The taxonomic composition of the donor intestinal microbiota is a major factor influencing the efficacy of faecal microbiota transplantation in therapy refractory ulcerative colitis

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Background: Faecal microbiota transplantation is an experimental approach for the treatment of patients with ulcerative colitis. Although there is growing evidence that faecal microbiota transplantation is effective in this disease, factors affecting its response are unknown.
Aims: To establish a faecal microbiota transplantation treatment protocol in ulcerative colitis patients, and to investigate which patient or donor factors are responsible for the treatment success.
Methods: This is an open controlled trial of repeated faecal microbiota transplantation after antibiotic pre-treatment (FMT-group, n = 17) vs antibiotic pre-treatment only (AB-group, n = 10) in 27 therapy refractory ulcerative colitis patients over 90 days. Faecal samples of donors and patients were analysed by 16S rRNAgene-based microbiota analysis.
Results: In the FMT-group, 10/17 (59%) of patients showed a response and 4/17 (24%) a remission to faecal microbiota transplantation. Response to faecal microbiota transplantation was mainly influenced by the taxonomic composition of the donor's microbiota. Stool of donors with a high bacterial richness (observed species remission 946 ± 93 vs no response 797 ± 181 at 15367 rps) and a high relative abundance of Akkermansia muciniphila (3.3 ± 3.1% vs 0.1 ± 0.2%), unclassified Ruminococcaceae (13.8 ± 5.0% vs 7.5 ± 3.7%), and Ruminococcus spp. (4.9 ± 3.5% vs 1.0 ± 0.7%) were more likely to induce remission. In contrast antibiotic treatment alone (AB-group) was poorly tolerated, probably because of a sustained decrease of intestinal microbial richness.
Conclusions: The taxonomic composition of the donor's intestinal microbiota is a major factor influencing the efficacy of faecal microbiota transplantation in ulcerative colitis patients. The design of specific microbial preparation might lead to new treatments for ulcerative colitis.

Trial setup: all patients get abx. 27 patients recruited and 17 given FMT, then researchers noticed that the abx pre-treatment reduced the Mayo score, so they recruited 10 patients for abx-only treatment (no FMT). These 10 didn't do well, so they didn't keep recruiting more patients for the abx-only arm.

Inclusion criteria: all patients had treatment failures for at least one immunosuppressive agent and/or anti-TNF-antibody.

Patients were given 5 FMTs (endoscopy), 14 days apart

Donor selection: each patient got the same donor for all 5 FMTs (fresh samples each time, I think). 14 donors total. 2 donors were used for multiple patients. Most donors were unrelated to the patients (except for 3 relatives and 2 partners).

Trial outcomes, at day 90:

59% (10/17) in FMT-group had clinical response
4 (24%) patients achieved clinical remission

10% (1/10) in abx-only group had partial response

(trial failed primary endpoint, but ~25% remission rate is in line with previous FMT in UC studies)

Long term follow up for some patients:

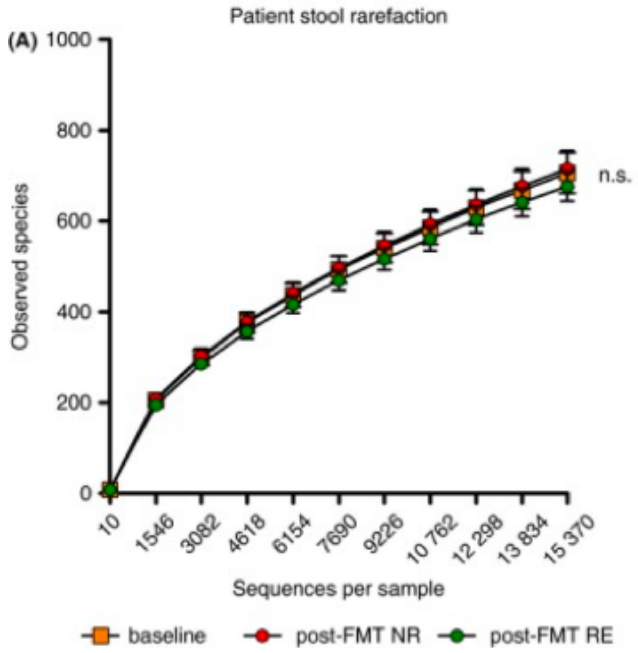
All 4 of the FMT group who achieved remission are still in remission or mild disease, without more drugs. All the others needed more therapies. One of the partial responders and one non-responder had a colectomy.

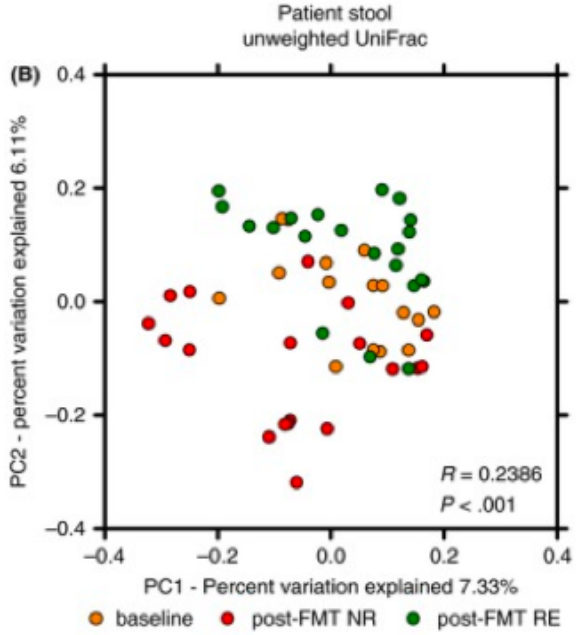
Donor heterogeneity:

Donor #1 served 3 patients: all non-responders
Donor #3 served 2 patients: one remission, one partial responder (who achieved remission 4 weeks later, day 120)

NR = no response
RE = remission

A. Recipients: No difference in diversity between pre-FMT and post-FMT responders and non-responders





B. Recipients: Weak stratification between pre-FMT, post-FMT responder, and post-FMT nonresponder

NR = no response
RE = remission

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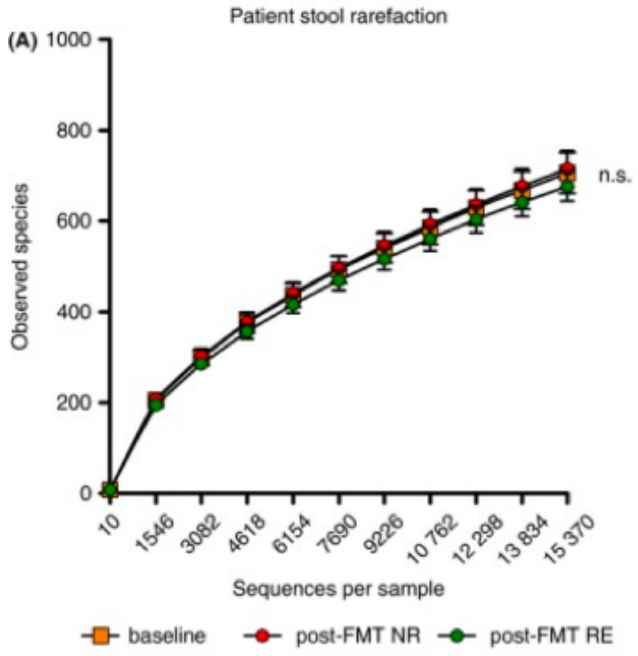
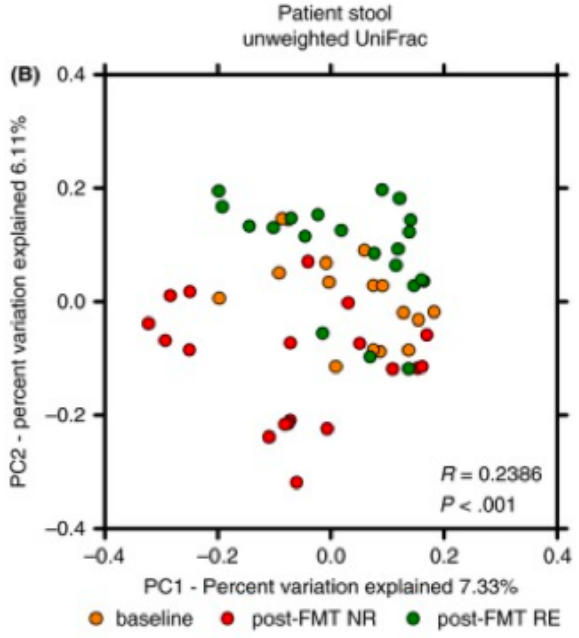
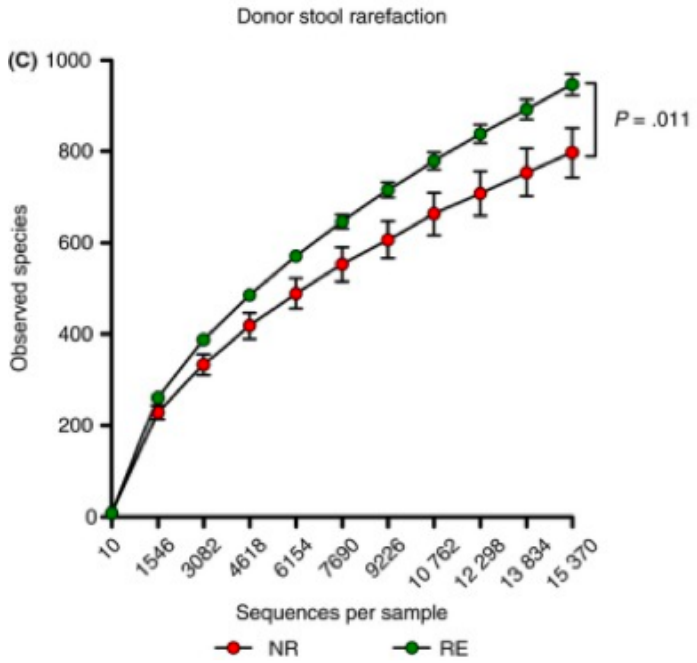
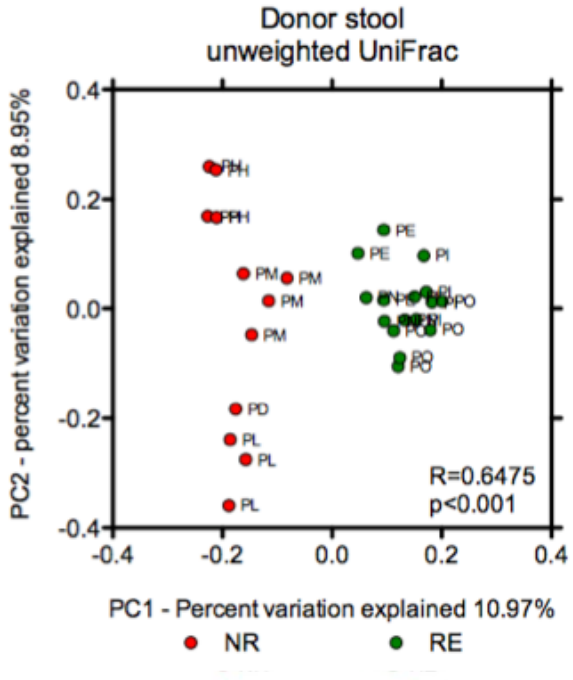




B. Recipients: Weak stratification between pre-FMT, post-FMT responder, and post-FMT nonresponder

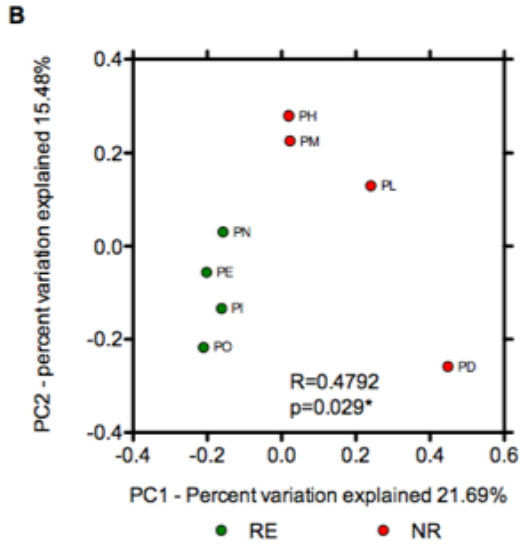
C. Donors: samples which led to *remission* have higher diversity than samples with no response. (No difference in diversity btw response vs. no response, in supplement)





D. Donors: Strong strafication between *remission* vs. no response (weak strafication between response vs. no response, in supplement). Letters are from Fig S7, and indicate individual donors

More figures about the donors bc it's super cool!



Same as Fig 1D, but only including each donor's first sample.

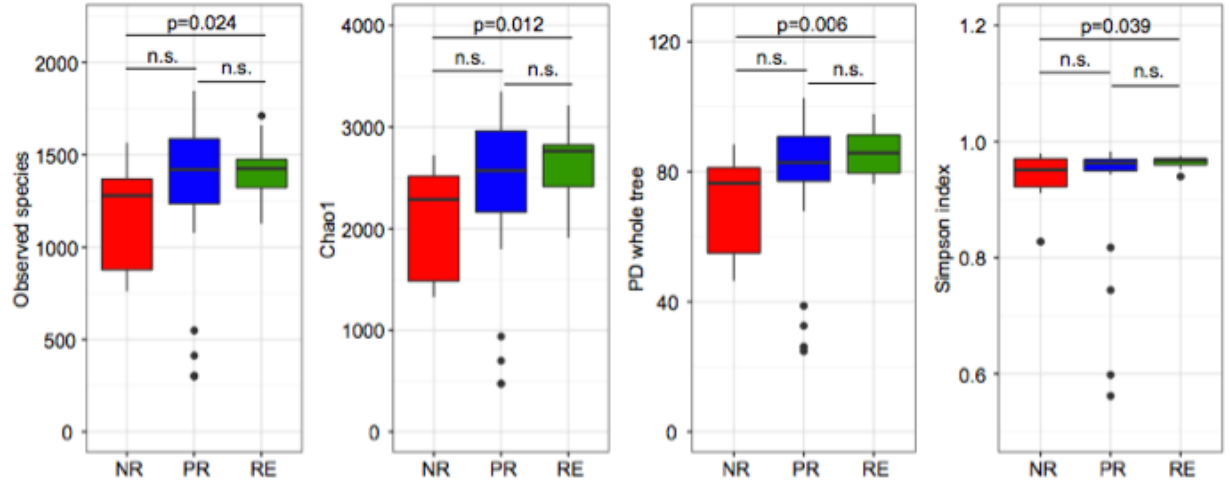
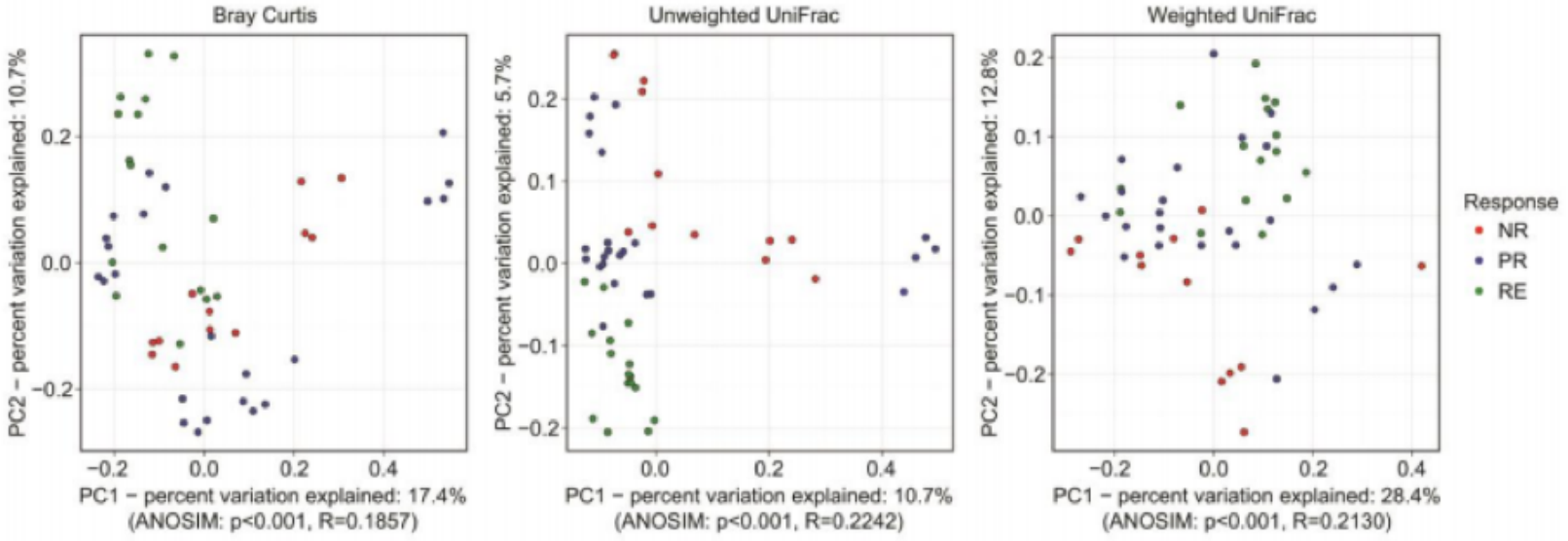


Figure S5. Microbial diversity of donor stools stratified according to patient's FMT response. A statistically significant difference was observed between donors inducing remission (RE) compared to donors inducing partial response (PR) or no response (NR). The observed species, Chao1, PD whole tree and Simpson indices are shown (red: NR; blue: PR; green: RE; n=12-23; 32672 reads/sample; nonparametric t-test, 999 Monte Carlo permutations, Bonferroni post-test).



Donor microbiomes, including partial responders (PR). Difference btw groups is still significant but less strong than remission (RE) vs. no response (NR).

Figure 3: abundances in *recipient* stools associated with remissions or no response.

A. Akkermansia is basically absent in baseline patients and donors which did not induce response.

B. Note: this is patient longitudinal data (x-axis is time) Akkermansia was increased by FMT in patients who achieved remission, but not in patients with partial or no response. But **regardless of response, doesn't seem to be long-term colonization.**

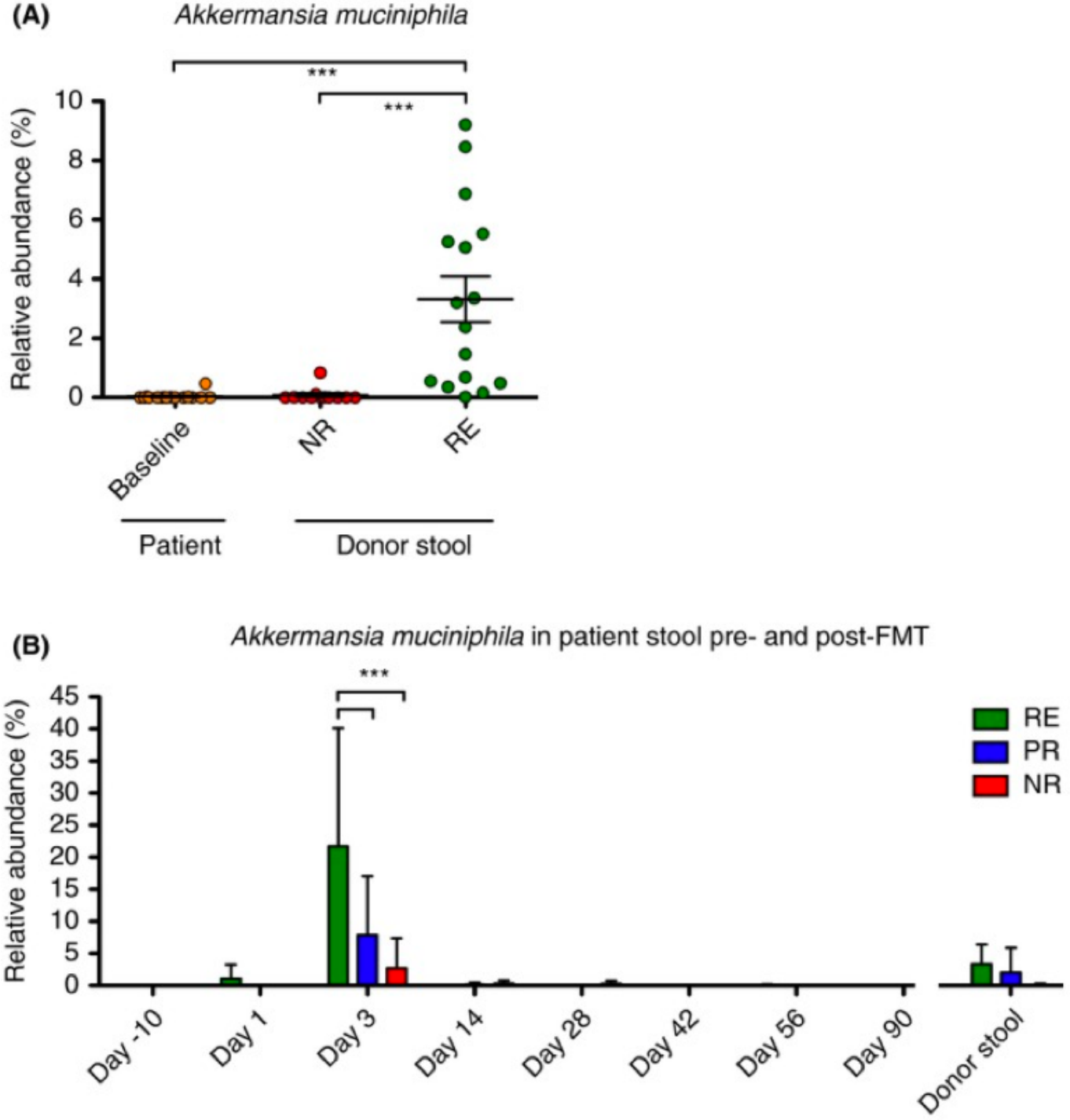


Figure 4: engraftment of total community doesn't seem to matter for remission.

Unifrac distance between recipient and donor, over course of trial. All patients got more similar to their donor, regardless of response.