Microbiome alterations in IBS

We commend the editors of *Gut* for publishing the article by Hugerth *et al*[1] given that negative results are conspicuously missing from the microbiome literature. The paper reports that in a randomly recruited Swedish cohort of individuals meeting Rome IV criteria for irritable bowel syndrome (IBS), there was marked heterogeneity of the gut microbiota, but no distinct 'signature' was evident. However, some qualifying caveats for future research are worth highlighting.

First, while the overall pool of study subjects was drawn from a large population of volunteers, the *actual* numbers studied by Hugerth *et al*[1] with respect to IBS were modest: 63 sigmoid biopsy samples from confirmed IBS cases, and 32 faecal samples, 29 of which were from subjects that also provided a biopsy. This casts doubt on the statistical power of the study if the original question related to the presence or absence of a difference in microbiota composition in IBS.

Second, in designing and powering a study of IBS microbiota, effect size is linked with the severity of the disorder. Previous reports have shown that the microbiota configuration changes with severity, where more severe IBS is associated with greater microbiota alterations, increased abundance of *Ruminococcus* spp and lower abundance of *Blautia* spp.[2] The individuals identified as having a lower IBS-associated morbidity were more frequently associated with fewer microbiota alterations.[2] This seems to have been corroborated by Hugerth *et al*[1] in their 'new findings', with a significant correlation between microbiome diversity and self-rated health for both stool and sigmoid biopsies. Thus, a combination of small sample size and relatively mild symptom severity may be contributory factors to their overall non-detection of microbiota alterations in IBS.

Third, statistical power and effect size are compounded by the heterogeneity of IBS noted by Hugerth *et al*[1] and previously reported in other studies. Indeed, a review of the beta-diversity analyses presented in the literature (where unsupervised analyses are available,[3–5] shows poor support for global microbiota alterations.

Fourth, we have reported the distinction between IBS and controls based on the faecal microbiome and metabolome in 80 IBS subjects and 65 controls.[6] Machine learning could distinguish IBS cases from controls with an area under the curve of 0.814 (sensitivity 0.875 and specificity 0.497). In shotgun sequencing data, 232 bacterial metabolic pathways were significantly more abundant in IBS cases than controls. Faecal metabolomes were also discriminatory, and these metabolites co-associated with microbiome differences by network analysis and were predictive of bile acid malabsorption in IBS subjects as defined by the SeHCAT assay for retention of a radiolabelled bile acid analogue.

We believe the heterogeneity of IBS may mask subsets of patients including those with and without an altered microbiome and that such subsets may be more relevant for future research than persistence with the categorisation of patients based solely on symptoms such as constipation-predominance and diarrhoea-predominance.

Ian B Jeffery ,[1] **Eileen O'Herlihy,**[1] **Fergus Shanahan,**[1,2] **Paul W O' Toole** [1,3]

[1]4D Pharma Cork Ltd, Cork, Ireland
[2]APC Microbiome Ireland, University College Cork, Cork, Ireland
[3]School of Microbiology and APC Microbiome Ireland, University College Cork, Cork, Ireland

Correspondence to Dr Paul W O' Toole, 4D Pharma Cork Limited, Cork T12 YN60, Ireland; pwotoole@ucc.ie

Contributors All authors contributed equally.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests IBJ, FS and PWO are founders 4D Pharma Cork Limited, which is a wholly owned subsidiary of 4D Pharma plc, a company developing live biotherapeutics for diseases including Blautix, which is in clinical trials for irritable bowel syndrome.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Jeffery IB, O'Herlihy E, Shanahan F, *et al*. *Gut* 2020;**69**:2263–2264.

Received 17 February 2020
Revised 20 February 2020
Accepted 24 February 2020
Published Online First 5 March 2020

Gut 2020;**69**:2263–2264. doi:10.1136/gutjnl-2020-320919

ORCID iDs
Ian B Jeffery http://orcid.org/0000-0001-9183-7292
Paul W O' Toole http://orcid.org/0000-0001-5377-0824

REFERENCES

1 Hugerth LW, Andreasson A, Talley NJ, *et al*. No distinct microbiome signature of irritable bowel syndrome found in a Swedish random population. *Gut* 2020;69:1076–1084.
2 Tap J, Derrien M, Törnblom H, *et al*. Identification of an intestinal microbiota signature associated with severity of irritable bowel syndrome. *Gastroenterology* 2017;152:111–23.
3 Codling C, O'Mahony L, Shanahan F, *et al*. A molecular analysis of fecal and mucosal bacterial communities in irritable bowel syndrome. *Dig Dis Sci* 2010;55:392–7.
4 Lyra A, Rinttilä T, Nikkilä J, *et al*. Diarrhoea-predominant irritable bowel syndrome distinguishable by 16S rRNA gene phylotype quantification. *World J Gastroenterol* 2009;15:5936–45.
5 Rajilić-Stojanović M, Biagi E, Heilig HGHJ, *et al*. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology* 2011;141:1792–801.
6 Jeffery IB, Das A, O'Herlihy E, *et al*. Differences in fecal Microbiomes and metabolomes of people with vs without irritable bowel syndrome and bile acid

malabsorption. *Gastroenterology* 2019. doi:10.1053/j.gastro.2019.11.301. [Epub ahead of print: 14 Dec 2019].