Dear Editor,

I am delighted to submit the manuscript, “Framework for rational donor selection in fecal microbiota transplant clinical trials,” for your consideration as a *PLOS Medicine* research article.

Fecal microbiota transplantation (FMT) has shown remarkable efficacy as a treatment for recurrent *Clostridium difficile* infection and is expanding to new indications, driven in part by emerging research linking the microbiome to an increasing number of diseases. However, researchers are recognizing that donor heterogeneity may play a role in patient response in at least some of these emerging indications, reducing the success of FMT in these cases. Thus, **clinical trials in diseases with donor-dependent FMT effects may fail not because the indication is not amenable to FMT but because sub-optimal donors were selected**. Despite this important factor in clinical trial success, there is almost no research addressing how to choose donors for FMT clinical trials in non-*C. diff* indications.

Here, we describe a novel systematic framework for performing rational donor selection in FMT trials. Through this framework, clinicians apply their clinical experience and insights from previously published work to select donors rationally during clinical trial design, **optimizing for FMT success and increasing the likelihood that their trials succeed**. In this manuscript, we:

* present four types of disease models that may underlie microbiome-mediated diseases;
* suggest associated donor selection strategies for each type of disease model; and
* discuss approaches to select donors in cases where the underlying disease model is unknown

We analyze published microbiome datasets to **demonstrate our framework** **and** **identify key considerations** for performing discovery-based analyses of FMT trials:

* We illustrate the process of performing rational donor selection for two case studies (IBD and liver cirrhosis), and show that taxa-based rational donor selection may be less effective than function-based approaches in diseases like IBD.
* Critically, we perform a simulation study which suggests that most FMT trials are not powered to make discoveries, and we suggest alternative clinical trial design approaches to maximize what can be learned from completed FMT trials.

Rational donor selection is of significant interest to clinician-researchers at the cutting-edge of FMT research, an area which is growing very fast. This is the first work to systematically address how rational donor selection can be applied in practice. More broadly, we expect that rational donor selection will be one of many novel clinical trial design approaches developed to increase the success of FMT trials and more rapidly advance translational microbiome research into clinical impact and patient benefit.

As such, our manuscript should appeal to the readership of *PLOS Medicine* and has clear implications for clinical research agendas, and we hope that you will consider it for publication.

Sincerely,



Eric Alm

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