

Fecal Microbiota Transplantation

2020(is the worst) Update

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Disclosures

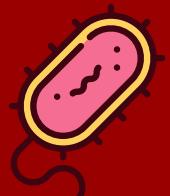
- No conflicts of interest.
- Opinions my own.

Fecal microbiota transplantation (FMT):

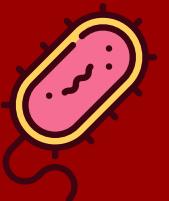
- *Clostridioides difficile* infection
- inflammatory bowel disease (IBD)
- oncology: auto-FMT post allo-SCT; immune checkpoint inhibitors

FMT regulatory oversight (& COVID-19)

Does it work? why?

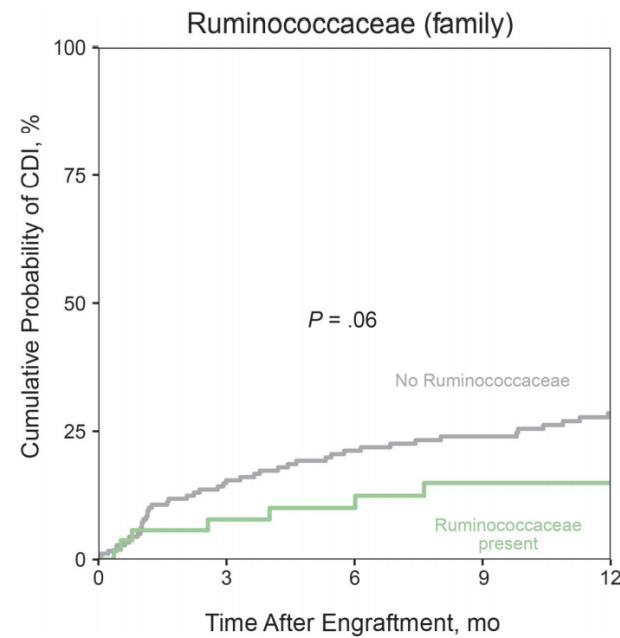
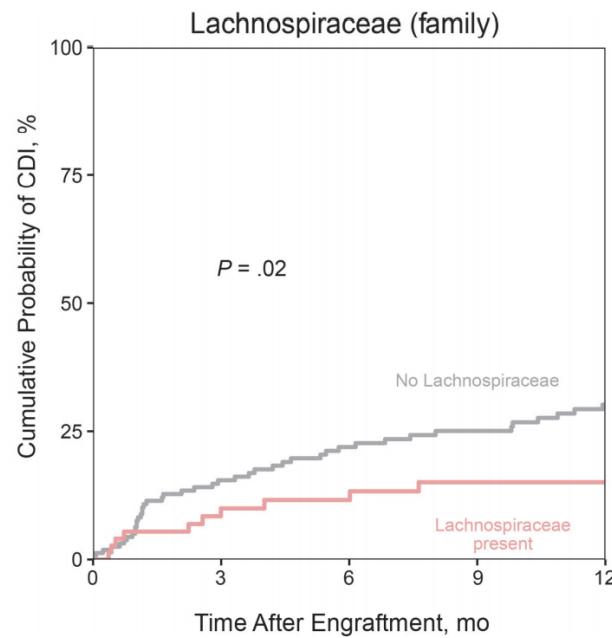
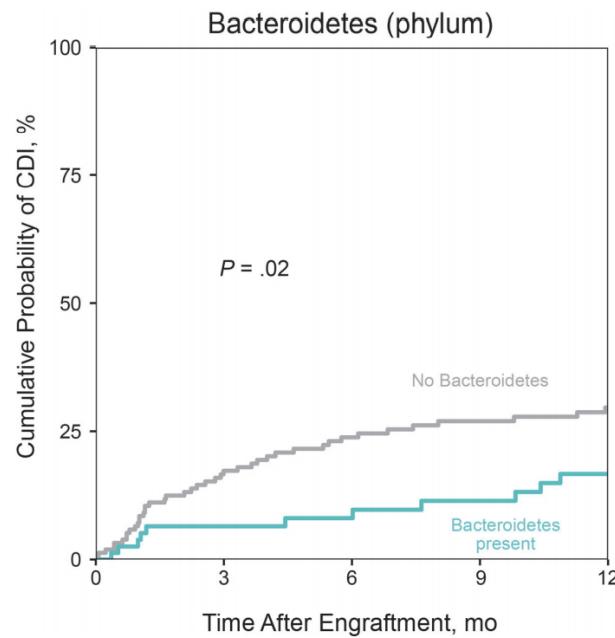


FMT → CDI



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 |
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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

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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

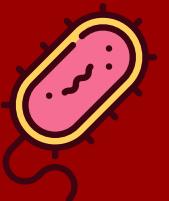
- Multiple companies with "ecobiotic" FMT alternatives in phase 2/3 trials:
 - Finch, Rebiotix, Seres, Vedanta
 - FDA update planned after meeting November 4, 2019: concern that waiver of IND requirement limits RCTs
- May 6, 2020: "Rebiotix and Ferring are the first to announce positive preliminary results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

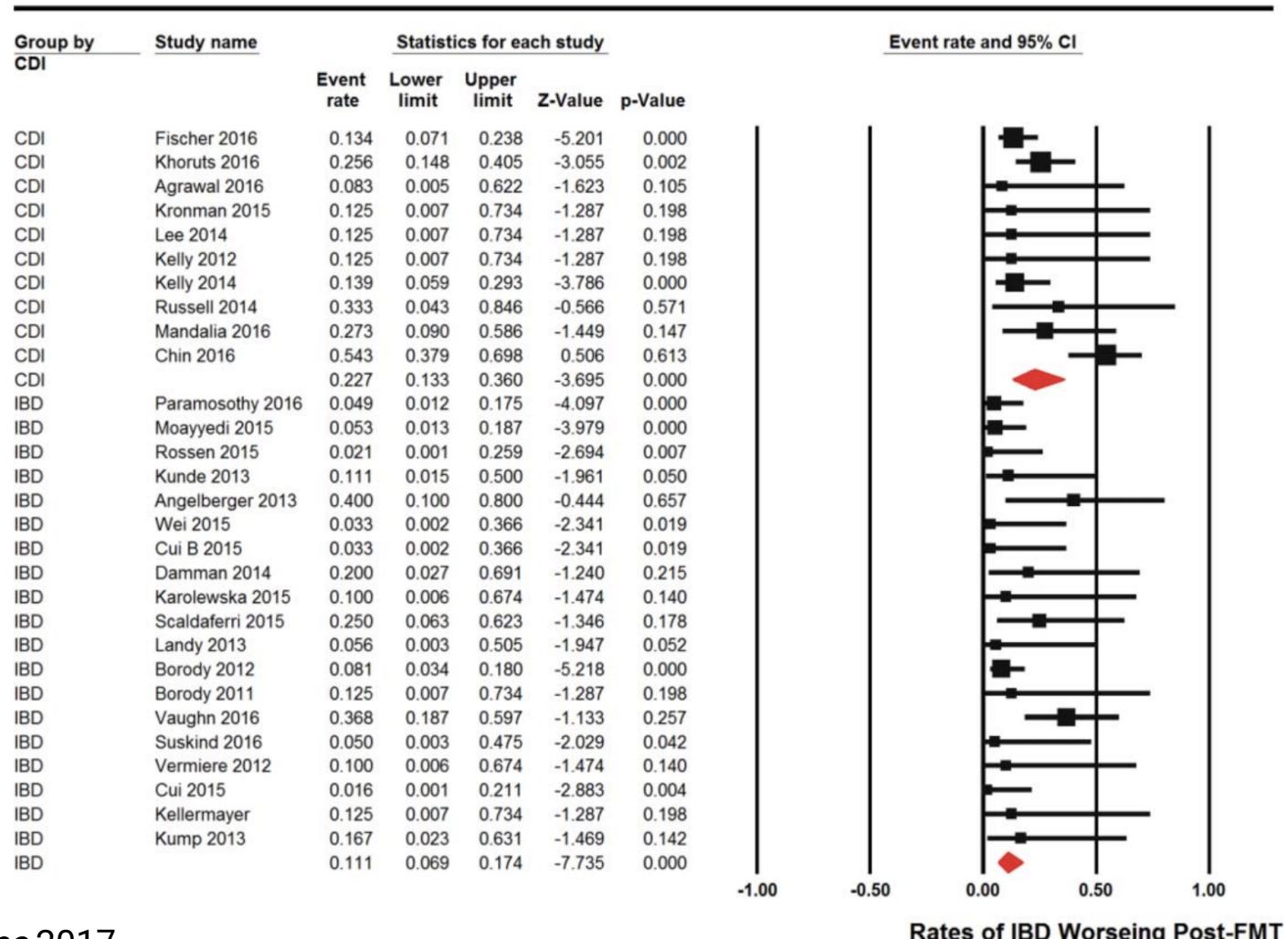
FMT → IBD



| | 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.

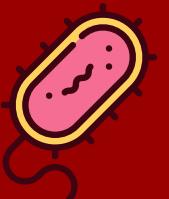
Table 2: Primary and secondary outcomes at week 8



Misclassification Matters

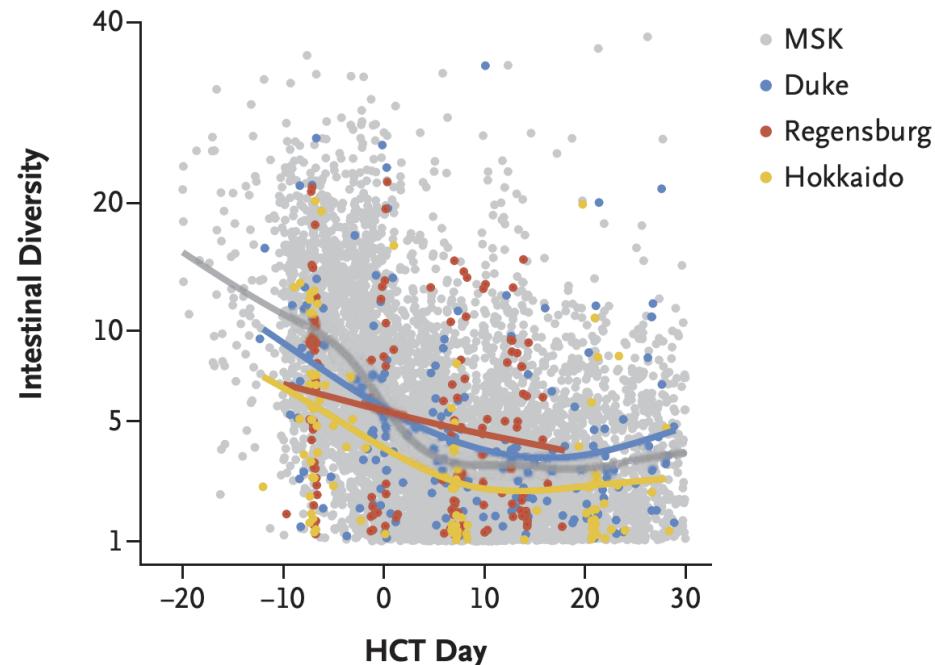
- Lesson from FMT for CDI trials (e.g., Seres):
 - misclassification of NAAT+ disease → bias
- Discordant results from IBD trials:
 - sub-phenotypes of IBD?
 - differential effects of microbial ecology?
- Active FMT trials on clinicaltrials.gov: 23 for UC & 11 for Crohn's

FMT → post-allo-SCT

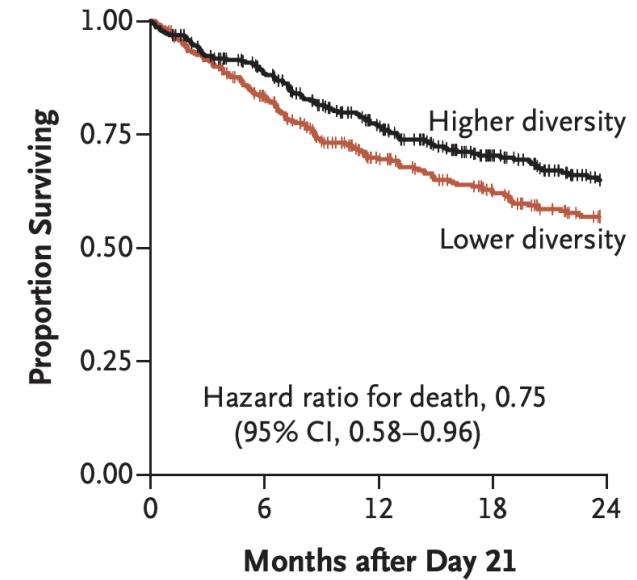


Dysbiosis & Death

A Change in Diversity of Intestinal Microbiota during HCT Period

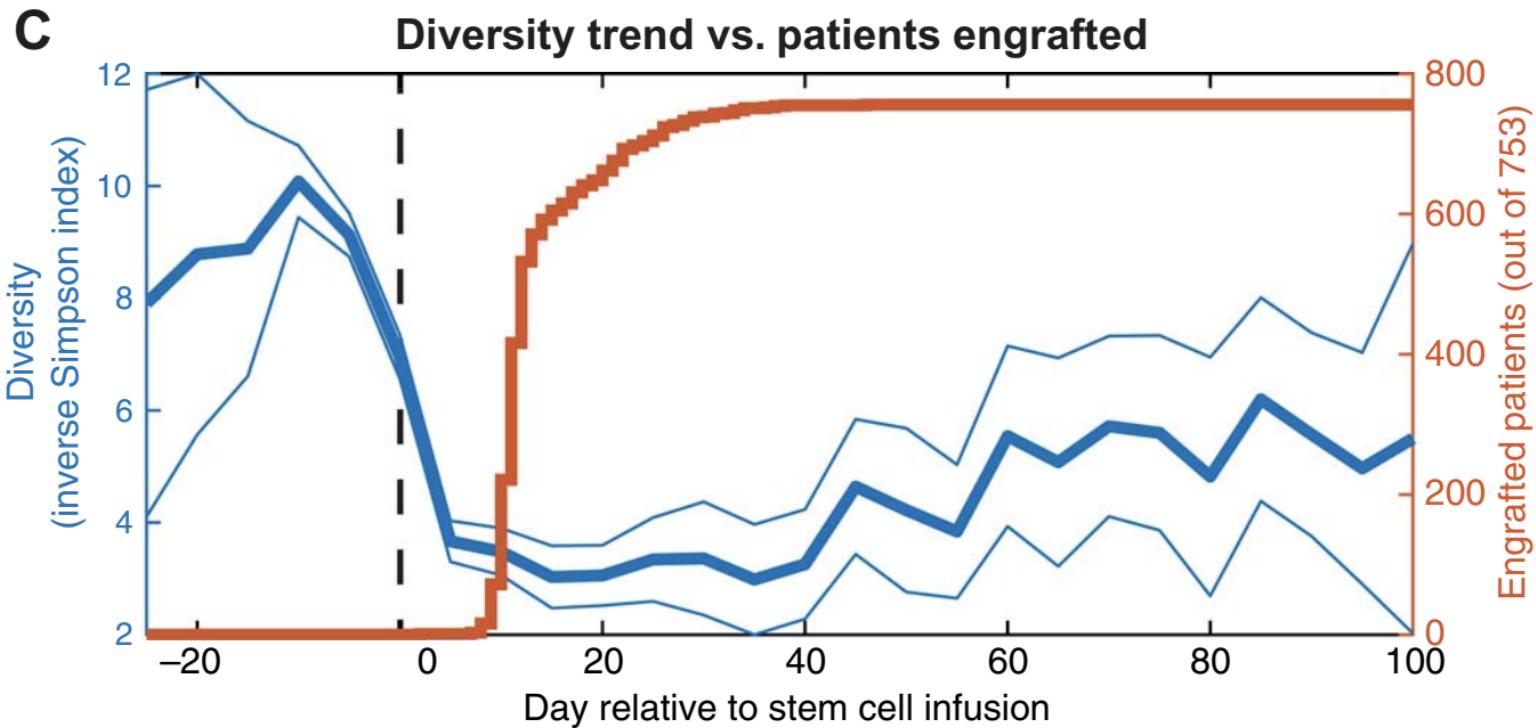


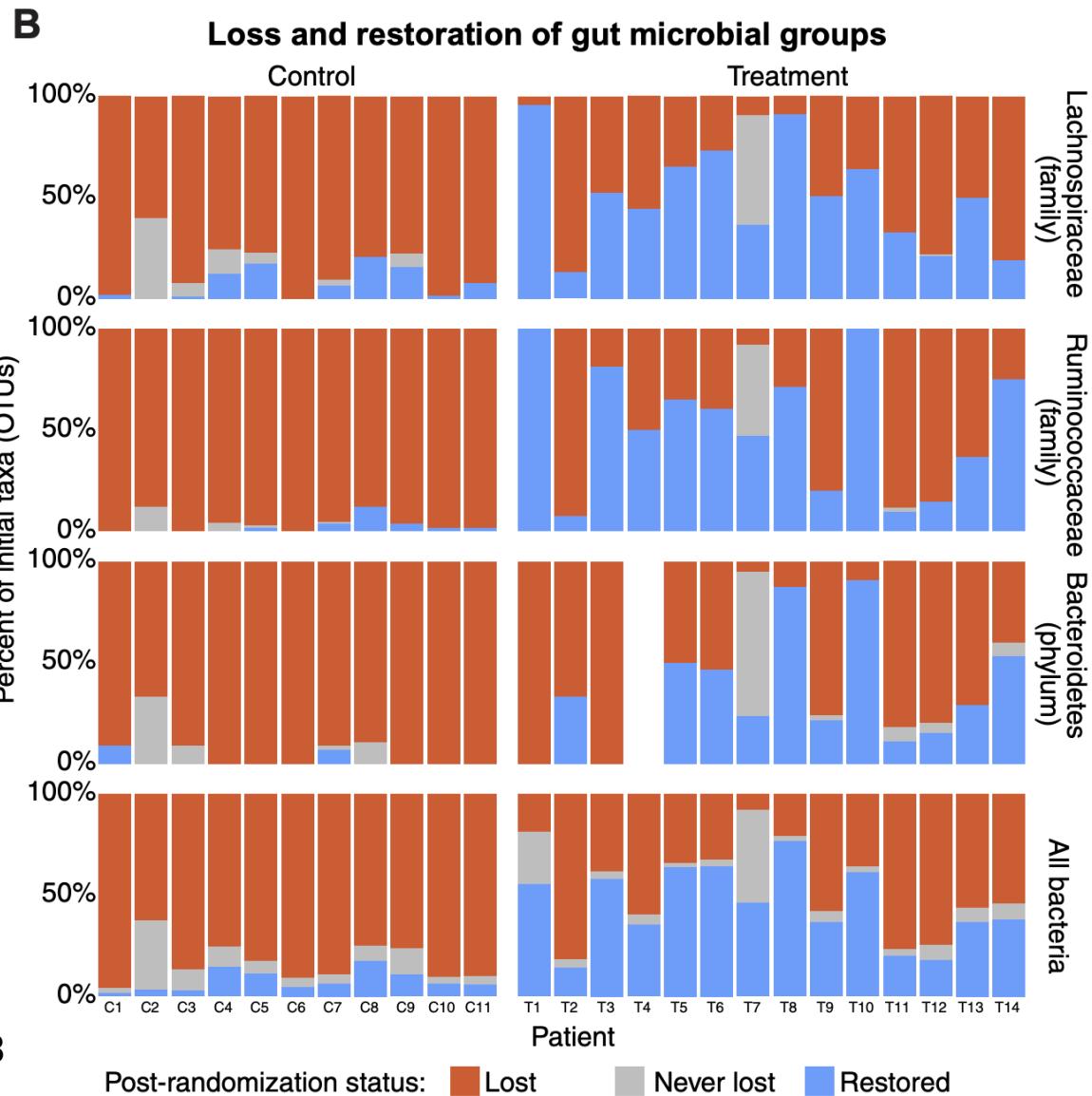
B Overall Survival — Cohort 1



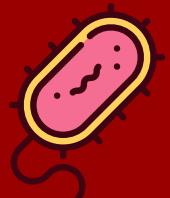
No. at Risk

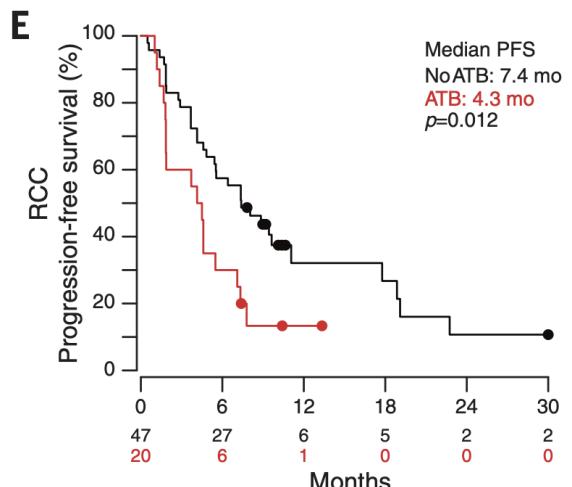
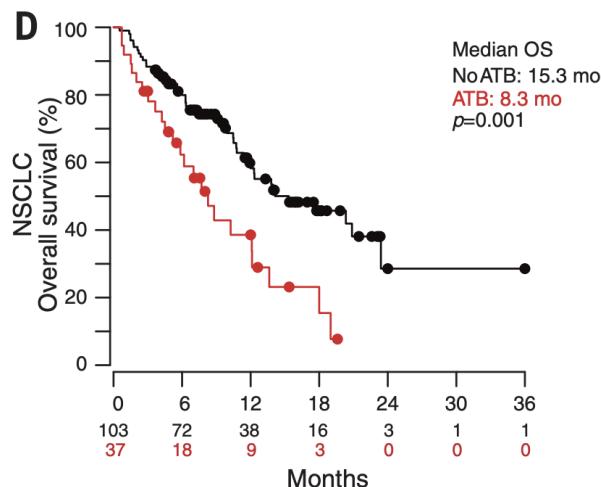
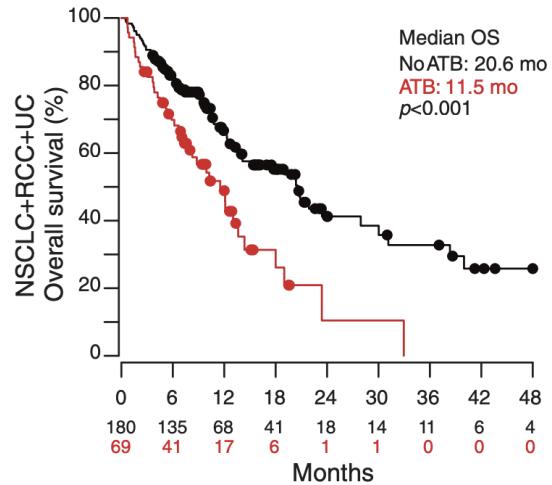
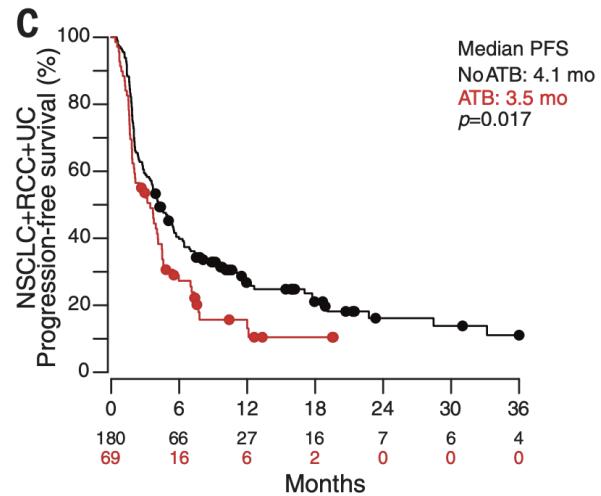
| | | | | | |
|--------|-----|-----|-----|-----|-----|
| Higher | 354 | 289 | 220 | 159 | 116 |
| Lower | 350 | 281 | 204 | 164 | 129 |





FMT → immune checkpoint inhibitors



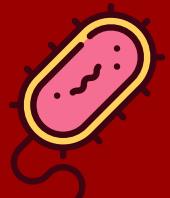


Routy et al *Science* 2018; Gopalakrishnan et al *Science* 2018; Matson et al *Science* 2018

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



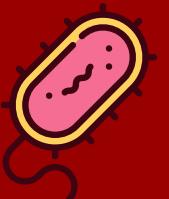
FMT Regulation (pre-COVID-19)

- 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?

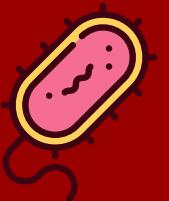
- FMT contains multitudes:
 - bacteria, fungi, archaea...
 - ... bacteriophage, eukaryotic viruses (e.g., TTVs) ...
 - ... human colonocytes, metabolites
- Transfer of sterile filtrates from donor stool also cures CDI?

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

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