Reply to HEP-17-1121

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To the Editor

The letter by Mullish et al sets out a few key points about our paper(1). Medical therapy for recurrent hepatic encephalopathy (HE) in the United States consists of first-line lactulose followed by rifaximin in lactulose failure/intolerance(2). Since our inclusion criteria required recurrent HE with the last episode being >1 month ago, patients were on the maximal therapy for at least one month. Rifaximin has been associated with changes in gut microbial functionality and not composition in cirrhosis(3). Our participants were already on rifaximin before being randomized. Therefore all changes that occurred after FMT were likely related to the intervention. We included this population since these patients do not place high on the liver transplant list, yet suffer multiple HE readmissions with significant healthcare burden.

The machine learning to define a rational donor was based on sequences derived from prior HE patients and healthy controls with the assumption that a higher relative abundance of *Lachnospiraceae* and *Ruminococcaceae* indicated a healthier microbiota, including their functionality. Current mechanistic understanding of the functional role played by the microbiota in HE is insufficient to select a donor based purely on their presumed functional phenotype, which is why this data-driven approach was adopted.

While the exact microbial structure may not have changed radically, we did find an increase in beneficial taxa such as *Lactobacillaceae* and *Bifidobacteriaceae* after FMT.

The improvement in HE events was over 150 days and not 15 days as suggested in the letter. However, the mechanism of PHES/EncephalApp-Stroop improvement remains under investigation since it may not be related entirely to microbiota dysbiosis. This follows other studies that report only partial change in microbiota after successful FMT(4, 5). We agree that utilizing microbial functionality, rather than composition, could be a better methodology to define future donors and look forward to a greater understanding of the relative importance of microbes and their metabolites in driving clinical outcomes.

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