Autologous fecal microbiota transplantation combined with healthy diets induces strain-level microbial shifts and attenuates body weight regain

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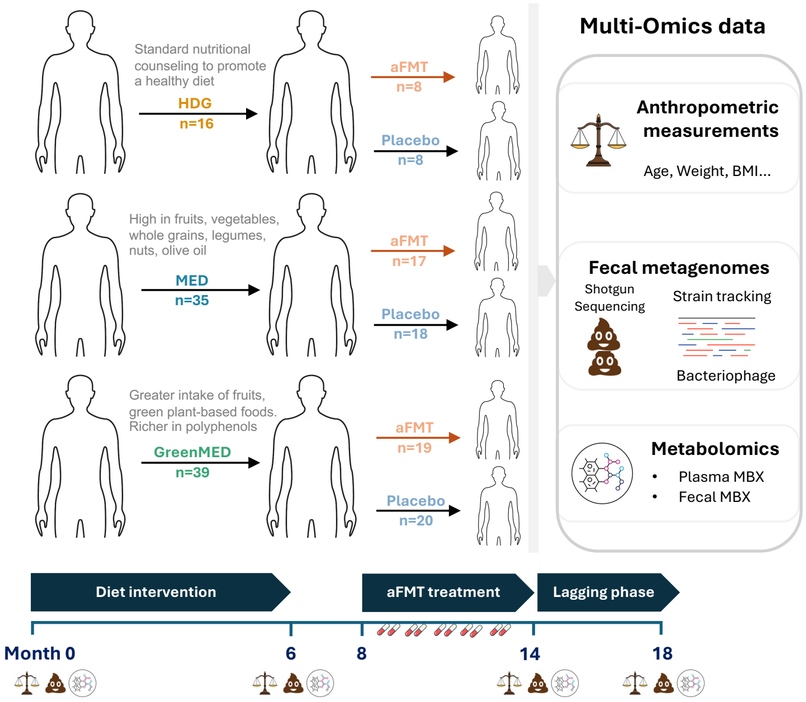
DIRECT-PLUS aFMT Trial

The gut microbiome plays a key role in regulating metabolic health, and dietary interventions can beneficially reshape its composition and function, contributing to weight loss and improved metabolic outcomes. However, weight regain—often observed after 6 months of active intervention—may be partly driven by a reversion of the microbiome toward its baseline state. Autologous fecal microbiota transplantation (aFMT), which uses an individual's own stool collected during a metabolically healthier state, offers a minimal-risk strategy that may preserve diet-induced microbial shifts and reduce weight regain.

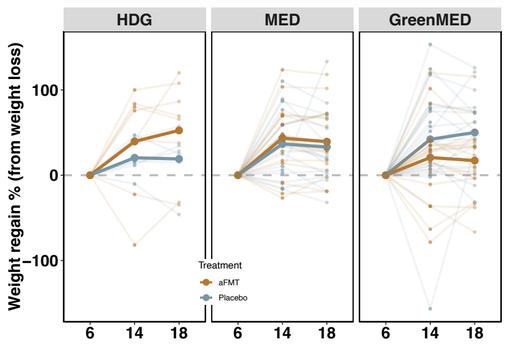
Study Design



HDG: Healthy dietary guidance, MED: Mediterranean diet , GreenMED: Green Mediterranean diet

In this trial, we examined the effects of randomized aFMT vs. Placebo on gut microbiome—particularly strain-level changes—and their role in mitigating weight regain in 90 adults. Participants who **lost ≥3.5%** of body weight during a 6-month dietary intervention provided fecal samples that were processed into oral capsules.

Synergistic Effects of aFMT + GreenMED on Weight Regain



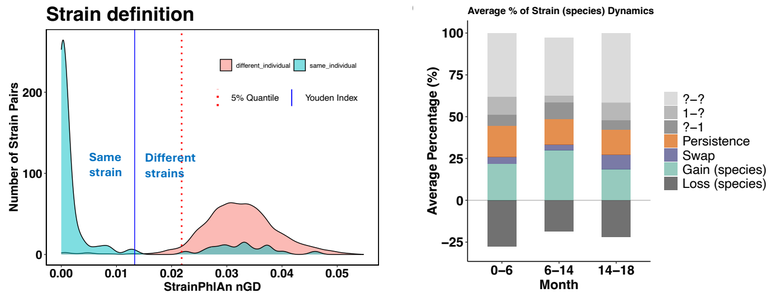
During the 6-month follow-up, aFMT recipients experienced **significantly less** weight regain compared to placebo, especially when combined with GreenMED.

Individual responses are shown as light lines; bold lines indicate group averages (aFMT vs. Placebo)

Boundaries of Diversity: Quantifying Strain-Level Differences

Precision Strain Delineation with StrainPhlAn

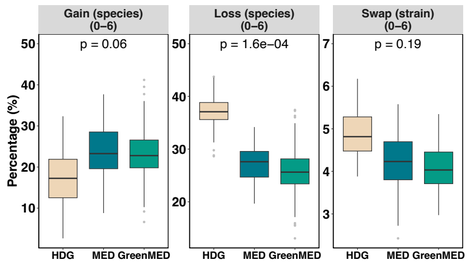
Before tracking strain dynamics, we first had to define what constitutes a unique strain—the foundational pillar of microbial dynamics research. For this purpose, we utilized species-specific phylogenetic genetic distance (nGD) cutoffs using StrainPhlAn v4.1, a validated bioinformatics tool for strain profiling from metagenomic data which leverages single-nucleotide polymorphisms (SNPs) in species-specific marker genes to differentiate bacterial strains.



- **Strain cutoff** = minimum of the Youden index (optimizing sensitivity/specificity) or the 5th quantile of distances.
- **Strain-level dynamic metrics**: Loss, Gain, Persistence, and Swap.
- **Limitation to ambiguous scenarios** (?-?, 1-?, ?-1): StrainPhlAn cannot detect very low abundant strains, while their species are detectable.

aFMT + GreenMED Preserves Diet-induced Strain Changes

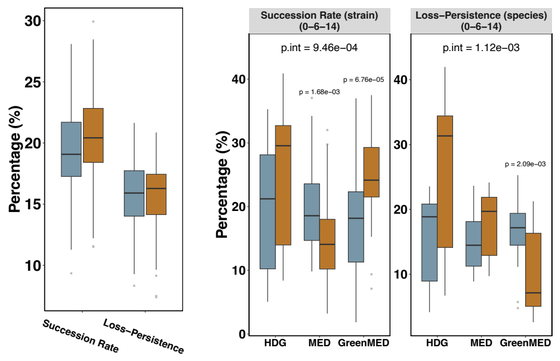
Diets Induce Distinct Strain Change Patterns



- Significantly reduced species loss with near-significant gain, but unaffected strain swaps.
- MED/GreenMED enhanced species acquisition while reducing depletion and strain type exchanges.
- *p-values derived from linear regression

aFMT+GreenMED Synergistically Preserves Strain-Level Changes

- **Overall aFMT population**: aFMT did not differ from placebo in preserving prior diet-induced microbial strain-level changes.
- **When combined with GreenMED**: aFMT effectively preserved these strain-level changes for both succession rate and loss-persistence during the follow-up period (Month 6-14).



Succession rate: % of strains that were either gained or swapped during month 0-6 and remained detectable during 6-14.

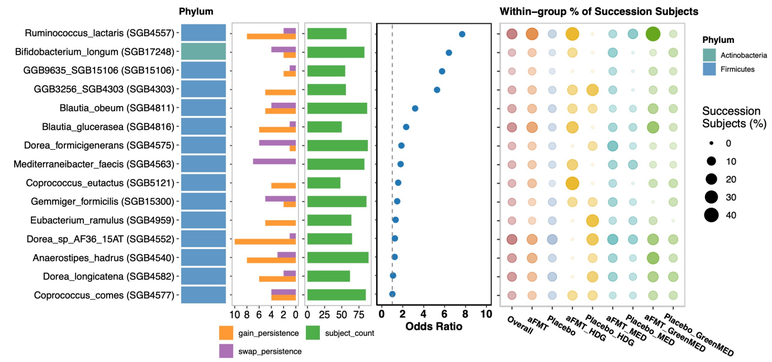
Loss-Persistence: % of species lost during month 0-6 that persisted between month 6-14.

Left: the overall level
Right: stratified by diets
p.int: interaction effect of aFMT and Diet with linear model

*p-values derived from linear regression models

aFMT + GreenMED Enhances Key Strain Persistence

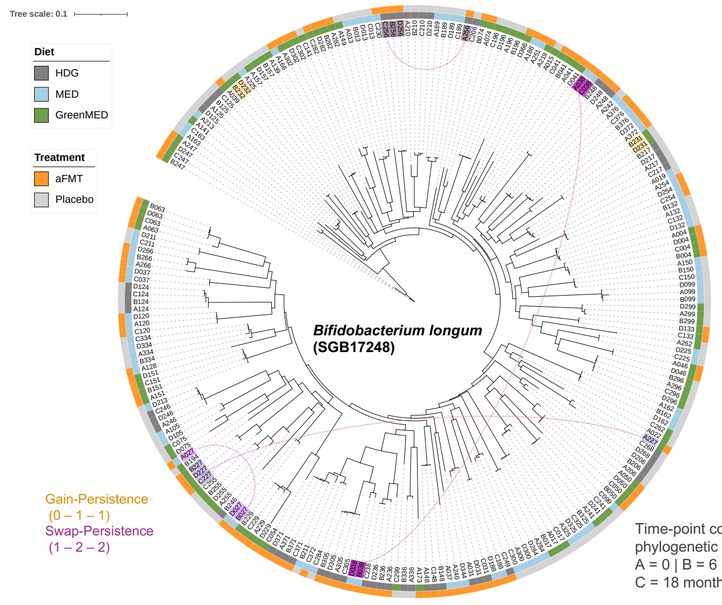
- Enhanced persistence of specific strains in aFMT, such as *R. lactaris*, *B. longum*, and *B. obeum*, particularly when combined with GreenMED.
- These strains degrade dietary polyphenols → bioactive metabolites (e.g., SCFAs), bridging diet-host health via microbial conversion.
- Highlighting aFMT's potential to sustain key microbial converters of complex dietary compounds.



Left panel: Bar plots display strain counts exhibiting gain-persistence or swap-persistence, and the number of subjects harboring the strains. **Middle panel**: Odds ratio for strain succession rate shows aFMT recipients were X-fold more likely to maintain gained/swapped strains compared to Placebo. **Right panel**: Bubble plot displays the prevalence (% of subjects) harboring persistent strains within overall, treatment, and each diet-treatment group.

Phylogenetic evidence of *B. longum* strain gain-/swap-persistence

Strain-specific intervention efficacy for aFMT and the clinical relevance of precision microbial therapy.



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