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MILESTONE 17

Microbiome analyses in large human populations

Microbiome composition and function have been implicated in various diseases. However, understanding and exploiting the interactions of the microbiome with the human host is tempered by the huge diversity of the microbiome within and between individuals. Advances in metagenomics and high-throughput sequencing in the early 2000s, inspired projects aimed at capturing microbiome diversity in large human populations. For example, one of the first such projects, Metagenomics of the Human Intestinal Tract, studied faecal samples from 124 individuals, generating 576.7 gigabases of sequence data. The authors noted that this is "almost 200 times more than in all previous studies" and "provides a broad view of the functions important for bacterial life in the gut".

Besides the scientific achievement of this and similar projects, such as the Human Microbiome Project, Belgian Flemish Gut Flora Project, Dutch LifeLines-DEEP study and others, one should note and acknowledge the fruitful collaboration of these large scientific consortia, lately even including citizen scientists in American Gut. Furthermore, dedicated support from several funders has been essential.

As mentioned above, initial studies looked at around 100 individuals; by contrast, today's studies can contain samples from several thousand participants. Larger numbers, as well as refinement and standardisation of protocols and pipelines, and the availability of larger reference data sets — all of which have profited hugely from early microbiome population studies — add to the robustness of results. Sometimes it has been difficult to compare studies and there have been studies with contradictory results. Nevertheless, large population studies have greatly advanced our understanding of what constitutes a 'normal' human microbiome, although this statement should be qualified by the fact that North Americans and Europeans are the best-studied populations. Projects are underway to ameliorate this bias.

In general, the microbiome differs not only between healthy individuals and those with diseases, even between healthy people there is a large diversity — there is no uniform 'healthy' microbiome. Some general measures, such as high taxonomic and functional richness, which usually correlate with a diverse, fibre-rich diet, seem to be beneficial.

Population studies have also identified factors that shape the microbiome, and have helped quantify their impact, including body site, diet, drugs, host genetics and others.

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Furthermore, it has been possible to identify disease-specific microbiome signals, for example, for type-1 diabetes mellitus (MILESTONE 9), metabolic syndrome, obesity (MILESTONE 12), inflammatory bowel disease and others. Notably, the second phase of the Human Microbiome Project used an integrative approach that combines several 'omics techniques to study the role of the microbiome in preterm birth, the development of type-2 diabetes mellitus and inflammatory bowel disease over time. Identifying such signals is a first step towards understanding how the microbiome might contribute to disease development, and towards the development of preventative and therapeutic applications.

For example, individual microbiome differences are associated with the response to cancer treatment (MILESTONE 24). This finding and other studies have inspired plans to exploit microbiome differences for individualized therapies and interventions.

In summary, large population studies have greatly advanced our understanding of gut microbiome diversity and have identified numerous potential links to health and disease, inspiring many new research avenues. They have also made essential contributions to establishing methods and standards on which future work can build. Finally, these studies have highlighted the importance of the microbiome, not only for scientists but also for the general public.

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