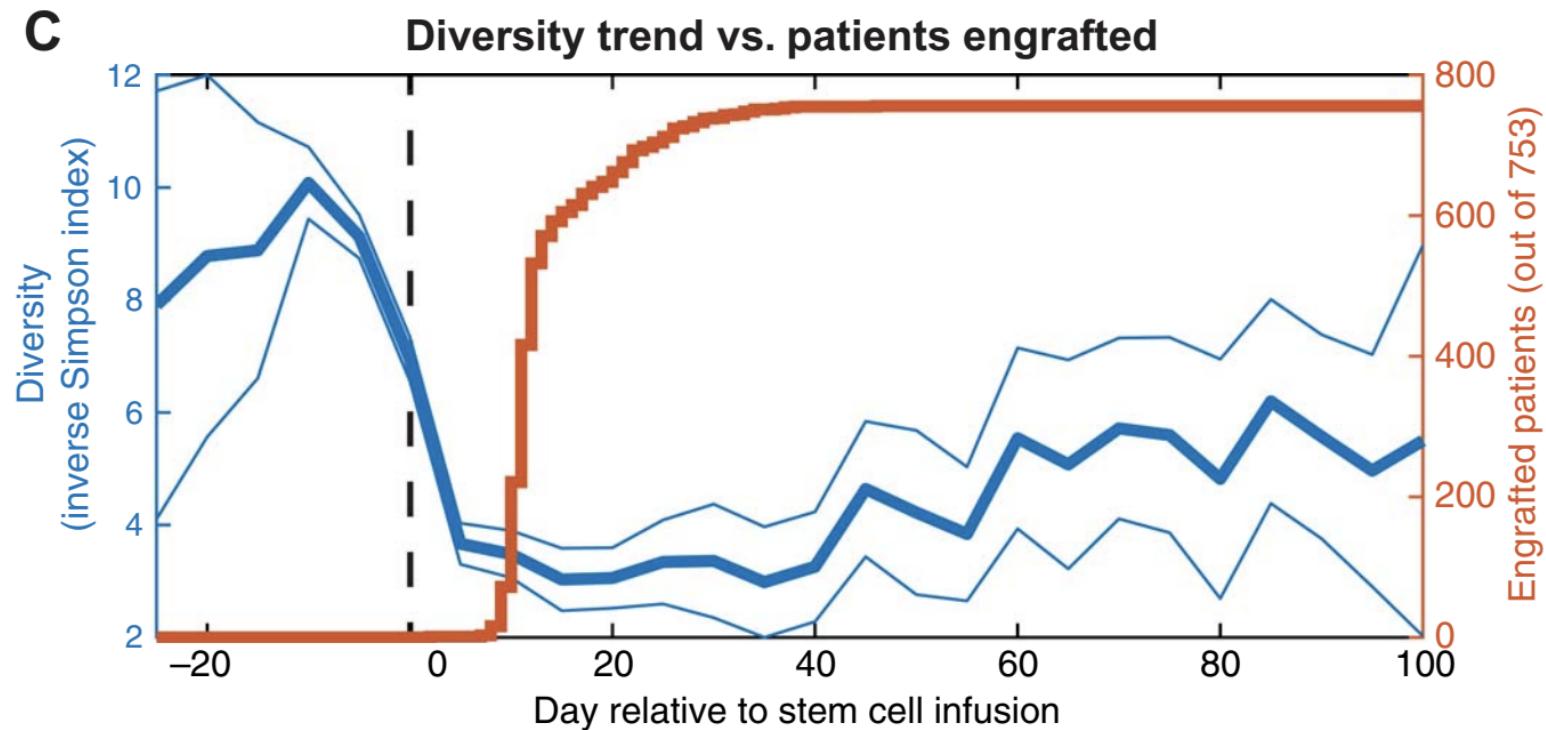
B Overall Survival — Cohort 1

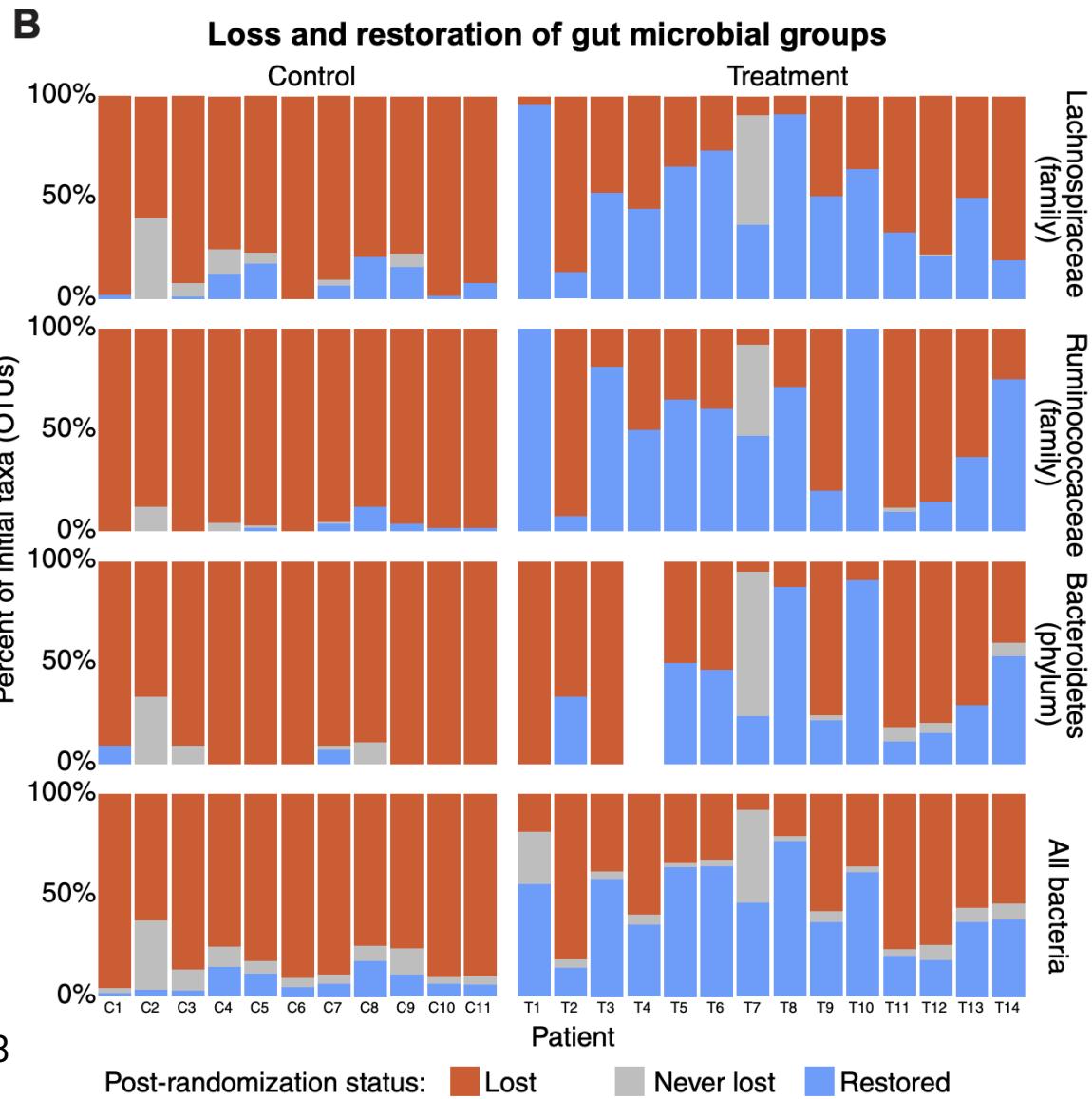


No. at Risk

Higher	354	289	220	159	116
Lower	350	281	204	164	129

# Auto-FMT Post Allo-SCT





# FMT & Immune Checkpoint Inhibitors

- Differential bacterial signatures of ICI responders versus non-responders
- Modulation of the gut microbiome via FMT from patients alters antitumor immunity and response to ICI therapy in gnotobiotic mice
- FMT also applied to & resolves ICI-related colitis:
  - variable (donor-dependent) effects on microbiome
  - increase proportion of regulatory T-cells in colonic mucosa

Routy et al *Science* 2018; Gopalakrishnan et al *Science* 2018; Matson et al *Science* 2018; Wang et al *Nat Med* 2018

# FMT & GVHD

- Disruption of intestinal microbiota associated with GVHD
- Recent prospective single-arm study:
  - 15 post-allo-HCT with steroid-dependent, acute or late-onset acute intestinal GvHD
  - effect of donor FMT on GVHD symptoms and biomarkers
  - 10 of 15 study participants with complete clinical response observed within 1 month after FMT, without additional interventions to alleviate GVHD symptoms
  - associated increase in gut microbial alpha-diversity, a partial engraftment of donor bacterial species, and increased abundance of butyrate-producing bacteria, including *Clostridiales* and *Blautia* species

# Risks of FMT in Oncology Patients

- Disseminated bacterial infection:
  - ESBL *E. coli* sepsis and death\*
- CMV & EBV:
  - CMV colitis post-FMT has been reported
  - risk of CMV listed on informed consent for our PMT products  
(donors are screened for CMV/EBV but not restricted)
- GVHD: given heterogeneity of FMT, potential for exacerbation?

\*DeFilipp et al *NEJM* 2019



Questions?