The Human Gut Microbiome

MICROBIOLOGY SOCIETY

What is a microbiome?

A microbiome is a dynamic habitat made up of micro-organisms, their functions and related components within a specific host or environment [1]. The community of micro-organisms within a microbiome – the microbiota – can be extremely diverse, with bacteria, viruses, fungi, archaea and other microbial species all contributing to this complex network of interactions. Environments such as soils and oceans host microbiomes which are responsible for carrying out fundamental life processes. Humans, animals and plants also host microbiomes. Within these host organisms, individual organs, such as the gut, skin or lungs, create unique microbial environments. This briefing will focus on the human gut microbiome and its role in health and disease.

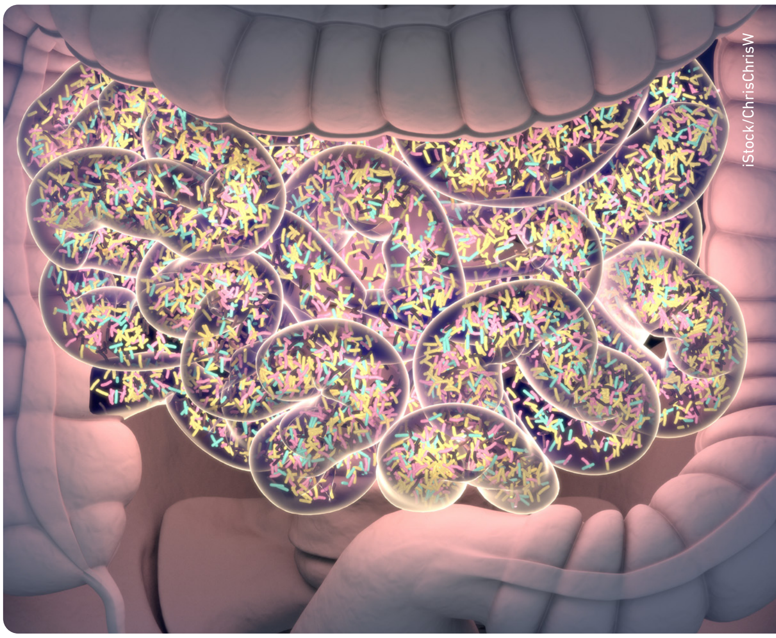
Why does human microbiome research matter?

Human microbiome research is an exciting and dynamic field that has the potential to benefit many areas of our society and the economy. Microbiome research has progressed rapidly since the development of new genomic technologies and investment in large-scale, collaborative projects such as The Human Microbiome Project, a ten-year research initiative launched in 2007 which set out to characterise the human microbiome and its role in health and disease [2]. Evidence from this project, alongside more recent studies, suggests that the findings from microbiome research can be used to improve human health.

The wider public is increasingly engaging with this concept, particularly in relation to the human gut [3], and public health practices are beginning to be informed by the latest microbiome research [4]. Investment from industry stakeholders is also growing rapidly. The global human microbiome market is expected to reach $1.2 billion by 2030 [5] and increasing research-industry partnerships will drive the development of new medicines and technologies [6]. Institutions across the UK are conducting cutting-edge microbiome research with a range of potential applications, including developing new therapeutics and improving the efficacy of current medical treatments.

How does the gut microbiome affect human health?

Humans have coevolved with micro-organisms and, because of our shared history, we have grown to depend on them. The gut microbiome is our only source of multiple key metabolites [7] and is involved in nutrition, development and the immune response. Studies in germ-free mice, which have never been exposed to microbes, show that a whole range of bodily functions are affected if organisms develop without their natural microbiota [8]. The gut microbiome is in constant communication with other human organs and the composition of an individual's gut microbiota can affect these signals [9].



Although the gut microbiome is intrinsically linked to human health, defining a 'healthy' gut microbiome is difficult because microbes behave differently in different contexts. Many health issues correlate with changes in gut microbiota composition [12,13], but further research is required to assess the causality of these associations, given that multiple risk factors, such as diet and lifestyle, also correlate with many of these diseases [10,11]. Nevertheless, these associations demonstrate that a range of health issues might be able to be treated, or even prevented, by manipulating the composition of our gut microbiomes.

Health issues associated with changes to the gut microbiota in preliminary studies [12,13]

- Colorectal cancer
- Depression, anxiety and stress
- Obesity and type II diabetes
- Autoimmune diseases
- Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD)
- Cardiovascular diseases
- Respiratory diseases

Can the gut microbiome be managed to reduce the risk of disease?

The NHS Long Term Plan emphasises that preventing disease will be key to managing the burden on health services and helping people to live longer, healthier lives [14]. It is well evidenced that lifestyle choices, including diet, can affect the composition of an individual's gut microbiome [15]. However, significantly more basic research and clinical trial data is required to assess whether microbiome-based interventions can prevent disease and improve public health. As such, it will be crucial to recruit more computational and artificial intelligence experts into the field to analyse the vast amounts of data being generated by microbiome research.

The gut microbiome and vaccine efficacy

Currently, an area of gut microbiome research with exciting potential for preventing disease is exploring the link between the gut microbiota and vaccine efficacy. Gut microbiota appear to modulate the immune response [19], and clinical studies suggest that variation in gut microbiota composition influences the efficacy of multiple vaccines, including COVID-19 vaccines [20]. Microbiota-targeted interventions may therefore be able to improve the level of protection that vaccines offer against disease, particularly in vulnerable populations such as the elderly [21].

Using diet to manage our gut microbiomes is a hot topic across academia, industry sectors and the general public.

Despite continued progress in this field, the recent boom in at-home microbiota sampling kits and microbiome-based nutrition plans has been criticised by experts [16]. It may be of personal interest to the healthy individual to find out the composition of their gut microbiome, but experts maintain that clinicians cannot currently make any useful recommendations based on this data [17]. Further investment and research are required to establish genuine causal links between these technologies and proposed health benefits. However, the extent of public engagement and private investment in these products (one startup, ZOE, is valued at over £200 million [18]) illustrate the field's high commercial value.

CASE STUDY: miGut-Health

miGut-Health is a collaborative project funded by Horizon Europe, the EU funding programme for research and innovation, which aims to develop a personalised blueprint of intestinal health to predict and prevent inflammatory bowel disease (IBD). In 2023, the project successfully created a benchtop model of the human gut which can now be used to assess the effect of diet on intestinal inflammation and validate key characteristics of gut health [22]. Collaborative projects such as miGut-Health are helping to determine whether the gut microbiome influences the onset of IBD, and whether gut microbiota composition can be manipulated to prevent IBD.

Can the gut microbiome be manipulated to treat disease?

In addition to using gut microbiome research to prevent disease, innovative methods have been developed to manipulate gut microbiota composition in order to treat existing health issues. Multiple avenues for manipulating gut microbiota composition have been explored, including prebiotics, probiotics (live microbes) and faecal microbiota transplantation (FMT). FMT involves transferring microbes from the stool of a healthy donor to the intestine of a patient and has been the most successful microbiome-based method for treating disease to date, with robust clinical evidence indicating that FMT can be an effective treatment for antibiotic resistant *Clostridioides difficile* infection (CDI), ulcerative colitis and inflammatory bowel disease (IBD) [26]. In 2022, the National Institute of Health and Care Excellence (NICE) recommended FMT for treating recurrent CDI [27] and this treatment is now offered by the NHS.

FMT could also help us overcome the antimicrobial resistance (AMR) crisis, with recent studies suggesting that the re-introduction of a normal gut microbiota (via FMT) after taking a course of antibiotics can reduce the chance of an infection becoming resistant [28,29]. Many industry stakeholders are developing new technologies to improve FMT, with biotech company Seres Therapeutics recently developing the first FDA-approved, orally administered microbiota-based therapeutic for treating recurrent CDI [30].

Obesity and the gut microbiome

One in four adults in England are living with obesity, costing the NHS an estimated £6.5 billion every year [23]. Although the role of gut microbiota in obesity is not yet fully understood, multiple studies have identified that obesity is associated with characteristic features of the gut microbiota [24]. These associations require validation and may not play a causative role in disease, but studies indicating that certain prebiotic treatments (molecules to feed specific microbes) are associated with weight loss in obese rats [25] provide hope that manipulating the gut microbiota could provide an additional therapeutic avenue for managing obesity.

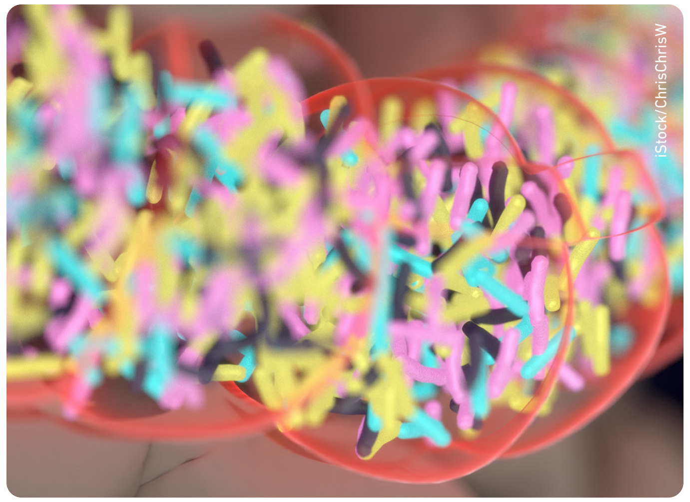
Getting microbiota-based therapeutics through regulatory bodies is currently slow because the microbes involved often do not have a history of safe use as treatments. However, the number of microbiota-based therapies reaching the market will increase as regulatory bodies streamline approval processes and this area of industry continues to grow.

The gut microbiome and the brain

Current research suggests that the gut microbiome influences the signals released by the nervous system in our gut and may therefore affect brain function and behaviour. Links have been found between gut microbiota composition and various mental health issues, including depression and anxiety. These associations are particularly apparent in patients with irritable bowel syndrome (IBS). Although this field still lacks strong causative evidence, small-scale studies have reported that FMT can significantly improve minor depressive symptoms in adults [31,32].

Gut microbiota and cancer immunotherapy

One of the best-evidenced areas of microbiome research explores how manipulating the gut microbiota can affect the efficacy and toxicity of cancer immunotherapies. Recent studies indicate that dietary interventions, probiotics, prebiotics and FMT can all alter gut microbiota composition in ways that increase the effectiveness of cancer immunotherapies [33]. Clinical studies have demonstrated that FMT not only makes immune checkpoint inhibitors (a common immunotherapy) more effective, but can also reduce their adverse effects in some patients [34]. New technologies are being developed based on this research, with the aim of personalising cancer immunotherapy treatments. For example, BiomeOne, the first diagnostic tool released by BiomeDx [35], samples a patient's gut microbiota to predict how beneficial, and potentially harmful, a certain cancer immunotherapy will be to that patient.



Conclusions

Significantly more basic research is needed to establish whether the gut microbiome plays a causative role in human health, and to understand how this role varies in relation to different diseases. It will therefore be crucial to manage public expectations and continually assess the safety of commercial products as the field progresses. Nevertheless, gut microbiome research remains a fast-paced and exciting field with promising future applications and many opportunities for cross-sector collaboration across academia, industry and public health. As such, further investment into gut microbiome research has a huge potential for stimulating innovation and may lead to the development of novel approaches to treating health and disease.

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