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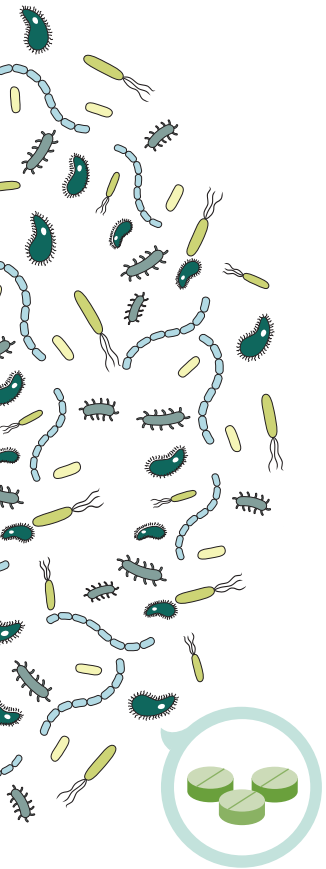
GUT MICROBIOTA

Diagnosing IBD with the gut microbiome

> …new insights reveal noninvasive methods that might enable more accurate diagnoses of IBD…



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Two new studies have performed longitudinal analyses of the human gut microbiome in patients with IBD. Both studies showed dynamic shifts between the microbiomes of healthy individuals and patients with IBD, as well as between patients with ulcerative colitis and Crohn's disease, which led to promising diagnostic models.

Although dysbiosis of the gut microbiota has been associated with IBD, prior studies have relied upon single time points or few individuals. Now, in the first new study (published in *Nature Microbiology*), a multidisciplinary team assessed the long-term dynamics of the gut microbiome to see if patients with IBD have gut microbiota that change the same way as healthy individuals. Using a mixed IBD cohort ($n = 137$) and nine healthy individuals as controls, 16S ribosomal RNA (rRNA) sequencing of the gut microbiome was performed from faecal samples taken at 3 month intervals for up to 2 years, combined with clinical data, faecal calprotectin levels and host genetic markers. "The data were modelled to determine the dynamics of the gut microbiome and the features that were most predictive of different IBD diseases," explains author Janet Jansson.

Examining UniFrac distances (a metric used for microbial community comparisons) by principal coordinate analysis revealed distinct clusters corresponding to the healthy controls and different IBD subtypes. However, variation over time in the healthy controls was highly constrained compared to individuals with IBD. "This led us to develop a new mathematical approach where we defined a 'healthy plane' … relative to which we could track the approach and departure of the microbiome in IBD," explains Jansson.

The investigators found that all IBD subtypes deviated substantially from the 'healthy plane'. Colonic Crohn's disease and ulcerative colitis samples were the least distant, whereas ileal Crohn's disease samples showed the greatest divergence, particularly in patients who had undergone surgical resection of the colon. "Amazingly, distance from the 'healthy plane' we defined could diagnose disease better than calprotectin assays that are the most commonly used noninvasive diagnostic approach," reports Jansson.

The researchers are now planning to apply their model to a larger IBD cohort with more time points. "In addition, in the future, it will be important to explore whether attempts to maintain patients with IBD in the 'healthy plane' have a beneficial effect on the clinical course needed," concludes author Jonas Halfvarson.

In the second study (published in *Gut*), Pascal *et al.* also longitudinally examined the faecal microbiomes of patients with IBD, but with a focus on the differences between ulcerative colitis and Crohn's disease. 16S rRNA sequencing was also used in this study, but in a cohort of 2,045 individuals from four countries (Spain, Belgium, Germany and UK).The researchers first characterized the microbial communities of patients with ulcerative colitis and Crohn's disease in a discovery cohort of 178 Spanish participants, which included related and nonrelated healthy individuals. The stability of the gut microbiota was evaluated using UniFrac distances between faecal samples taken at 3 month intervals for 1 year total.

"Dysbiosis appears to be greater in Crohn's disease than ulcerative colitis, involving more groups of microorganisms," says author Chaysavanh Manichanh. The investigators found that patients with Crohn's disease had a more unstable microbial community over time, lower microbial diversity and a more altered gut microbiota than ulcerative colitis. Additionally, Crohn's disease was more associated with a loss of beneficial microorganisms (such as butyrate producers) than a gain in pathogenic species.

An algorithm was developed to discriminate between Crohn's disease and non-Crohn's disease based on eight selected microbial genera that showed the greatest changes between different groups of the discovery cohort. This algorithm was then tested and validated using several additional datasets, including those containing patients with IBS or anorexia, as well as a large cohort of healthy twin individuals from the UK. Overall, the test showed a sensitivity of ~80% and a specificity ranging from 89.4–94.4% for Crohn's disease detection versus healthy individuals and patients with IBS, anorexia or ulcerative colitis.

"The microbiomarkers identified in this work will facilitate the discrimination between Crohn's disease and ulcerative colitis, and might decrease the systematic use of endoscopy for the diagnosis of this disease," explains Manichanh. These findings could also help tailor future treatments for IBD based on faecal microbiota transplantation.

Together, these new insights reveal noninvasive methods that might enable more accurate diagnoses of IBD, help with uncertain clincial decision-making and potentially guide future personalized therapies.

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ORIGINAL ARTICLES Halfvarson, J. *et al.* Dynamics of the human gut microbiome in inflammatory bowel disease. *Nat. Microbiol.* http://dx.doi.org/10.1038/nmicrobiol.2017.4 (2017) | Pascal, V. *et al.* A microbial signature for Crohn's disease. *Gut* http://dx.doi.org/10.1136/gutjnl-2016-313235 (2017)