

Fecal Microbiota Transplantation

2020 Update

Brendan J. Kelly, MD, MS

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Disclosures

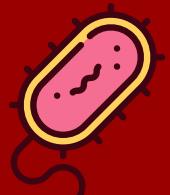
- No conflicts of interest.
- Opinions my own.

Fecal microbiota transplantation (FMT):

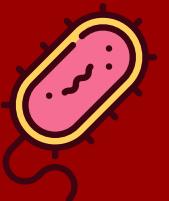
- *Clostridioides difficile* infection
- MDRO colonization
- inflammatory bowel disease (IBD)
- oncology: auto-FMT post allo-SCT; immune checkpoint inhibitors

FMT regulatory oversight (& COVID-19)

Does it work? why?

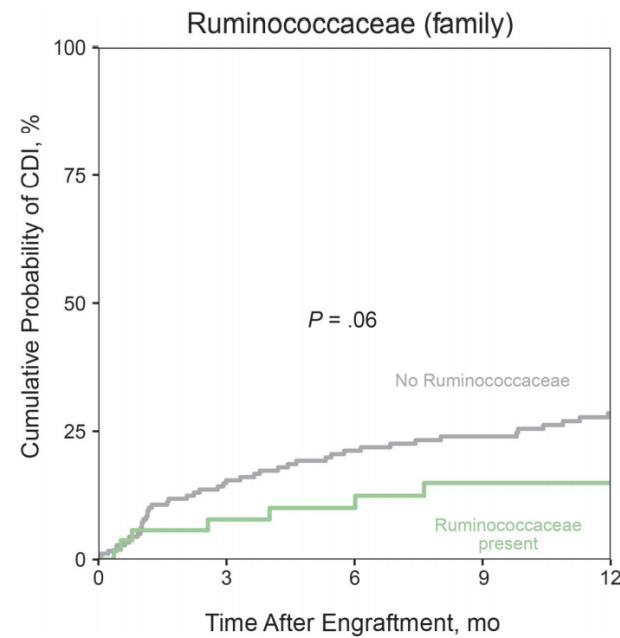
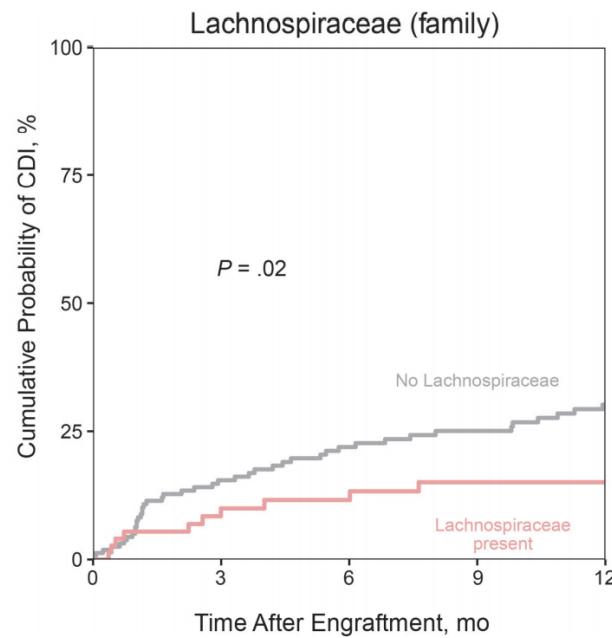
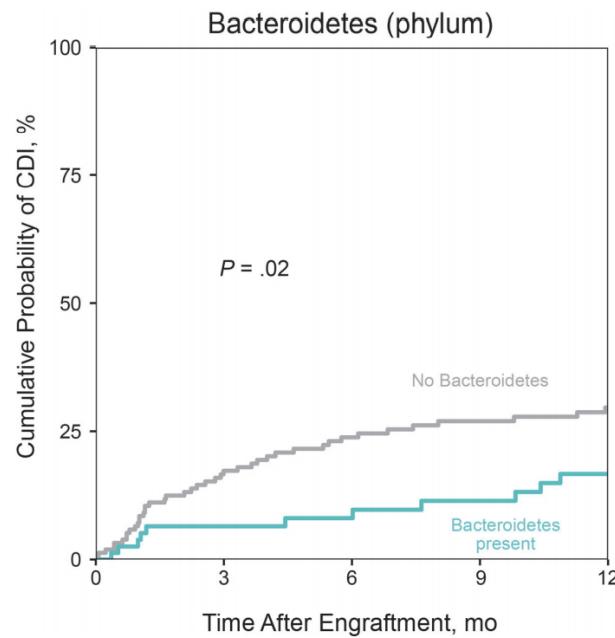


FMT → CDI



Clostridiooides difficile Infection

- 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



Authors	Publication Year	Population	Study Design	FMT Dose (g stool)	FMT Formulation	FMT Administration	Risks
Hamilton et al	2012	R-CDI	single-group trial	50g stool	250mL suspension	colonoscopy	diarrhea, flatulence
van Nood et al	2013	R-CDI	randomized trial	(not reported)	500mL suspension	duodenal tube	diarrhea, cramping, belching
Youngster et al JAMA	2014	R-CDI	single-group trial	48g stool	30 capsules	oral	cramping, bloating
Kelly et al	2016	R-CDI	randomized trial	64g stool	500mL suspension	colonoscopy	chills, abdominal pain, bloating, nausea, flatulence
Kao et al	2017	R-CDI	randomized trial	80-100g stool	40 capsules or 180mL suspension	oral or colonoscopy	nausea, vomiting, fever, abdominal discomfort
Weingarden et al	2013	S/SC/F-CDI	case series	50g stool	250mL suspension	colonoscopy	(not reported)
Agrawal et al	2015	S/SC/F-CDI	case series	~30-60g stool	150-500mL suspension	upper endoscopy, lower endoscopy, enema	diarrhea, constipation, abdominal pain, ileus
Aroniadis et al	2015	S/SC/F-CDI	case series	(not reported)	suspension	upper endoscopy, lower endoscopy, enema, colonoscopy	diarrhea, abdominal pain
Fischer et al	2015	S/SC/F-CDI	case series	50-100g stool	300mL suspension	sigmoidoscopy or colonoscopy	treatment failure and death
Fischer et al	2017	S/SC/F-CDI	case series	50-100g stool	300mL suspension	sigmoidoscopy or colonoscopy	treatment failure and death

C. difficile Treatment Guidelines

- IDSA/SHEA guidelines:
 - EIA vs PCR for diagnosis
 - vanco/fidaxo > metro
 - **FMT** for R-CDI

Clinical Infectious Diseases
IDSA GUIDELINE



Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,¹ Dale N. Gerding,² Stuart Johnson,^{2,3} Johan S. Bakken,⁴ Karen C. Carroll,⁵ Susan E. Coffin,⁶ Erik R. Dubberke,⁷ Kevin W. Garey,⁸ Carolyn V. Gould,¹ Ciaran Kelly,⁹ Vivian Loo,¹⁰ Julia Shaklee Sammons,⁸ Thomas J. Sandora,¹¹ and Mark H. Wilcox¹²

¹Centers for Disease Control and Prevention, Atlanta, Georgia; ²Edward Hines Jr Veterans Administration Hospital, Hines, and ³Loyola University Medical Center, Maywood, Illinois; ⁴St Luke's Hospital, Duluth, Minnesota; ⁵Johns Hopkins University School of Medicine, Baltimore, Maryland; ⁶Children's Hospital of Philadelphia, Pennsylvania; ⁷Washington University School of Medicine, St Louis, Missouri; ⁸University of Houston College of Pharmacy, Texas; ⁹Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; ¹⁰McGill University Health Centre, McGill University, Montréal, Québec, Canada; ¹¹Boston Children's Hospital, Massachusetts; and ¹²Leeds Teaching Hospitals NHS Trust, United Kingdom

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 $\leq 15\,000$ cells/mL and a serum creati- nine level < 1.5 mg/dL	<ul style="list-style-type: none">VAN 125 mg given 4 times daily for 10 days, ORFDX 200 mg given twice daily for 10 daysAlternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Strong/High Strong/High Weak/High
Initial episode, severe ^b	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">VAN, 125 mg 4 times per day by mouth for 10 days, ORFDX 200 mg given twice daily for 10 days	Strong/High Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	<ul style="list-style-type: none">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 (intrave- nous metronidazole)
First recurrence	...	<ul style="list-style-type: none">VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, ORUse 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), ORFDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Low Weak/Low Weak/Moderate
Second or subsequent recurrence	...	<ul style="list-style-type: none">VAN in a tapered and pulsed regimen, ORVAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, ORFDX 200 mg given twice daily for 10 days, ORFecal microbiota transplantation^c	Weak/Low Weak/Low Weak/Low Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

Commercial FMT: Phase 2/3 Trials

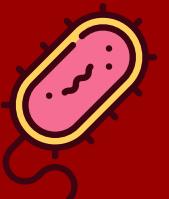
- Multiple companies with "ecobiotic" FMT alternatives in phase 2/3 trials:
 - Finch, Rebiotix, Seres, Vedanta
 - FDA update planned after meeting November 4, 2019: concern that waiver of IND requirement limits RCTs
- May 6, 2020: "Rebiotix and Ferring are the first to announce positive preliminary results on primary efficacy endpoint from ongoing pivotal Phase 3 clinical trial for RBX2660"

Backlash Against FMT

- Limited access and adverse events:
 - March 19, 2019: OpenBiome nearly doubles prices
 - June 13, 2019: FDA safety alert regarding FMT-related sepsis and death
- Can same efficacy be achieved with antibiotics?
 - "Fecal microbiota transplantation (FMT) for C. difficile infection, just say 'No'" - Xing Tang & Stuart Johnson

Tan X & Johnson S *Anaerobe* 2019; Defilipp Z et al *NEJM* 2019; Blaser M *NEJM* 2019

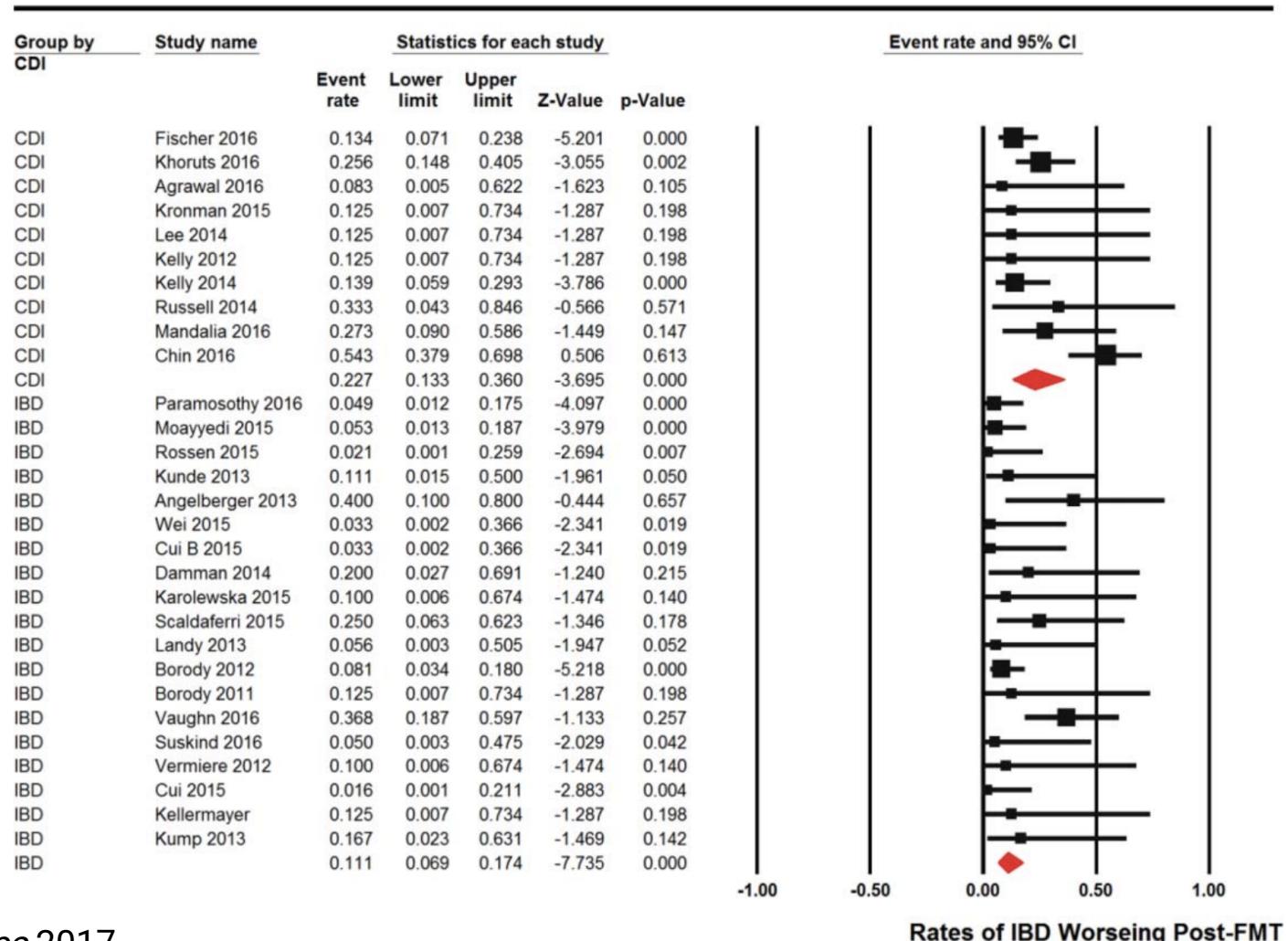
FMT → IBD



	Faecal microbiota transplantation (n=41)	Placebo (n=40)	Risk ratio (95% CI)	p value
Primary outcome				
Steroid-free clinical remission and endoscopic remission or response*	11 (27%)	3 (8%)	3·6 (1·1–11·9)	0·021
Secondary outcomes				
Steroid-free clinical remission†	18 (44%)	8 (20%)	2·2 (1·1–4·5)	0·021
Steroid-free clinical response‡	22 (54%)	9 (23%)	2·4 (1·3–4·5)	0·004
Steroid-free endoscopic remission§	5 (12%)	3 (8%)	1·6 (0·4–6·4)	0·48
Steroid-free endoscopic response¶	13 (32%)	4 (10%)	3·2 (1·1–8·9)	0·016

*Total Mayo score ≤2, with all subscores ≤1, and ≥1 point reduction from baseline in endoscopy subscore.
 †Combined Mayo subscores of ≤1 for rectal bleeding plus stool frequency. ‡Decrease of ≥3 points or ≥50% reduction from baseline (or both) in combined Mayo subscores for rectal bleeding plus stool frequency. §Mayo endoscopy subscore 0. ¶Mayo endoscopy subscore ≤1, with ≥1 point reduction from baseline.

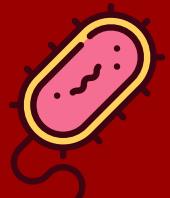
Table 2: Primary and secondary outcomes at week 8



Misclassification Matters

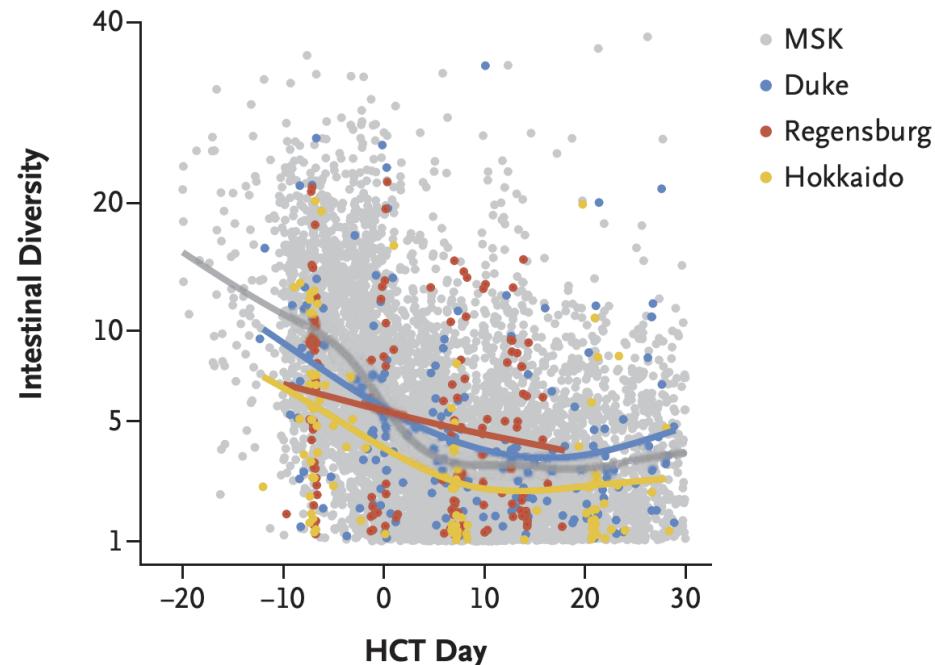
- Lesson from FMT for CDI trials (e.g., Seres):
 - misclassification of NAAT+ disease → bias
- Discordant results from IBD trials:
 - sub-phenotypes of IBD?
 - differential effects of microbial ecology?
- Active FMT trials on clinicaltrials.gov: 23 for UC & 11 for Crohn's

FMT → post-allo-SCT

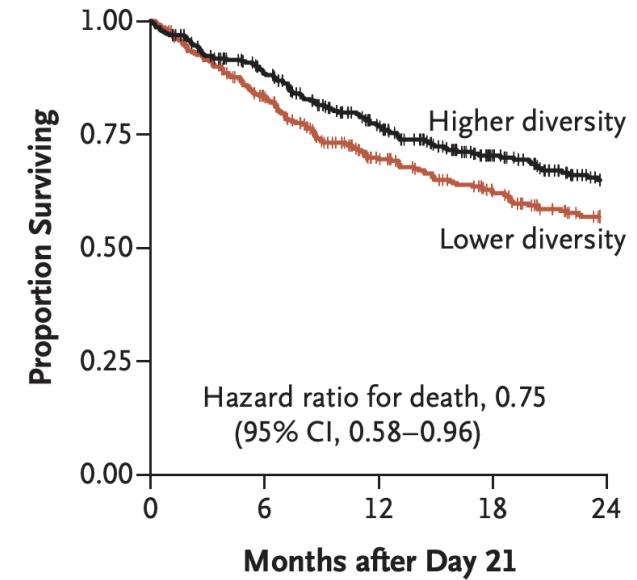


Dysbiosis & Death

A Change in Diversity of Intestinal Microbiota during HCT Period

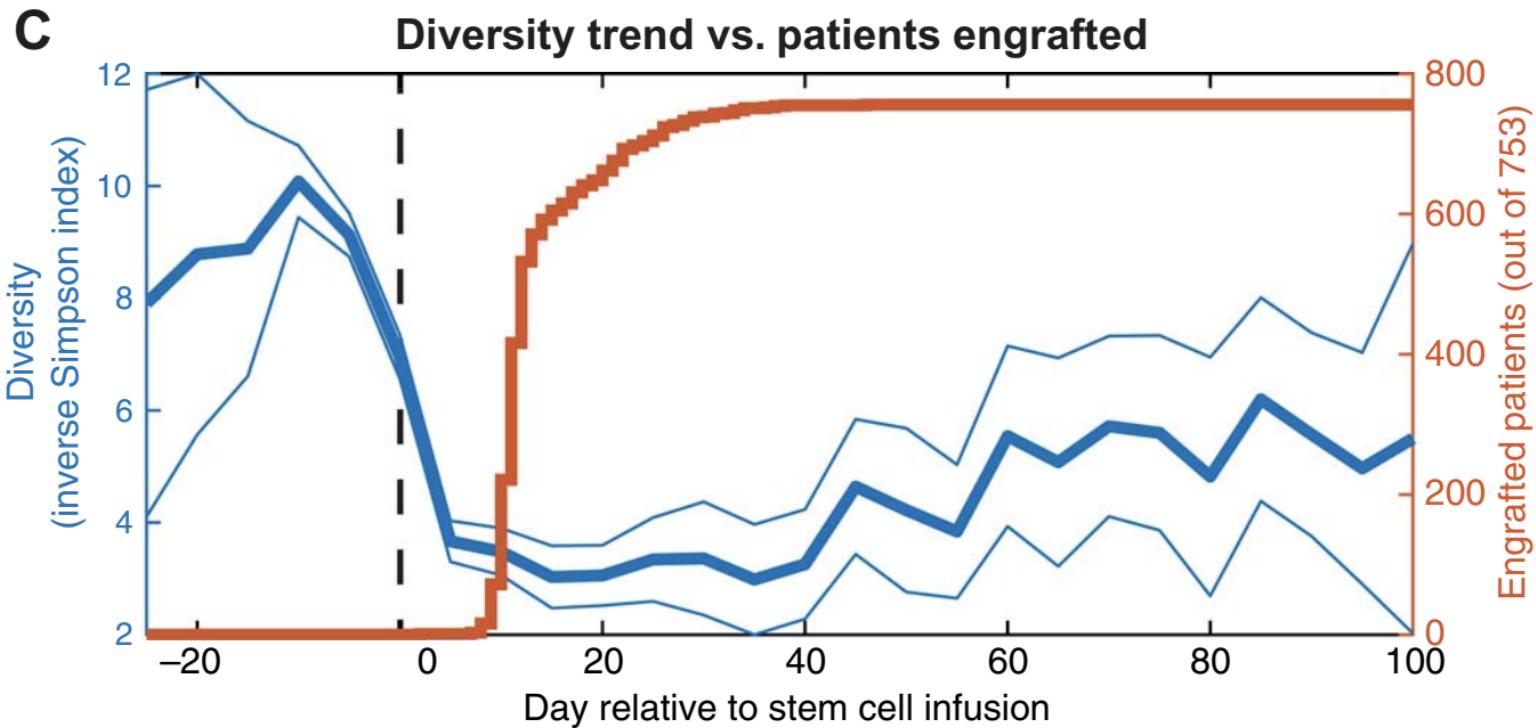


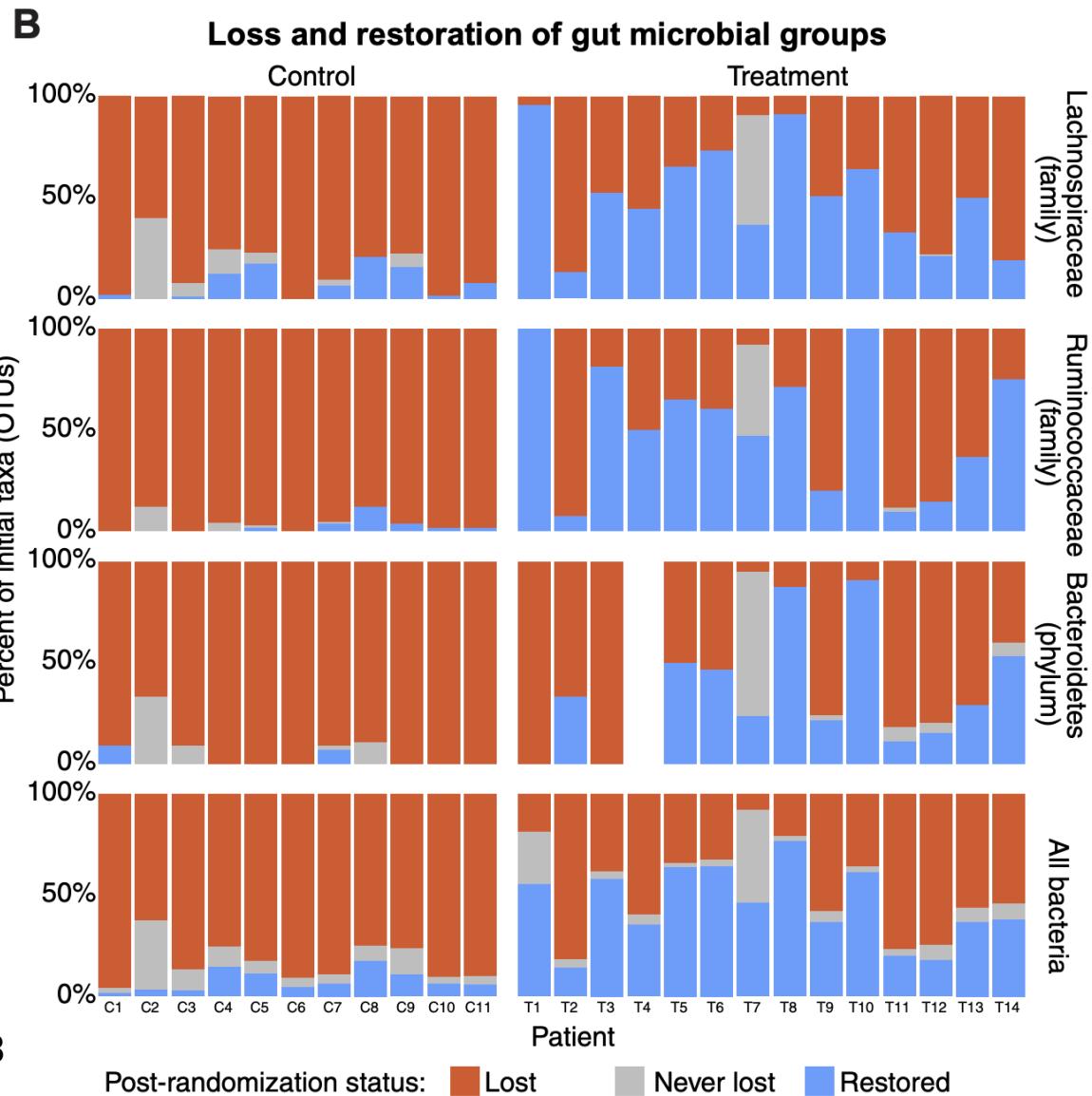
B Overall Survival — Cohort 1



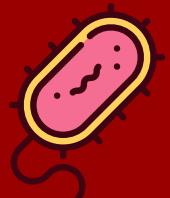
No. at Risk

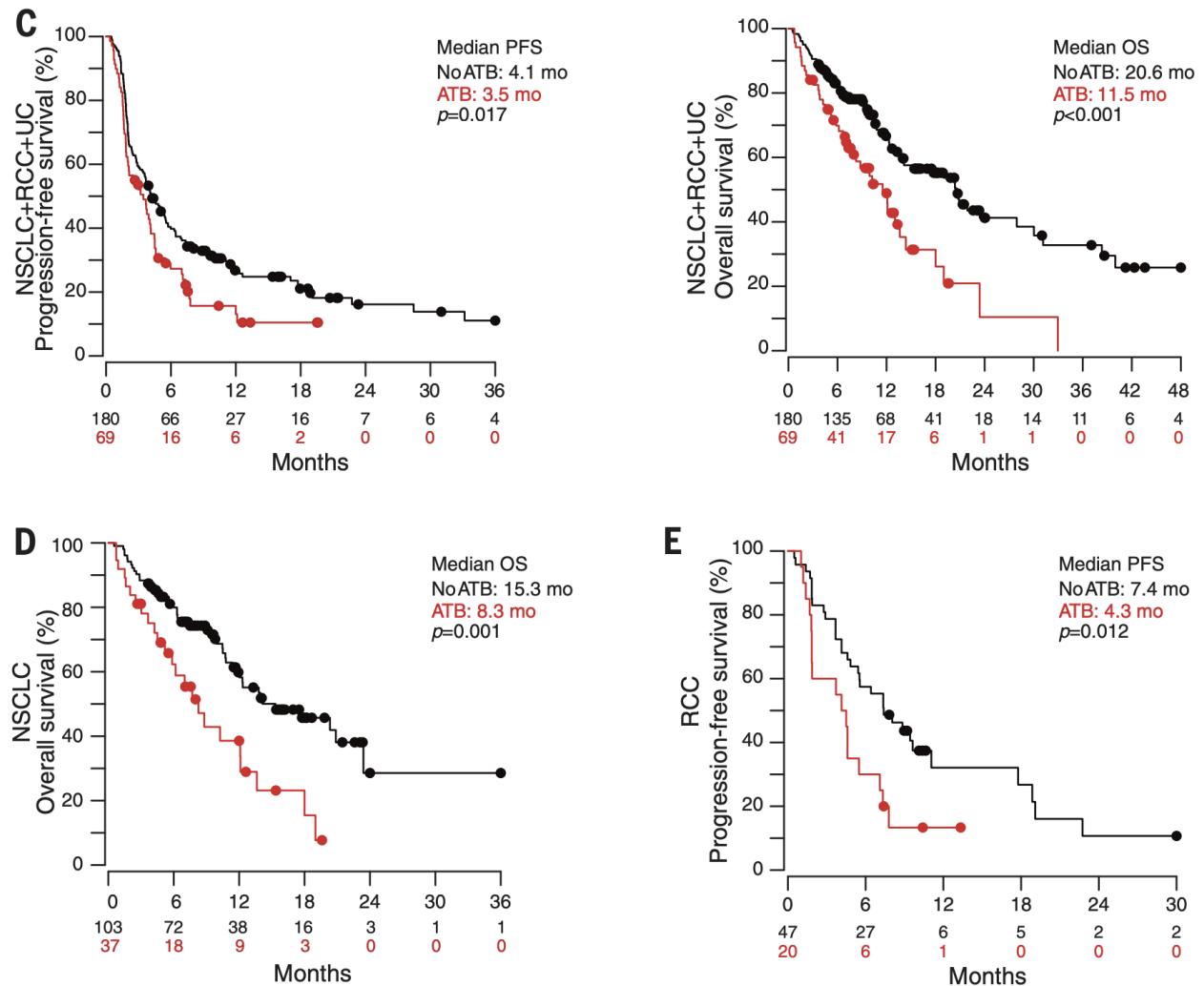
Higher	354	289	220	159	116
Lower	350	281	204	164	129





FMT → immune checkpoint inhibitors



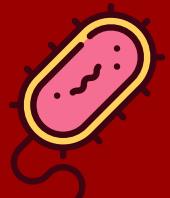


Routy et al *Science* 2018; Gopalakrishnan et al *Science* 2018; Matson et al *Science* 2018

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

FMT regulation



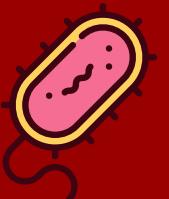
FMT Regulation (pre-COVID-19)

- Guideline-recommended for CDI but no FDA-approved product
- IND required for non-CDI indications
- For CDI, FDA exercises "enforcement discretion"
- Concern that OpenBiome availability limiting RCT enrollment

Impact of COVID-19 on FMT

- 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

Does it work? why?



What's in an FMT?

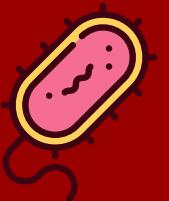
- FMT contains multitudes:
 - bacteria, fungi, archaea...
 - ... bacteriophage, eukaryotic viruses (e.g., TTVs) ...
 - ... human colonocytes, metabolites
- Transfer of sterile filtrates from donor stool also cures CDI?

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

Causal Models

- Direct bacterial interaction?
- Bile acid metabolism-mediated interaction?
- Bile acid metabolism & Th17 regulatory cells?

Questions?



Thank you!

Slides available: github.com/bjklab

brendank@pennmedicine.upenn.edu

