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Recent advances in our understanding of the gut microbiome: an analysis from the Gut Microbiota for Health Expert Panel of the British Society of Gastroenterology

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gutjnl-2026-338252).

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Received 29 January 2026
Accepted 21 May 2026

Check for updates

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To cite: Alexander JL, Mullish BH, Thomas L, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2026-338252

ABSTRACT

At around 10 years ago, at the time of the first publication by the Gut Microbiota for Health Expert Panel of the British Society of Gastroenterology, recognition of the gut microbiome's importance in health and disease was transitioning from fringe interest towards major global pursuit. A decade on, we appraise the considerable progress made in the field, while acknowledging ongoing challenges. Earlier human work characterising the 16S rRNA gene amplicon signature of particular conditions in small cohorts has been superseded by larger, multicentre studies with extensive metadata. Studies increasingly employ shotgun metagenomics and other 'omic' techniques—coupled with refined bioinformatic tools and disease models—to better characterise perturbation in gut microbiome functionality. The arrival of 'gold standard' pipelines for microbiome analysis and increased mechanistic validation of signals are key developments towards more clinically-translatable outcomes. Novel clinical areas where the gut microbiome has relevance have emerged, including early life and the efficacy of certain treatments (including immune checkpoint inhibitors and vaccination). Enthusiasm for 'microbiome diagnostics and treatments' has grown, but barriers to widespread adoption remain. Faecal microbiota transplant (FMT) is established for treating recurrent *Clostridioides difficile* infection, with donor-derived 'next generation' FMT products licensed for this condition in certain countries. Beyond FMT, other microbial therapeutic techniques—including nutritional, bacteriophage and probiotic therapies—show promise, but have not fulfilled their high expectations yet. Gut microbiome research is now well-established and shows significant translational potential; the future focus will be translational work to drive its utility in clinical diagnostics, prognostics and therapeutics.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In 2016, a landmark review in *Gut* hailed the gut microbiota as a new clinical frontier in human health.

⇒ At that time, human studies were generally limited to describing the 16S amplicon gene signature (taxonomy) of a select number of disease states, including inflammatory bowel disease (IBD), colorectal cancer and liver-related disorders.

⇒ In 2016, there had been minimal development of microbiome-based diagnostics and clinical use of microbiota-targeted therapeutics was in its infancy, with the nascent application of faecal microbiota transplant (FMT) in recurrent *Clostridioides difficile* infection.

INTRODUCTION

A landmark review published in this journal a decade ago described rapidly growing awareness of the contribution of the gut microbiota to mammalian health and disease, envisaging this as of comparable significance to the discovery of a new organ.[1] A major focus related to the emergence of largely cross-sectional studies that reported differences in the stool microbiome composition between a range of different disease groups from controls, proposing the gut microbiome as a largely overlooked contributor to disease pathogenesis. A second focus related to the potential for gut microbiota manipulation as a novel therapeutic strategy, with the emergence of early randomised trials of faecal microbiota transplant (FMT) for recurrent *Clostridioides difficile* infection (rCDI)[2] demonstrating proof-of-concept translational potential. A final area of interest related to next-generation sequencing techniques (at the time, focused around 16S rRNA gene amplicon sequencing), and associated systems biology ('omic') techniques, to better interrogate the gut microbiome.

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WHAT THIS STUDY ADDS

⇒ A decade on, we analyse the considerable progress made and ongoing challenges in the field of gut microbiota research pertaining to human health.
⇒ Human gut microbiota studies are increasingly sophisticated, integrating multiomic approaches and more robust bioinformatic analytical pipelines to investigate large multicentre populations.
⇒ Microbiome diagnostics are now commercially available but there is significant concern about validity and clinical utility.
⇒ Microbial therapeutic applications are expanding beyond FMT, with next-generation products selecting specific microbial strains - and the development of nutritional, bacteriophage and novel probiotic therapies - all in the pipeline.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Key research priorities for the coming decade include the development of a robust understanding of a healthy gut microbiota, greater utilisation of mechanistically-informed studies, and further movement towards evidence-based microbiome testing and therapeutics in diseases such as IBD and cancer.
⇒ Using an increasingly-sophisticated toolkit developed in recent years, the mission for the gut microbiota scientific community should be to focus on synthesis of current knowledge, development of well-powered, novel studies with scientific rigour aimed directly at causality and application, and a determined drive towards clinical translation.

A 2025 conference hosted by the British Society of Gastroenterology Gut Microbiota for Health expert panel was the trigger for this comprehensive literature review. This meeting brought together leading UK and international experts within the gut microbiome field, occurring a decade after the first collective meeting of this group,[3] all of whom agreed a narrative review updating our collective knowledge was overdue. Each speaker was asked to update and expand upon their given topic with reference to the current literature; the resultant sections were drawn together into a single narrative to construct this review. This enabled a critical appraisal of how the field has evolved within the past decade, highlighting areas of significant progress but also acknowledging the challenges and complexities in the study of gut microbiota that were not initially appreciated. Regarding successes—some of the best examples have been multicentre, prospective studies with deep clinical phenotyping of well-characterised patient groups, increasingly using metagenomic sequencing (potentially characterising taxonomy to strain level), along with multiomic approaches to better characterise microbiota functionality and microbiota–host interactions. Most recently, analysis of such datasets has employed a range of established bioinformatic approaches, which are increasingly integrated with machine learning techniques to delineate signals associated with health conditions. Several key examples of gut microbiota signals of disease contributors or prognostic markers have since been described.[4] Model systems including *in vitro, ex vivo* and *in vivo* models have allowed mechanistic validation of the contribution of the gut microbiota, each with their own inherent strengths and weaknesses.[5–7]

Furthermore, new clinical areas in which the gut microbiota has pertinence to human health have emerged, some of which have been surprising, including the impact of the gut microbiota on the efficacy of a range of therapeutics or the influence of early life microbiota on health in later life. Chronic inflammatory conditions represent another major clinical domain in which the gut microbiome is increasingly recognised as a key modulator of disease risk, progression and therapeutic response. Perhaps the area with the most marked degree of clinical translation has been modulation of the microbiota via FMT, which has become standard of care in treating rCDI in many territories and shows promise in a range of non-CDI trials but has not yet reached mainstream clinical use. FMT has clear drawbacks and several established and/or novel approaches to manipulating the gut microbiota also show potential.

Complexities and challenges in the field remain, including the lack of an agreed definition of a 'normal/healthy' gut microbiota, coupled with recognition of the considerable scope for methodological biases at different points in a microbiome study. With no universally accepted standard approach we are some way off using standardised microbiome 'diagnostics' in clinical settings. An additional complexity relates to microbial taxonomy being updated in 2021,[8] with the names of the four most commonly identified gut bacterial phyla changing from Bacteroidetes, Firmicutes, Proteobacteria and Actinobacteria to Bacteroidota, Bacillota, Pseudomonadota and Actinomycetota, respectively. Of direct relevance to gastroenterologists, the phylum Campylobacterota (including *Campylobacter spp* and *Helicobacter spp*) was also separated from the previously named Proteobacteria. We mention this here both to acknowledge our awareness of these changes, and also to recognise the impact of such a change on largely retrospective/historic synthesis pieces such as this. Revisiting classification within each individual article would be both cumbersome and likely inaccurate, and the authors here have therefore chosen to retain the taxonomy as originally reported throughout this review. It is worth noting that the distinction between formal taxonomy and clinical nomenclature is recognised and has been addressed with a parallel naming process (List of Recommended Names) for bacteria of human or veterinary importance.[9] A detailed discussion of this is beyond the scope of this review.

In summary, this narrative review aims to give a focused critical overview of gut microbiome research over the past decade and potential avenues for direction in the coming few years, with a focus on clinically orientated studies.

CURRENT STATUS OF THE GUT MICROBIOME IN MAJOR HUMAN DISEASES

Overview

Since the review of Marchesi and colleagues in 2016, the fundamental concept of the definition of a 'normal' or 'diseased' microbiome—and the relative contribution of host factors (such as genetics) and environmental factors in influencing this—has itself been an active and ongoing area of debate (table 1). This earlier review particularly focused on four major gastrointestinal (GI) disease areas as being ripe for clinical exploitation of the gut microbiome: inflammatory bowel disease (IBD), colorectal cancer (CRC), liver diseases and obesity-related diseases.[1] Over the intervening period, we have seen further developments in these key disease areas, but the reach of the gut microbiota now stretches much further, including areas not originally highlighted, including in early life (figure 1). The following section summarises developments in both established and emergent areas; online supplemental table 1 also summarises some of the foremost updates. A further major update since a decade ago

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Table 1 Fundamental concepts about a healthy versus diseased microbiome, and the relative contributors to this

Concept	Details
Defining a 'healthy gut microbiome'	► The term 'dysbiosis' is still often used as a description of a perturbed microbiota, but is problematic for several reasons,[265] not least since no widely-accepted definition of a 'normal/healthy gut microbiota' exists (although recent projects have attempted to do so).[266] ► Large global projects such as the Human Microbiome Compendium have undertaken microbiome profiling of >160 000 gut microbiomes from 68 countries, highlighting the influence of factors including biogeography, environmental and dietary factors in shaping the microbiome.[267] There has also been expansion beyond earlier Western-focused studies, with a large recent profiling exercise in Africa demonstrating differences between rural and urban population microbiomes.[268]
A unifying microbiome signature of disease?	► Conversely, the large-scale Dutch Microbiome Project somewhat surprisingly revealed the presence of shared microbiome features across many disease states, including gastrointestinal, neurological, psychiatric and metabolic diseases and cancers.[269] ► Nine core species were identified (*Subdoligranulum spp, Alistipes onderdonkii, Alistipes putredinis, Alistipes shahii, Bacteroides uniformis, Bacteroides vulgatus, Eubacterium rectale, Faecalibacterium prausnitzii* and *Oscillibacter spp*) that are highly consistent with those found in the UK, the USA, European and non-western populations. Five of them (*A. putredinis, A. shahii, F. prausnitzii, Oscillibacter spp* and *Subdoligranulum spp*) are 'keystone species' (central nodes in microbial networks), implying that they also have central roles in the gut microbiome ecosystem.[269]
Interaction between environment, genetics and gut microbiome	► While host genetics play a role in microbiome composition, environmental factors appear to be more important. For instance, cohabiting first-degree relatives have a more similar microbiome than cohabiting non-relatives or random non-cohabiting pairs; however, the gut microbiome of non-cohabiting first-degree relatives is similar to random non-cohabiting pairs, showing that environment dominates host genetics in shaping the gut microbiome.[269] ► To further study the contribution of host genetics, several studies have combined host genotyping and gut microbiome data. However, only a few genetic loci have been consistently confirmed across multiple studies.[270] Genetic variants within the *LCT* gene, which encodes the lactase enzyme that cleaves the milk sugar lactose into glucose and galactose, are associated with abundance of *Bifidobacterium*.[271] Furthermore, the ABO locus and its interaction with FUT2 secretor status have been associated with the abundance of multiple taxa including *Faecalibacterium*, *Bacteroides* and *Collinsella*.[272]

also relates to the recognition of the role of the microbiome of other mucosal surfaces—including the vaginal and respiratory epithelium—as having potential clinical pertinence, which has been reviewed elsewhere.[4]

The 'big four' from a decade ago: IBD, CRC, liver disease and obesity-related disease, where are we now?

Inflammatory bowel disease:

In IBD, the last decade of research has expanded beyond single-centre analyses which had, for example, identified *Faecalibacterium prausnitzii* as depleted in patients with Crohn's disease (CD), especially ileal CD[10–12] (although it should be noted that *F. prausnitzii* depletion is seen in a range of chronic diseases, and a causal link with IBD aetiology has yet to be proven). With large-scale, cross-continental projects, gut microbiome profiles are now showing promise as having a potential diagnostic role for the condition[13] (discussed in more depth in the later section, 'The gut microbiome as a diagnostic or prognostic tool'), correlating with disease activity and quality-of-life measures.[14] The first longitudinal, integrative multiomic analysis of the gut microbiome in IBD was published in 2019, mapping functional perturbations of the IBD gut microbiome in an American cohort,[15] with several other large longitudinal IBD cohorts now in existence across the globe.[15–19] Additionally, there is growing appreciation of an association between the gut microbiota and heterogeneity of therapeutic responses to IBD treatment,[20] exemplified by the identification of specific microbial acetyltransferases that lead to 5-aminosalicylate (5-ASA) inactivation.[21] There has also been a maturation of research harnessing microbial modulation to treat IBD, including several randomised controlled trials (RCTs) using FMT, and now second-generation microbial therapeutics, which are covered in more detail in the later section, 'Application of the gut microbiome to therapeutics'.

Colorectal cancer

A decade ago, studies first linked *Fusobacterium nucleatum* to CRC.[22] We now know that intratumoural *F. nucleatum* can influence tumour progression, metastasis, resistance to chemotherapy and recurrence risk.[23–25] *Escherichia coli* (carrying the pks pathogenicity island) have been implicated directly in colorectal carcinogenesis through production of the genotoxin colibactin.[26] Multiomic studies have revealed that loss of commensal species and their mutualistic co-metabolic and immune functions play a critical role in cancer causation and tumour behaviour.[27] Evidence linking microbiota (both gut microbiota and other mucosal microbiotas) to the initiation and propagation of neoplasia has emerged across a wide range of intestinal and extraintestinal cancer types, notably in the pancreas and gynaecological tract.[28] Beyond pathogenesis, modulation of efficacy of chemotherapy through microbiome pathways has become a topic of great interest.[29]

Immune checkpoint inhibitors (ICIs) have been revolutionary drugs across a range of cancer types, including skin, lung and kidney malignancies, and they are also used in mismatch repair-deficient CRC.[30] ICIs are now placing the microbiota in the oncology spotlight with multiple studies demonstrating that the gut microbiota is a crucial determinant of ICI response. For example, *Akkermansia muciniphila* promotes dendritic cell activation and IL-12 production within the tumour microenvironment, while *Prevotella merdae* enhances cytotoxic T-cell tumour infiltration, both boosting anti-PD-1 efficacy.[31–33]

Liver disease

The 'gut-liver axis' is now accepted as a fundamental concept explaining the bidirectional relationship between the GI tract, its microbiota and the liver. Disturbances in the mucosal intestinal barrier can result in an influx of microbes or their byproducts into the liver, culminating in endotoxaemia, hepatic and systemic inflammation and immune dysfunction, each of which can worsen liver function.[34 35] Compelling data link perturbations in the gut microbiota with the pathogenesis and progression of chronic liver disease.[35 36] Changes in gut microbiota profiles occur at an early stage, especially in alcohol-related and metabolic dysfunction-associated liver disease.[37–39] A body of work has explored the contribution of bacterial virulence factors—including proteins or peptides that help such bacteria colonise the intestine or contribute directly to pathogenesis—to such liver diseases, with the best characterised example being alcohol-associated hepatitis (AH). Specifically, the presence in the gut microbiome of *Enterococcus faecalis* cytolysin and *E. coli* with KpsM (a polysialic acid transporter protein,

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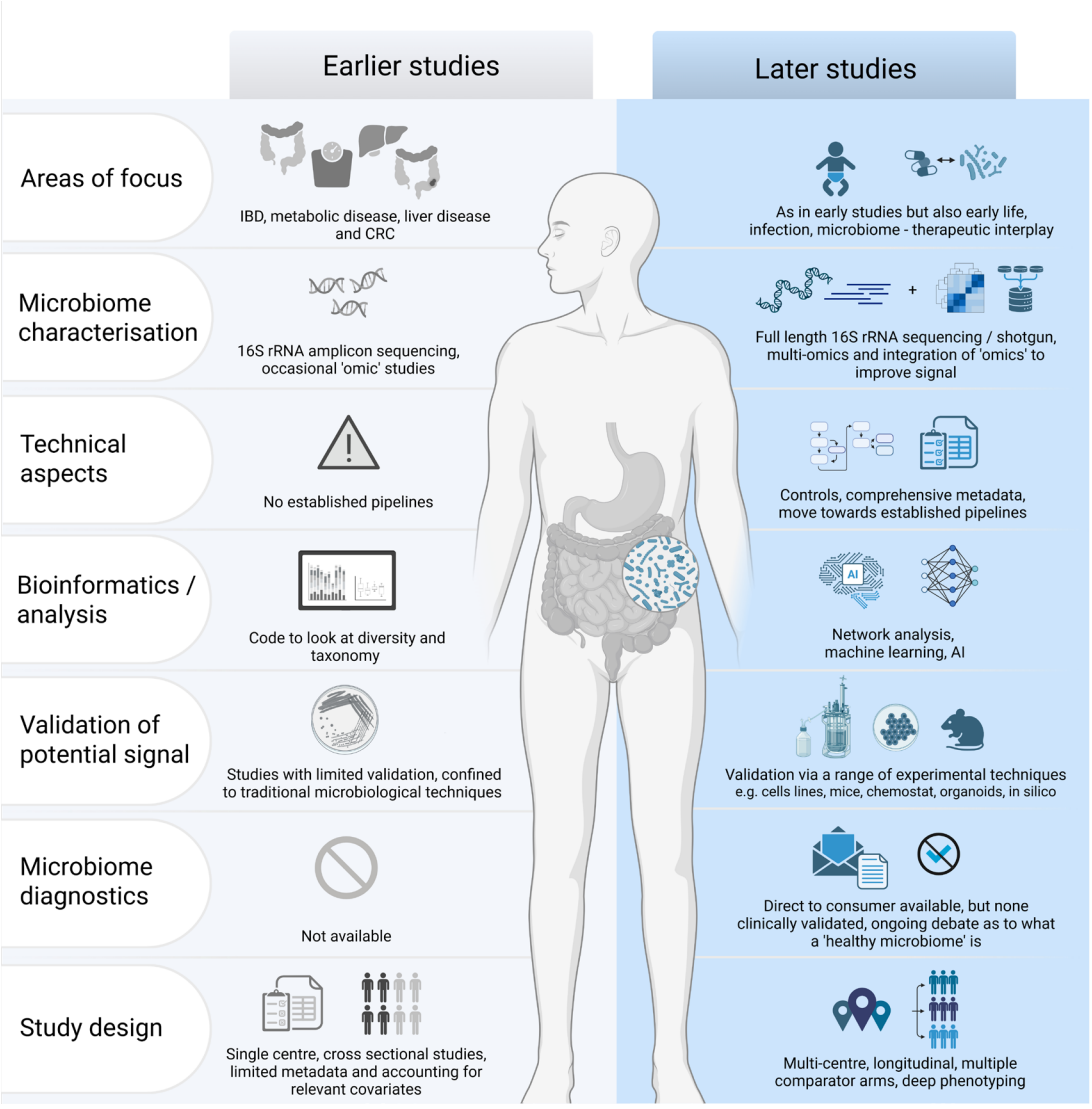

Figure 1 A summary of key developments and updates with regard to translational microbiome studies over the past decade. This excludes therapeutics, which is discussed elsewhere. Figure created using BioRender. AI, artificial intelligence; CRC, colorectal cancer; IBD, inflammatory bowel disease; rRNA, ribosomal RNA.

impacting bacterial outer membrane synthesis) are associated with increased mortality and exacerbation of AH disease in mouse models.[40 41] Importantly, inhibition of cytolysin-derived hepatocyte toxicity with a targeted bacteriophage—and prevention of KpsM *E. coli* from evading phagocytosis by Kupffer cells via use of a small molecule—reversed liver damage in preclinical models.[40 41] The mechanisms of efficacy of lactulose in chronic liver disease have been delineated: increasing intestinal *Bifidobacteria* abundance, which in turn metabolise lactulose to acetate, acidifying the gut and influencing gut microbiota composition.[39] Rifaximin, a non-absorbable antibiotic which is highly efficacious for hepatic encephalopathy (HE), reduces gut-derived systemic inflammation by augmenting gut barrier integrity and reducing bacterial translocation[42]; however, there is potential for rifaximin prophylaxis to promote resistance to the 'last resort' antibiotic of daptomycin.[43] This is particularly pertinent given the prevalence of multidrug-resistant bacterial infections in cirrhotic patients, which increased from 29% in 2011 to 38% in 2018.[44]

Obesity and metabolic disorders

20 years ago, murine studies suggested that obesity could be transferred via FMT,[45] bringing a spotlight to obesity-related disease as a prime arena for potential clinical translation of the microbiome. By 2016, a more nuanced relationship was described, highlighting the role of diet (particularly high fat diets) rather than obesity *per se* in explaining correlations with gut microbiome signatures.[1] Others have subsequently argued that there has been excessive reliance on murine models with limited comparability to humans in gut microbiome-related obesity research.[46] While rodents are convenient models for such studies, they have a number of limitations, including: the marked differences in the microbiome between rodents and humans; the variability in anatomy and physiology between both (including fermentation being predominantly in mouse caecum but human colon); and the concern regarding comparability of an obese phenotype induced by genetic mutation and/or high fat diet in laboratory mice with that occurring in free-living humans in an obesogenic environment.[47] Indeed, as in other disease areas, initial enthusiasm for specific taxonomic groups or

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features driving a single obesogenic pathophysiological pathway has come unstuck amidst the complexity and variability of multi-member microbial niches influenced by countless environmental factors[48] with, for example, *Prevotella* and *Ruminococcus* genera being associated with Western obesity but also Eastern leanness.[48] Nonetheless, it is clear that the gut microbiota produces an array of compounds which affect host energy metabolism and fat storage.[49]

Gut microbiome research related to obesity has progressed into more interventional studies since 2016. The first placebo-controlled RCT of FMT from a lean donor into obese individuals did not result in body mass index (BMI) reduction,[50] and other trials in this space have also given negative results. Other interventional studies have given signals of interest—for instance, a double-blind RCT of healthy-donor FMT in obese adolescents showed no between-group difference in BMI at the time of initial study or later follow-up, however, FMT recipients had a smaller waist circumference and lower metabolic syndrome severity score at 4 years after the original trial.[51] A further study gave FMT with fibre to patients with severe obesity and metabolic syndrome, with the primary outcome being impact on insulin resistance; somewhat counter-intuitively, it was only the arm receiving FMT together with non-fermentable fibre who reached the primary endpoint, with those receiving FMT alone or FMT with fermentable fibre having no benefit in insulin resistance.[52] The negative correlation between the mucin-degrading commensal *A. muciniphila* and metabolic syndrome has motivated trials supplementing the bacterium in overweight or obese individuals.[53 54] Initial proof of concept data suggested modest effects on biochemical parameters of liver dysfunction and insulin resistance, but a more recent trial has demonstrated improvements in harder endpoints such as body weight and glycated haemoglobin, specifically in individuals with low baseline faecal levels of *A. muciniphila*.[54] *Bacteroides thetaiotaomicron* depletion has been linked to obesity, consistent with murine model data demonstrating that gavage of *B. thetaiotaomicron* alleviates adiposity via increased glutamate fermentation. Bariatric surgery has also been associated with partial reversal of *B. thetaiotaomicron* depletion.[55]

The therapeutic landscape in obesity has shifted with the introduction of glucagon-like peptide (GLP)-1 analogues since the seminal report of a successful double-blind RCT.[56] Understandably, this has led to a broader interrogation of mechanisms of action, which in turn has led to consideration of the microbiome,[57] although mostly on animal models to date.[57] The findings of human studies have varied with some genera increased and others diminished but no convincing unifying signal. The obvious confounder on microbiome studies in this setting is the impact of GLP-1 analogues on appetite and dietary choices and portions. Indeed, perhaps more than in any other clinical sphere, the potential for dietary-associated confounding generating a microbiome signal is perhaps at its most significant in the obesity space.

Emergent clinical areas in which the importance of the gut microbiome is being recognised

Early life

The gut microbiota in early life did not feature in the 2016 review, but its pivotal role during the first 1000 days of life—a critical developmental window when metabolic, immune and neurological pathways mature—is now widely appreciated.[58] It is now well reported that birth mode (ie, vaginally delivered infants having higher *Bacteroides* spp for at least the first year of life) and breastfeeding (ie, infants receiving human milk having higher *Bifidobacterium* spp) are of critical importance in shaping the early life microbiome.[59–61] So much so, interventions including maternal FMT for caesarean section infants and human milk oligosaccharide (HMO) supplementation of bovine formula are gaining traction, but the short- and long-term impacts (including potential risks) are not yet understood.[62 63] In term infants, exposure to human milk and promotion of *Bifidobacterium* spp delays maturation and diversification of the gut microbiome, and this early development may be important for reducing the risk of asthma and autoimmune diseases.[59 61 64]

The gut microbiome of moderate preterm infants is generally comparable to term infants,[65] but extremely preterm infants (born before 32 weeks of gestation) are particularly vulnerable to gut microbiota-associated perturbations due to a multitude of factors, including immature gut physiology, high rates of caesarean delivery, neonatal intensive care unit stays and frequent antibiotic exposure (in 75%–95%).[66] Disruptions in early microbial communities are linked to necrotising enterocolitis (NEC), late-onset sepsis (LOS) and impaired immune development.[67 68] Recent findings indicate that gut microbiome-associated changes can compromise host resistance against infection, primarily due to the absence of beneficial bacteria, most notably HMO-utilising *Bifidobacterium*, that typically dominate in breastfed full-term neonates.[68 69] This may facilitate blooms in Pseudomonadota that promote inflammation through TLR4 and likely other, yet to be characterised, mechanisms, increasing gut permeability and contributing to NEC and LOS risk.[70] NEC is a multifactorial condition, with host and microbial factors contributing to its aetiology. Clostridial species have been associated with NEC, including recent work linking *Clostridium perfringens* strains carrying the pfoA toxin gene, which encodes the pore-forming toxin perfringolysin O[79], to epithelial damage in preclinical models. Conversely, *Clostridium* lacking the pfoA gene are potentially beneficial.[71–75] Specifically, *C. perfringens* can metabolise HMOs which are generally linked to beneficial bacteria (eg, *Bifidobacterium*), producing beneficial metabolites including short-chain fatty acids (SCFAs) and tryptophan catabolites that inhibit pathobiont microbes and suppress inflammation in a preterm intestinal organoid model.[75] These findings underscore the importance of strain-level microbiome analyses in understanding disease mechanisms and guiding targeted interventions.

Beyond neonatal health, epidemiological studies increasingly point to microbiota-modulated exposures (maternal nutrition during pregnancy, breastfeeding, avoidance of unnecessary antibiotics, etc) which promote good health in later childhood and adult life.[76–78] Elucidating the interface of these multitudinous early life environmental exposures on subsequent disease development, including allergic, metabolic and autoimmune disorders, is a difficult challenge increasingly being embraced by microbiome researchers[79] in recent years. Over the course of the next decade, a research priority is understanding the mechanisms and longer-term impacts of abnormal microbiome development in early life, and potential treatment strategies to mitigate against this.

Infection and antimicrobial resistance

The contribution of the gut microbiota to 'colonisation resistance' (ie, protection against infection) is well-established in the context of CDI and has been exploited in the use of FMT. This has been the launchpad for a larger body of research exploring the role of the gut microbiome in protection against infection,

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with a major driver being the rapidly rising global burden of antimicrobial resistance (AMR). One area of research in this field has mechanistically explored the routes by which the gut microbiome influences host immune function.[80 81] A range of different commensal microbiota products have been associated with protection against colonisation and invasive infection with multidrug-resistant organisms (MDROs), including gut microbial metabolites such as SCFAs[82] (with acidification of the gut itself being protective against MDROs),[83] and lantibiotics/antimicrobial peptides,[84] with competition between commensal bacteria and MDROs for a nutrient niche also being of pathogenic significance[85]. Beyond FMT, approaches using both microbiome depletion and microbiota restoration may be beneficial in protection against infection. As an example, transient gut microbiota depletion to reduce colonisation resistance—followed by exposure of the gut to a pathogen of interest—results in high intestinal densities of the pathogen antigens, an expanded pool of tissue resident memory $CD8^+$ cells and enhanced protection against future infection by that pathogen.[86] As an example of restoration, 18 commensal strains derived from human stool have been demonstrated—via regulation of gluconate availability—to decolonise Enterobacteriaceae from the gut in mice.[87] Inflammation itself is a major ecological and evolutionary driver of AMR, and the microbiome sits at the centre of that dynamic. Inflammatory states reshape the gut environment, for example, in ways that selectively favour facultative anaerobes—particularly Enterobacteriaceae—by increasing oxygen tension, generating host-derived electron acceptors[88] and releasing nutrients that support the expansion of pathobionts.[89] This ecological shift not only reduces colonisation resistance but also creates conditions that promote horizontal gene transfer, including the exchange of plasmids carrying AMR determinants.[90 91] Inflammation-associated oxidative stress further accelerates microbial mutation rates, enhancing the likelihood of resistance emergence.[92]

Collectively, these data support the role for targeted gut microbiome manipulation as being a strategy to mitigate intestinal pathogens and/or reduce the burden of AMR, but the preferred therapeutic approaches are still an area of uncertainty. FMT studies in patients with intestinal MDRO colonisation have shown variable outcomes, with certain randomised trials suggesting that decolonisation is a feasible outcome, while others have not observed this[93]; certain case series have suggested that even in the absence of decolonisation, FMT may reduce the burden of invasive infection via reducing abundancy of the MDRO within an altered gut microbiome.[94] Heterogeneity of FMT protocol and patient cohorts may be one explanation for the variability of trial results seen in this area; however, addressing inflammatory microenvironments is likely to be as important as targeting pathogens themselves when designing microbiome-focused strategies to mitigate AMR,[95] and this may require consideration in future trials.

Irritable bowel syndrome and disorders of gut-brain interaction

Irritable bowel syndrome (IBS) remains a contentious area for clinical application of the gut microbiota. As a disorder characterised by symptom-defined criteria and spanning multiple subtypes, including diarrhoea-predominant (IBS-D), constipation-predominant (IBS-C) and mixed (IBS-M),[96] cause and effect are particularly difficult to disentangle, given the confounding effects of diet, motility and psychological comorbidity on microbiota composition. Systematic review of the gut microbiota in patients with IBS has revealed increases in Enterobacteriaceae, Lactobacillaceae and Bacteroides, with decreases in *Faecalibacterium* compared with controls, but these findings are tempered by criticism of the lack of clinical matching between cases and controls in a large proportion.[91] Mechanistically, classical understanding of gut-brain communication as a bidirectional nerve axis has been augmented in recent years by the evolving understanding of the role of molecules both derived from and altered by gut microbiota that influence local gut function as well as central nervous system activity (from both functional and emotional perspectives).[52] A seminal multiomics study utilising longitudinal sampling and well-defined IBS clinical subtypes identified purine metabolism as a novel host-microbial co-metabolic pathway of potential therapeutic importance.[92] Subtype-specific microbiota signatures have also been linked to differential responses to the low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet,[56] which is known to reduce faecal microbial diversity, particularly of SCFA producers[57] (discussed further in the 'Diet and gut microbiome' section). Microbiome-directed therapeutics for IBS have been extensively studied, with variable results. Meta-analyses of probiotic interventions demonstrate modest, strain-specific benefits for global symptom scores, bloating and stool consistency in IBS-D, though effect sizes are generally small and heterogeneity between trials remain high.[97] FMT has been evaluated in several RCTs in IBS with conflicting findings[98]; a Norwegian RCT of FMT administered via colonoscopy to the caecum demonstrated significant symptom relief in patients with IBS.[99] Another Norwegian study administering FMT via gastroscope demonstrated significant symptom improvement over placebo at 3 months,[100] with follow-up studies showing the benefits persisted at 2 and 3 years post-treatment.[101] However, subsequent systematic reviews have yielded more modest and inconsistent results, likely reflecting the importance of donor selection, route of administration and IBS subtype.[102 103] These data emphasise that IBS represents a heterogeneous condition in which microbiome-targeted interventions are unlikely to produce universal benefit, and that precision approaches - accounting for subtype, baseline microbiota composition and dietary context - will be essential to realising therapeutic potential.

The gut–brain axis in neurological, psychiatric and neurodevelopmental disease

Beyond IBS, the past decade has seen rapidly-expanding evidence linking gut microbiota perturbation to neurological, psychiatric and neurodevelopmental conditions, with the classical bidirectional gut-brain axis now understood to encompass vagal, immunological, endocrine and metabolite-mediated communication pathways.[90] Parkinson's disease (PD) has attracted the most compelling translational evidence. The 'gut-first' hypothesis, supported by Braak staging of α-synuclein pathology, posits that neurodegeneration may originate in the enteric nervous system before propagating centrally via the vagus nerve.[104 105] Consistent with this, patients with PD demonstrate consistent gut microbiota changes (including depletion of SCFA-producing bacteria and enrichment of pro-inflammatory taxa), alongside increased intestinal permeability.[106–108] Small pilot studies of FMT in PD have reported improvements in constipation and non-motor symptoms, and larger trials are now underway[109]; bacterial tyrosine decarboxylase activity, which degrades levodopa in the gut, has been identified as a microbiome-mediated determinant of pharmacokinetic variability in PD patients, with direct implications for drug dosing.[110] Evidence for a microbiota-dementia axis is at an earlier stage,[111] but systematic reviews have identified consistent associations between gut dysbiosis

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and Alzheimer's disease pathology, with proposed mechanisms including microbial modulation of neuroinflammation and amyloid aggregation.[112]

In psychiatric disease, the gut microbiota has been implicated in the pathophysiology of depression, anxiety and schizophrenia, primarily through immune and metabolic pathways including tryptophan-kynurenine metabolism, gamma-aminobutyric acid (GABA) signalling and systemic inflammation.[113–116] Systematic reviews of gut microbiota in patients with major depressive disorder have identified reductions in *Lactobacillus*, *Bifidobacterium* and *Faecalibacterium*, with corresponding enrichment of pro-inflammatory taxa. Probiotic interventions ('psychobiotics') have shown modest but statistically significant reductions in validated depression and anxiety scores in human RCTs, though effect sizes are small and long-term data limited. In schizophrenia, altered gut microbiota composition and increased intestinal permeability have been reported across multiple cohort studies,[117] though clinical intervention data in humans are lacking.

Neurodevelopmental disorders have attracted particular attention. In autism spectrum disorder (ASD), gut microbiota alterations, including depletion of Prevotella and enrichment of Clostridiales, have been reported consistently across paediatric cohorts, with GI symptoms being both prevalent and correlated with behavioural severity[118 119]; however, understanding these changes in the context of the restricted diets often seen in ASD has been challenging and is rarely controlled for in analysis.[120 121]

A landmark open-label study of microbiota transfer therapy in children with ASD demonstrated durable improvements in both GI and core autistic symptoms at 2-year follow-up, with parallel microbiota normalisation,[122 123] and RCTs are now in progress. The evidence base for attention deficit hyperactivity disorder (ADHD) is more nascent; population-level analyses and cross-sectional studies have identified differences in gut microbiota composition compared with neurotypical controls, with proposed links to dopaminergic and serotonergic signalling pathways, but microbiota-based interventional data are currently limited[124–127] by few RCT studies and small sample sizes. Collectively, while causal relationships remain to be firmly established in most of these conditions, the gut–brain axis represents one of the most dynamic and clinically consequential frontiers in microbiome research, with a growing portfolio of human intervention studies beginning to translate mechanistic insights into potential therapeutic strategies.

THE GUT MICROBIOME AS A DIAGNOSTIC OR PROGNOSTIC TOOL

The original review from a decade ago envisaged that taxonomic signals associated with or contributory to diseases may eventually have roles as diagnostic or prognostic tests.[1] Since then, interest has grown as the number of disease states with an association to the gut microbiota builds—coupled with the increasingly high throughput and availability of microbiome sequencing data. One particular example of the gut microbiota as a diagnostic was applied to almost 6000 stool metagenomes in IBD from patients with different ethnicities from different countries, looking to establish a multiplex droplet digital PCR test.[13] Such models achieved areas under the curve as high as 0.90 in the discovery cohort. While achieving numerically higher diagnostic performance overall than faecal calprotectin, results were broadly comparable. Given the low cost and ready availability of faecal calprotectin, the degree to which this test could meaningfully advance the current IBD diagnostic algorithm remains doubtful. One challenge related to the development of microbiome-based diagnostic tools in the context of chronic diseases such as IBD is that samples are often collected from patients with established disease, when it is increasingly recognised (primarily from induction IBD cohorts) that the chronicity of disease, medications, diet and other clinical factors modify the gut microbiota composition and functionality markedly compared with the point of diagnosis.[128 129]

A further area of interest has related to the use of the gut microbiome as a biomarker for response to a range of clinical interventions. In particular, high level diversity metrics of the gut microbiome have been associated with hard clinical endpoints such as mortality in haematopoietic cell transplantation, as well as solid organ transplantation,[130 131] demonstrating that the utility of the microbiome as a prognostic biomarker in these conditions. There has been similar promise shown in the use of the ileal microbiota to predict postoperative recurrence in CD.[132] While there is great enthusiasm related to the use of the gut microbiome to predict response to pharmacological agents, results are mixed across disease/therapy pairings. Specifically, there is evidence the gut microbiome may have a role in predicting response to ICIs in lung cancer patients,[133] but microbiome-based prediction of response to biologicals in IBD has given conflicting results, suggesting the need for further investigation within large, longitudinal cohorts of tightly-selected well-phenotyped patients.[134–136]

Based on the current status of research in the gut microbiome as a diagnostic tool, an international expert-based consensus recently stated that there is currently no proven value for direct-to-consumer testing.[137] Some of the concerns were the lack of reliable and reproducible panels of taxa, the lack of standardisation (in terms of the protocols for DNA extraction, sequencing, pipelines for data analysis and beyond) and opacity in certain cases of the control/comparator groups used. A recent study demonstrated marked variability between gut microbiome test results when different aliquots of the same stool sample were sent to different commercial direct to consumer microbiome testing suppliers.[138] As such, it remains the case that there is currently no condition where microbiome profiling has a clinical indication or can add to clinical care. However, it is hoped that a move towards standardisation of sequencing (as discussed in Section 5.1) will be overcome at least one major barrier towards moving research in this field meaningfully forward.

APPLICATION OF THE GUT MICROBIOME TO THERAPEUTICS

The area of perhaps greatest interest over the past decade with regards to exploitation of the gut microbiome in clinical practice relates to the gut microbiome and therapeutics. While this has seen many advancements and new avenues of research, there have also been challenges which have not been resolved in all cases. These are discussed below and summarised in figure 2.

Diet and the gut microbiome

In health, diet is widely recognised as one of the most important regulators of gut microbiota composition and function.[139 140] Diet supplies nutrients to the gut microbiota for its growth and the microbiota reciprocates by producing important metabolites for host health. In healthy individuals, diets rich in plant-based food and fibre (eg, vegetarian or mediterranean type diet) increase the abundance of fibre-degrading or fermenting microorganisms like *Faecalibacterium*, *Roseburia*, *Bifidobacterium* and *Prevotella*, whereas Western diets have been associated with increases in *Cutibacterium*/*Propionibacterium*, *Bilophila*

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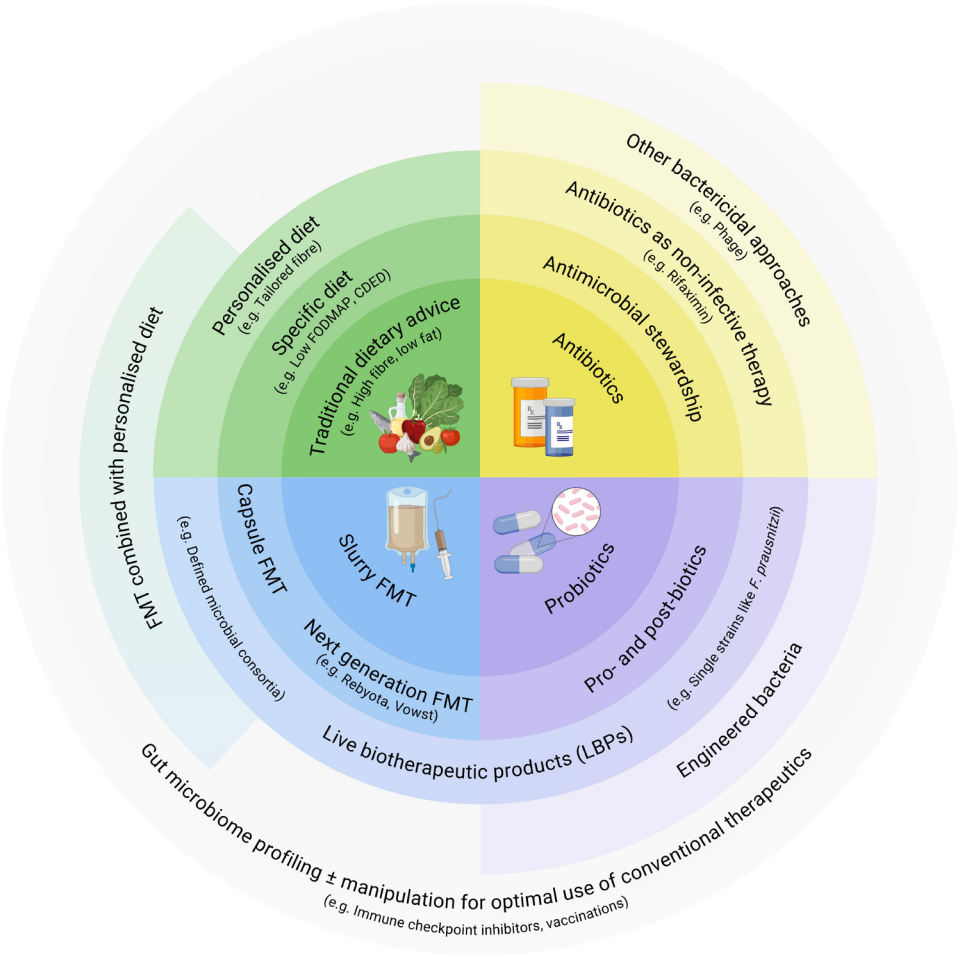

Figure 2 A summary of the evolution of key gut microbiome-related therapeutic advances over time. Progress across time is represented by increasing distance from the centre of the circle (although two boxes at the same radius from the centre of the circle do not necessarily represent developments occurring at the same time). Figure created using BioRender. CDED, Crohn's disease exclusion diet; FMT, faecal microbiota transplant; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; LBPs, live biotherapeutic products.

and *Alistipes* and associated harmful metabolite by-products like hydrogen sulphide and trimethylamine.[139 140]

Currently, there is significant interest in the effect of food industrialisation and food additives on the gut microbiome and host.[141] In preclinical and *in vitro* models, certain food additives caused microbiome perturbation and compromised gut barrier function, thus potentiating gut inflammation.[142–144] Nonetheless, these findings have either remained unconfirmed in clinical trials, or any positive signals observed were of modest size compared with those observed in preclinical experiments.[145]

As not all individuals harbour the same type of microbes, it is logical to assume that the effects of diet on the gut microenvironment and, by extension, to host health will vary too—more so in conditions associated with disturbance of the gut microbiome. For example, the *in vitro* ability of fermentable fibre to modulate the microbiota is diminished in patients with IBD[146] as compared with healthy controls, whereas unfermented fibre fuelled inflammation in select patients with the same condition, *ex vivo*.[147]

In the causal pathway linking microbiota to disease, diet can play several critical roles. Diet can confound the association between gut microbiota and development of disease, as in patients with coeliac disease on treatment with a gluten-free diet, where almost two-thirds of the alterations observed in the gut microbiome of the sufferers are attributed to their dietary habits.[148] The gut microbiota may also promote or prevent the effect diet has on disease development, like with the effect of trimethylamine N-oxide production from bacterial metabolism of dietary choline on development of atherosclerosis and cardiovascular disease.[140]

Gut microbiota-modifying dietary therapies have also been trialled alone or as adjunct to pharmacological agents to manage disease outcomes in patients with GI diseases. Collectively, the literature suggests that the effectiveness of dietary manipulation of the gut microbiome varies depending on the condition tested, even in conditions which are very similar and affect the same organ system.[149] Remarkably, even within the same condition, the therapeutic outcome of a dietary intervention can be dependent on the pretreatment microbiome signatures of individual patients. Vervier *et al* showed that the efficacy of a low FODMAP diet in patients with IBS was more pronounced in patients who had a pathogenic microbial community as opposed to those whose microbiome profile was similar to healthy individuals.[150] The microbiome of patients who responded better to a FODMAP diet was enriched in Firmicutes and genes for amino acid and carbohydrate metabolism but depleted in species from within the phylum Bacteroidota.[150 151] Likewise, in children with CD, efficacy of induction treatment with exclusive enteral nutrition, whose mode of action is mediated through the gut microbiome, could be predicted by pretreatment microbiome compositional and diet-originating bacterial metabolites, observations aligning

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to the concept of precision nutritional therapy.[151] There is scarce literature where dietary modification of the gut microbiome has been tested as an adjunct to pharmacological or other microbial therapeutics, although a few such studies exist, including potentially promising signals when an 'anti-inflammatory' diet was combined with FMT in treating UC,[152] or when UC patients received a dietary intervention and FMT from donors who had also received a dietary intervention.[153]

Probiotics and postbiotics

The global probiotics market has experienced significant growth and is currently valued at around US$100 billion, with compound annual growth rate of 14.1% projected until 2030.[154] The vast majority of research and commercial manufacturing is focused on live microbial therapy, termed 'probiotics', that is, live microorganisms which when administered in adequate quantities confer a health benefit on the host.[155] This is an example of microbial therapy which in most cases seeks primarily to use well-characterised, non-pathogenic bacteria to impact host physiology (or—less often—to modulate the recipient gut microbiome) and, in turn, improve the health of the host. Other emerging but less studied microbial therapies can circumvent the need to provide live microbes, such as postbiotics, which are preparations of inanimate microorganisms and/or their bioactive components that confer a health benefit on the host.[156] Here, the beneficial metabolites produced by probiotic species are provided without the live organism. Despite the promise of this field of research, we still have an incomplete mechanistic understanding of how such therapies improve health. Uncertainties remain related to which bacterial strain(s) should be used, balancing efficacy with safety. As one example, probiotics have been used in preterm infants with NEC for over a decade, and they are the most impactful factor governing microbiome development in this population.[157] While overall meta-analyses suggest they can reduce NEC risk,[158 159] there is a potential risk of sepsis from live probiotics in preterm infants with compromised intestinal barrier integrity.[160] Notably, this risk appears very low in clinical practice to date and removing probiotics will likely contribute to more deaths due to associated increased NEC rates.[161 162]

Where a microbial therapy is expected to promote health through gut microbiome modulation and competitive exclusion (ie, to occupy specific niches to prevent colonisation by potentially pathogenic microbes), using an appropriate live therapy is likely critical. Furthermore, ensuring that appropriate substrates exist within the ecosystem is necessary if probiotic colonisation is required for the intended outcome. The first generation of probiotics have often been produced based on convenience of manufacturing and shelf life over specific microbial properties. As research and commercialisation of microbial therapy continues to grow, it is critical to move to precision products to deliver the right therapy, to the right person, at the right time and potentially even in the 'right place' (recognising that different bacterial strains are adapted to colonise different areas of the GI tract). Achieving this vision will require parallel advances in the design and delivery of probiotic and postbiotic interventions, together with multiomics-driven elucidation of their strain-specific and context-specific mechanisms of action.[163]

Faecal microbiota transplant

A growing body of evidence has demonstrated that FMT (also sometimes called intestinal microbiota transplant)[164] is safe and superior in efficacy when treating rCDI compared with standard antibiotic therapy.[165] Only a very small number of studies have questioned its use.[166] FMT has also been approved in several national and international consensus documents and guidelines,[167 168] including from the UK National Institute for Health and Care Excellence, which takes account of cost effectiveness as well as clinical efficacy.[169] More recent data (including clinical trials) suggest an emergent role for FMT in the context of a first or second episode of CDI rather than the more conventional context of multiple recurrences.[170–172] The risks of FMT in treating CDI are overall relatively small and relate particularly to the risk of transmission of infection, with one particularly high-profile scenario being two immunocompromised patients developing bacteraemias (one fatal) related to extended spectrum beta-lactamase *E. coli* transmission via FMT.[173] A recent critical appraisal of the potential risk of infection transmission of different pathogens via FMT may help refine donor screening pathways.[174] Previous further concerns related to FMT safety related to potential transmission of microbiome characteristics from donor to recipient that might increase their risk of future disease. This has been one of the drives to FMT services collecting longer term follow-up data for patients and the establishment of FMT registries in certain territories. Where such data have been reported to date, there has been no concerning signal for the potential transmission of disease risk by FMT, either GI or otherwise.[175 176] The development of 'stool bank' models has helped to improve safe and equitable access to FMT, but there remains variability in access across different countries or even different regions within a country.[177]

Part of the complexity of delivering FMT services remains the uncertainty of the regulatory status of FMT as a drug, tissue or another entity. Within the UK, FMT retains the status of an unlicensed medicinal product,[178] while updated European Union guidance has incorporated intestinal microbiota into 'substance of human origin' guidance.[179] Regulation and governance associated with FMT use varies widely across the world.[180]

While FMT for rCDI is highly effective, the failure rate is small but appreciable; retrospective analysis of outcomes from high-throughput FMT centres has helped identify clinical factors related to donors, recipients and material preparation/administration that may influence outcome.[181 182] Biological factors underpinning the efficacy of FMT have started to be defined, including that the degree of engraftment of FMT (at least where treatment is occurring in antibiotic-pretreated patients) may impact the likelihood of success.[183] Other factors that have been explored related to FMT outcome including changes in gut microbial metabolites,[184–186] non-bacterial microbiome components (including bacteriophages),[187–189] host glycans,[190] microRNAs[191] and host immune response.[192 193] An initial pilot study using sterile filtered FMT suggested comparable efficacy of this product to 'standard' FMT in treating rCDI, suggesting that soluble mediators may be equivalent or more potent actors than live bacteria in driving the efficacy of FMT,[194] although a contrasting recent large RCT showed lower efficacy of sterile filtered FMT compared to unfiltered.[195] Collectively, while these biological factors give insight into the efficacy of FMT, they have not become criteria by which donors are selected in standard clinical practice.

FMT use has remained investigational in a wide range of clinical conditions.[165 196] While the outcomes have been variable between different studies, the overall conclusion is that FMT has been less successful in treating other conditions compared with rCDI. For example, there has been a signal for FMT having statistically improved efficacy compared with placebo in the induction of remission of mild to moderate ulcerative colitis

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(UC).[197] However, the clinical development of FMT in UC has been limited by underpowered studies with lack of standardisation in design, including varied inclusion criteria, timing of assessment and study endpoints. Furthermore, existing studies employ various methods of donor selection (single vs pooled), route of administration and dosing intensity, which makes results challenging to interpret and firm conclusions difficult to form.[198] Non-bacterial components of FMT (including the mycobiome and virome) are rarely considered in study design or mechanistic analyses.[199] In addition, there are further potential practical barriers that might limit the use of FMT in more routine clinical practice for non-CDI disorders such as UC, not least the scalability of this as intervention.

A further advancement has been the transition from slurry-based FMT preparations towards capsulised treatments. These were initially encapsulated slurry but are more frequently now lyophilised faecal material with cryo-preservatives and lyo-preservatives included (although a range of technologies are being explored).[200] While capsules have been demonstrated to be of comparable efficacy to colonoscopic slurry in the treatment of rCDI,[201] it is not clear that it is reasonable to expect this should be the case for use of FMT in other conditions. Additionally, uncertainties remain as to the ideal characteristics of a 'perfect capsule', and whether these should relate to number of colony forming units, the presence or absence of specific taxa, or aspects related to microbiome functionality.[200]

A number of 'microbiome therapeutic' companies have investigated 'next generation' FMT products, with two such products now licensed in North America for the treatment of rCDI, one full faecal microbiota, donor-derived product administrated *via* the lower GI route (Rebyota),[202] and a donor-derived Bacillota spore-based encapsulated product (Vowst).[203 204] There has only been a limited retrospective comparison of FMT compared with these novel agents[205] but no prospective comparison by which to estimate relative efficacy. Next generation FMT products have also been used in investigational studies in the non-CDI setting, although with variable outcomes. For instance, another full faecal microbiota, donor-derived product has reported positive phase III data in the setting of treatment of refractory GI graft-versus-host disease[206]; conversely, a donor-derived spore-based product showed negative results in a phase II clinical trial for the treatment of UC.[207]

Future microbiome therapeutics

There is considerable academic and industry-based interest in the potential therapeutic role of 'live biotherapeutic products (LBPs)' in clinical practice, principally through the use of defined microbial consortia. One such approach to this is culturing bacteria from the stool of healthy screened donors and using clinical and biological criteria to select out non-pathogenic bacteria for inclusion in a bacterial cocktail; one high-profile use of that was the RePOOPulate study, when 33 isolates from FMT stool donors were shown as efficacious in treating rCDI.[208] An alternative approach is selecting out gut bacteria from large culture libraries, using model systems to establish potential efficacy, before combination into a product. As an example of the latter approach—a microbial consortium of eight defined non-pathogenic, non-toxigenic Clostridia strains showed positive outcomes in a phase II trial in the treatment of rCDI[204] and is currently being used in a phase III trial. While this approach is evidently of interest in non-CDI settings as well, some clinical trial results for LBPs have been disappointing despite showing preclinical promise, including a strain-based product being used in a phase II clinical trial for the treatment of UC that failed to meet primary endpoints.[209] One potential interpretation of the current data regarding 'next generation' FMT products and LBPs to date is that while a move towards targeted microbiota products that are not full-spectrum (and potentially not donor-derived) is attractive from the perspective of standardisation and regulation, the 'trade off' may be that a reductionist product loses complexity and potentially compromises efficacy. It is also arguable that this conflict reflects our lack of knowledge to allow us to do so.

A range of other approaches to microbiome therapeutics have been explored, but many currently remain at the exploratory/experimental stage. One such approach has been using synthetic biology to genetically engineer bacteria to alter their functionality, typically by using as a 'chassis' an established probiotic or commensal bacterium, such as *E. coli* Nissle 1917. It is then possible to 'knock in' or 'knock out' enzymatic function to alter metabolic function. This has been used successfully in a range of mouse models and other pre-clinical settings of disease, and even early clinical settings, but has not currently made the transition to clinical practice. For example, engineered *E. coli* Nissle 1917 was used to convert gut ammonia to L-arginine, with the vision that this would be a potential treatment strategy for HE and/or urea cycle disorders. Gavage of these bacteria reduced systemic hyperammonaemia and improved survival in mouse models of liver injury and urea cycle disorder and increased urinary nitrate in a phase I trial; however, a phase Ib/IIa trial was stopped early for futility, highlighting the challenges of translation from a preclinical to clinical setting.[210] One such challenge may relate to limited colonisation of such engineered bacteria; this has resulted in attempts to use native bacteria as the chassis for transgene delivery, with apparent success in a preclinical setting.[211 212] Further concerns relate to trying to identify a truly 'safe' bacterial chassis to use; for instance, *E. coli* Nissle 1917 has been described as producing colibactin, a genotoxic metabolite that has been linked to CRC pathogenesis.[213] Collectively, such issues with engineered bacteria strongly suggest that they will need restricted use and close regulation should they make the transition to clinical practice.

An alternative therapy of interest is the use of bacteriophage ('phage') therapy, that is, exploitation of viruses intrinsic to the gut microbiota, with high host specificity of these viruses for targeting specific bacteria. One attractive aspect of phage therapy is the potential for 'precision medicine', that is, selective targeting of pathogenic gut bacterial strains while minimising disruption to the commensal gut microbiota. This is of particular interest in AMR, where a phage that targets a specific AMR target could treat infection but without the risk of selection pressure for further drug resistance and/or the risk of secondary infection.[214] Furthermore, phages can self-amplify at the site of infection, providing a sustained therapeutic effect.[215] Extensive resources are required for the manufacturing of any bacteriophage—which will be amplified if this will be required at GMP level for use as a human therapeutic—and this will be among the barriers to its wider use.[216]

Interactions between the gut microbiome and conventional therapeutics

The interaction between (non-antibiotic) drugs and the gut microbiome is complex, bidirectional and an avenue of interest that had not previously been well-envisaged at the time of the 2016 review in this journal. This phenomenon is increasingly recognised to play a role in the heterogeneity in therapeutic

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response and the development of adverse events to drugs given the metabolic capacity of the gut microbiota. Drugs like proton pump inhibitors, metformin, laxatives, selective serotonin reuptake inhibitors and antibiotics can directly alter microbial growth and/or influence gut microbiota composition.[217] Conversely, the microbiota can also modulate drug responses through direct enzymatic interaction as is shown for, for example, the presence of specific microbial acetyltransferases that lead to 5-ASA inactivation.[21] In PD, the activity of gut bacterial tyrosine decarboxylase has been shown to restrict levodopa drug availability.[218] However, an area of interest which has generated particular clinical excitement in recent years is the interaction between the gut microbiome and therapies that target the immune system, as discussed in the following two sections.

Combining microbiota manipulation with immune-targeting therapies

The microbiome can influence therapeutic response indirectly via host-mediated immune responses, which is exemplified by the association of the gut microbiota with the response to immune checkpoint blockade in cancer treatment.[219] An emerging therapeutic paradigm in oncology involves the combination of gut microbiome manipulation with immunotherapy, with early phase trial data pointing to a potential role for PD-1 inhibitors with FMT (including that derived from immune checkpoint responders) to enhance anti-cancer response.[220–222] The recent publication of the phase II FMT plus immunotherapy in non-small cell lung cancer and melanoma (FMT-LUMINate) and Targeted fAecal miCrobIoTa transplantiOn (TACITO) trials in non-small cell lung cancer, melanoma and renal cell carcinoma have further raised hopes that this approach is both safe and may have genuine clinical utility.[223 224] Conversely—there is a growing body of work demonstrating that immunotoxicity-related adverse complications in association with immunotherapy use are related to the gut microbiome[225]; by extension, there have also been reports that FMT may be an effective treatment for such complications of immunotherapy (although in non-randomised trial settings), and particularly checkpoint-inhibitor induced colitis which is refractory to immunosuppressive therapy.[226]

The focus of microbial therapeutics in other disease areas such as conventional IBD has been in treating milder disease, usually with FMT monotherapy. While data for FMT as an alternative to immunosuppressive therapies in mild to moderate UC are promising,[227] this is arguably not the group of patients with the largest unmet need. Indeed, in IBD and other chronic inflammatory disorders, existing immune-targeted treatments consistently fail to breach a 'therapeutic ceiling', leaving many patients without any effective treatment.[228] In response, combinations of immunosuppressive therapies with multiple mechanisms of action are now in advanced stage trials,[229] but such approaches bring increased safety concerns. With emerging evidence that gut microbiota composition prior to starting immunosuppressive therapies may be able to predict treatment response,[20] there is biological plausibility to use microbial therapeutics as adjuvants to prime responsiveness to these treatments. The paradigm of microbiome manipulation as an adjuvant to advanced immunosuppressive therapy has yet to be convincingly exploited.

Vaccination and the gut microbiota

Vaccinations induce varying levels of immune response, and postvaccination breakthrough infection rates and severity of infection vary greatly between individuals and populations. Such variation is not fully explained by known mediators of vaccine immunogenicity such as age and sex. The gut microbiota is critical in shaping host immune responses, and microbiota function has been proposed as a potential modulator of response to vaccination. In addition to numerous studies indicating a link between the gut microbiota and response to oral vaccines such as cholera,[230] rotavirus[231] and polio,[232] a growing body of evidence supports that notion of gut microbiome influence on the immune response to parenteral vaccination. In a seminal study, adults given a broad-spectrum antibiotic intervention prior to vaccination against influenza showed reduced H1N1-specific neutralisation and IgG1 and IgA binding antibody titres. Lower antibody titres were correlated with both bacterial and metabolomic phenotypes.[233] This finding was followed by several clinical studies during the COVID-19 pandemic that showed associations between baseline gut microbiota profiles and vaccine immunogenicity.[234 235] Across studies in children and adults, Actinomycetota (particularly *Bifidobacterium*) have been associated with superior responses to vaccination, and Pseudomonadota (particularly *Gammaproteobacteria*) have been associated with poorer responses.[236]

The ability of FMT to rescue impaired immune responses to several vaccines has been demonstrated in preclinical models.[237] There is murine evidence that microbiota-dependent diminution of mucosal IgA responses to oral cholera vaccination can be augmented by transfer of microbiota from a more responsive host.[238] Proposed mechanisms for microbial modulation of responses to vaccination include enhancement of B and T cell activity by microbially derived SCFAs[239] and direct engagement of pattern recognition receptors on antigen-presenting cells by immunomodulatory molecules such as peptidoglycan, which act as natural adjuvants.[240] Manipulation of the microbiota to enhance vaccination responses has been explored with probiotics, and meta-analyses suggest that these may enhance immunogenicity compared with placebo,[241] although studies in larger cohorts are needed.

CHALLENGES AND FUTURE PERSPECTIVES IN TRANSLATIONAL GUT MICROBIOME RESEARCH

Technical approaches to microbiome studies

A major challenge in microbiome research is a lack of reproducibility and comparability between studies. The scientific community has increasingly attempted to grasp this nettle in the last decade. Variations in biosample collection, DNA extraction methodology, sequencing protocols and bioinformatics tools can lead to inconsistent or even contradictory findings.[242–245] Global harmonisation of data cannot be achieved if studies rely on varying standards. Well-characterised reference reagents (RRs)—such as the WHO International RRs—provide a crucial global benchmark, ensuring reproducibility and comparability across studies, as well as acting as a primary calibrant.[246–248]

While large public datasets of the human microbiome now exist, combining them for large-scale analysis is difficult due to a lack of standardisation and data availability. Incorporation of initiatives such as the FAIR Guiding Principles for scientific data management and stewardship are vital to progressing microbiome science. The FAIR initiative was launched in 2016 and intended to provide guidelines to improve the Findability, Accessibility, Interoperability and Reuse of digital assets. While not microbiome-specific, the FAIR Principles[249] put specific emphasis on enhancing the ability of machines to automatically find and use data, in addition to supporting its reuse by individuals. Recently, curatedMetagenomicData (cMD) 3, a uniformly

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processed collection of over 22 000 human microbiome samples with manually curated metadata from 94 studies and 42 countries, was launched.[250] cMD 3 enables meta-analysis and comparison with published data and has proved effective across a wide range of health outcomes, including cardiometabolic diseases.[251] These initiatives reinforce the benefit of making data publicly available to progress the field. Equally, the studies highlight the importance of a multidisciplinary approach to identify and handle the data.

Predominantly, microbiome studies have focused on the bacterial microbiome and more integration of the other microbiomes—the virome (including phageome), mycobiome and archaeome (surveyed to some extent alongside bacteriome but warranting targeted or parallel methodology, as well as the contribution from multicellular organisms such as helminths - should be a priority. Indeed, there has been a recent move within microbiome research towards considering the 'holobiome' or the 'holobiont', describing the human host and their resident microbiome as a collective entity. Similarly, gut microbiome analysis has been predominantly undertaken on stool samples with a much smaller number of mucosal biopsy studies published. There remains a lack of consensus on the optimal approach to sample collection for microbiome analysis. Currently, the 'gold standard' protocol suggests collection of biopsies and/or fresh whole stool with immediate DNA extraction or freezing at −80°C. However, while achievable for biopsies, this is impractical for most stool-based research, especially community-based and/or longitudinal studies where participants often self-collect samples at home. Furthermore, given the growing appreciation of the distinctive characteristics of the small intestinal microbiome as compared with the colonic microbiome,[252] further consideration will be required for optimal routes of sampling of small intestinal content; ingestible 'capsule-like' devices have been one route explored,[253] with an alternative approach related to specialised nasoenteric tube sampling.[254]

Sample collection, transportation and preservation represent the first crucial steps to ensuring microbiome integrity and stability. Decisions on methodology reflect analytical laboratory preference, feasibility and cost. Consistency of (1) collection approach, (2) time elapsed between stool collection and DNA extraction and (3i) number of freeze-thaw cycles are all factors that impart a unique signature on microbiome profiles and require meticulous documentation within study data collection (box 1). While there have been significant efforts made to systematically assess and standardise DNA extraction protocols for human stool microbiome analysis and effective approaches for metagenomic analysis, there is a significant lack of data and consideration regarding collection methods for preserving microbiome integrity in community-based studies, which often use hub and spoke models for sample returns. For example, Costea *et al* explored the effectiveness of 21 DNA extraction protocols to strive towards standardising human faecal sample processing in metagenomic studies. To determine the most effective DNA extraction method and ensure no bias or other influencing factors were considered, multiple aliquots from two samples were made and shipped to 21 collaborating laboratories in 11 countries.[242] Within 4 hours of collection, test samples were homogenised and frozen at −80°C.[242] However, the study did not consider standardisation of the sample collection step, and the optimal DNA extraction protocol was incompatible with several DNA stabilising buffers. A further consideration related to this step of initial collection of samples relates to whether sequencing alone is planned, or further 'omic' analyses, including culturomics or metabolomics; for instance, certain stool collection tubes with

Box 1 Optimal design of a gut microbiome study in 2026

1. Study design
   - Define the primary hypothesis and the exact outcome(s).
   - Choose a study design that matches the question, with appropriate comparator/control groups.
   - Consider contribution/impact of biogeography and decide whether longitudinal and/or multisite/international studies are required to achieve desired outcome(s).
   - Undertake power and sample-size planning.
2. Define inclusion/exclusion criteria and collect rich metadata
   - Minimum metadata to collect (use MIxS/GSC templates as baseline): subject ID, age, sex, weight/BMI, ethnicity, medication/antibiotic history (with dates), recent diet/fasting, bowel movement timing/consistency (Bristol stool type and gut transit time), stool collection time/date, sample storage/transport conditions, comorbidities, smoking, alcohol, hospitalisation.
   - Standardise how and when metadata are collected (questionnaires, electronic forms). STORMS recommends transparent reporting of metadata collection and covariates.
3. Sample collection— reduce technical variability
   - Use a consistent collection protocol across all participants (i.e. same collection kit, same preservative or immediate freezing). Decide upfront whether you will use a stabilisation buffer (store at room temperature) or immediate freezing (at least −70°C). Validate that your chosen method preserves targets of interest.
   - Consider the sample collection method and transport system are compatible with the intended 'omics' approach.
   - Record time between defecation and stabilisation/freezing.
   - Train participants/staff and provide clear instructions to avoid heterogeneity.
4. DNA extraction, library preparation and sequencing choices
   - DNA extraction method matters—use a validated, reproducible method and keep it consistent across all samples. Include a method evaluation step if switching protocols.
   - Sequencing strategy:
     - *16S rRNA gene amplicon*—cheaper, quicker and simpler, good for taxonomic surveys down to genus (depends on region) but limited functional resolution.
     - *Shotgun metagenomics*—more expensive, requires more storage and data processing but provides species/strain resolution and functional potential (genes/pathways).
     - *Metatranscriptomics/metaproteomics/metabolomics*—for activity/metabolism questions (requires specific sample consideration alongside extra QC and handling).
   - Choose depth based on the research question (i.e. rare taxa detection vs community composition).
5. Controls, blanks and mock communities
   - Include negative controls (extraction blanks), PCR negatives and positive controls/mock communities and/or spike-in standards on each plate/run. These help detect contamination and batch effects and permit benchmarking of processes. Recent guidelines emphasise contamination prevention and reporting.
6. Lab design to avoid batch confounding
   - Randomise samples from different groups across extraction plates and sequencing lanes.
   - Process cases and controls in mixed batches.

Continued

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Box 1 Continued

- Track batch variables (extraction date, technician, kit lot) so you can control for them during analysis.

7. Bioinformatics and statistical analysis—use appropriate compositional tools
   - Predefine analysis plan (primary/secondary analyses), data transformations, alpha/beta metrics and differential-abundance approaches.
   - Use compositional-aware methods with caution and proper normalisation, and non-parametric methods for diversity. Account for covariates with mixed models when repeated measures exist. See best-practice reviews for recommended pipelines.
   - Share code, parameter settings, and raw data where ethically permitted.
   - Incorporate AI/machine learning (ML) approaches to generate predictive modelling, feature selection, network inference, longitudinal series modelling and causal inference.*
8. Experimental validation
   - Use appropriate experimental models (animal models, human-derived organoids, *in vitro* systems including continuous culture chemostats or cell line systems to develop mechanistic understanding
9. Data sharing
   - Where possible, share sequencing data on open access repositories or make it or associated metadata available to benefit the wider scientific community, applying FAIR principles.

*AI and ML can strengthen every stage of study design but need to be incorporated intelligently and ethically.
AI, artificial intelligence; BMI, body mass index; FAIR, Findability, Accessibility, Interoperability and Reuse of digital assets; GSC, genomics standards consortium; MIxS, minimum information about any (x) sequence; QC, quality control; rRNA, ribosomal RNA; STORMS, strengthening the organisation and reporting of microbiome studies.

specific preservation buffers have been demonstrated to allow ambient collection and transfer of sample without compromising mass spectrometry-based analysis of SCFAs (with the volatility of these molecules being a key factor to consider when trying to analyse them).[255] In addition, rectal swabs may be comparable to stool samples for measurement of key gut microbial metabolites,[256] with 3D printed swabs potentially being a further advance on this yet.[257]

Sequencing technologies and bioinformatic approaches now enable comprehensive mapping of the microbiome. While most of the published research focuses on taxonomic differences between disease states and health, more sophisticated bioinformatic approaches now allow for strain-level analyses, functional annotation, network analyses, metagenome assembled genomes, analyses of microbial genomic variation (eg, structural variation) and integration with other levels of high throughput 'omics', including metabolomics, transcriptomics and, increasingly, single cell transcriptomics. These approaches will yield more insight into the role of the microbiome in health and disease, beyond taxonomy.[258 259] Acknowledging confounding factors within clinical metadata such as BMI, sex, age, Bristol stool scale and antibiotic or proton pump inhibitor use is also essential for obtaining reliable results.

Demonstrating mechanism in microbiome studies

It remains the case that much of the microbial ecology literature is based on associative rather than causal experimentally validated studies. Correlation (even when augmented by other data types) rarely provides reliable information on direct biological interactions in real-world ecosystems. Spurious correlations illustrate the pitfalls of an increasingly data-rich age; the larger the dataset and the more analyses, the more correlations will be identified, many of which may not be biologically meaningful. Confusing correlation with causation can lead to incorrect assumptions and overinterpretations related to causal involvement of specific microbes in disease.

The field is now moving to a more-evidence-driven and mechanistically informed phase. One parallel development has been a return to hypothesis-testing with specific microbial candidates, boosted by advances in experimental approaches, such as the use of microbiome-depleted, germ-free and Wildling mouse models, synthetic communities and human organotypic cultures,[260] which will help to establish causal relationships between altered microbiomes and pathologic conditions. While discussion of experimental models in microbiome research is outside of the remit of this paper, some further information regarding this is provided in box 1.

Optimal delivery of translational microbiome research

The discussions above demonstrate that the optimal delivery of high-quality translational microbiome research requires skilled multidisciplinary teams and significant infrastructure. These are often centres where universities with expertise in microbiome research work closely alongside healthcare centres with clinical academics. From a research perspective, this requires scientific teams with expertise in 'wet' aspects of sequencing and laboratory experimentation together with the computational expertise/established data analytical pipelines required for modern microbiome studies.[261] From a translational standpoint, centres require the ability to recruit patients and optimally collect well-phenotyped samples, experience in delivery of trials, and the resource to manufacture and distribute FMT and/or other microbiome therapeutics. Examples of best practice have been recently described.[262]

CONCLUSIONS

The first 'mainstream decade' of translational and clinical gut microbiome research has been a period of huge progress moving from descriptive studies to the investigation of function and therapeutic intervention. However, this period has been characterised by multiple barriers. Critics of gut microbiome research have often highlighted the myriad of myths, misconceptions and occasional disinformation surrounding the field that have infiltrated both professional and lay domains to varying degrees.[263] A more realistic overview may be that the challenges and pitfalls encountered thus far do not reflect a failure of gut microbiome science—or the clinicians, scientists or other professionals involved in its stewardship *per se*—but represent the natural progression of a scientific field as it matures from initial discovery to deeper mechanistic understanding. The mission for the microbiome scientific community for the next decade should be to strive to avoid transmitting hype and sensationalist messaging, and focus more on scientific rigour, critique and causality—the toolkit for which the prior decade has helped to define.[264] Such an approach will help transform its credibility and translational utility.

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Acknowledgements The authors would like to acknowledge the British Society of Gastroenterology Gut Microbiota for Health Expert Panel (BSG GMfH; https://www.bsg.org.uk/gut-microbiota-for-health-expert-panel) for their contributions to the 2025 meeting that triggered this review, and for their support during the development of this manuscript. The authors would also like to thank Professor Julian Marchesi (Imperial College London) for discussions regarding this manuscript.

Contributors JLA, BHM, RH and GH originated the idea for the manuscript. JLA, BHM, LT, RKW, HS, LAR, LAE, AE, KG, LJH, THI, JMK, JM, TMM, CSe, DLS, CSt, CAL, RH and GH contributed to the writing of the first draft of the manuscript. LT, CAL and HRTW gave critical insight and review of the first draft of the manuscript. LAR prepared the figures. All authors read, edited and approved the final submitted document. RH and GH are the guarantors.

Funding The Division of Digestive Diseases at Imperial College London receives financial support from the National Institute of Health Research (NIHR) Imperial Biomedical Research Centre (BRC) based at Imperial College London and Imperial College Healthcare NHS Trust (award ID: NIHR203323). BHM is the recipient of a Medical Research Council (MRC) Clinician Scientist award (MR/Z504002/1). RKW is supported by the Seerave Foundation (grant number: N/A), the EU Horizon Health consortium grant ID-DarkMatter-NCD (101136582) and the EU Horizon Europe Program grant miGut-Health: Personalised blueprint of intestinal health (101095470). LJH is supported by Wellcome Trust Investigator Award (no. 220876/Z/20/Z) to LJH, and a Biotechnology and Biological Sciences Research Council (BBSRC) Institute Strategic Programme, Food Microbiome and Health BB/X011054/1 and its constituent project BBS/E/F/000PR13631, and BBSRC grant BB/Y011619/1. THI receives support from the NIHR University of Birmingham Biomedical Research Centre (grant number: N/A). TMM's lab is supported by a Medical Research Council (MRC) award (APP33164), Biotechnology and Biological Sciences Research Council award (BBSRC; BB/Y007336/1), a UK Cystic Fibrosis Trust Strategic Research Centre grant (SRC 023) and Wellcome Trust Climate & Mental Health award (321312/Z/24/Z). CSt is supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (221745/Z/20/Z) and the Lister Institute Prize Fellowship (grant number: N/A). CAL acknowledges research support from the NIHR Newcastle Biomedical Research Centre (grant number: N/A), Medical Research Council (grant number: N/A), The Leona M. and Harry B. Helmsley Charitable Trust (grant number: N/A), Crohn's & Colitis UK (grant number: N/A), EU Innovative Medicines Initiative (grant number: N/A), Wellcome Trust (grant number: N/A), Open Targets (grant number: N/A) and European Bioinformatics Institute (EMBL-EBI) (grant number: N/A). RH's laboratory is funded by The Archie Foundation (grant number: N/A) and RH is supported by academic time from Tayside Medical Science Centre (grant number: N/A). GH was supported by an Australian Research Council Discovery Project (DP210103897) and currently by National Health & Medical Research Council/MRFF–Genomics Health Futures Mission (MRFF 2025116) and the McCusker Charitable Foundation (grant number: N/A).

Competing interests JLA has received speaker fees from Pfizer, J&J, Abbvie, Tillotts Pharma and Takeda, and support to attend meetings from Takeda, J&J, Celltrion and Tillotts Pharma. BHM has received consultancy fees from Ferring Pharmaceuticals and speaker fees from Tillotts Pharma. LT has been employed by Yakult UK and received consultancy fees from PrecisionBiotics (Novonesis OneHealth). RKW acted as a consultant for Takeda; received unrestricted research grants from Takeda, Johnson & Johnson, Tramedico and Ferring; and received speaker fees from MSD, Falk, AbbVie and Janssen Pharmaceuticals. HS discloses receiving lecture fees, serving on boards or providing consultancy for Carenity, AbbVie, Astellas, Danone, Ferring, Mayoly Spindler, MSD, Novartis, Roche, Tillotts, Enterome, BiomX, Takeda and Biocodex. Additionally, HS holds stocks in Enterome and is a co-founder of Exeliom Biosciences. LAE has previously served as a consultant for EnteroBiotix. KG received research funding or speaker's fees from Nestlé Health Science, Nutricia Danone, Abbott, Baxter, AbbVie, Janssen, BMS, Eli Lilly, Mylan, Servier. THI has research support funding from Hoffman-La Roche and received lecture fees from Pharmacosmos. JMK discloses speaker fees from Yakult and is a shareholder in Intus Biosciences. DLS has previously served as a consultant for Norgine, Alfa Sigma, EnteroBiotix, GenFit, Satellite Bio, Apollo Therapeutics and MRM Health. JM is employed by and holds shares in EnteroBiotix Limited. Additionally, JM discloses consultancy fees for Elicit Research and sits on the Advisory Board for EMIH. CSe was employed by the Medicines and Healthcare product Regulatory Authority (MHRA); the MHRA laboratories at South Mimms are part of an arm's length body of the UK Government. CSt declares lecture honoraria from Nestlé Nutrition Institute. CAL acknowledges research support from Janssen, Takeda, AbbVie, AstraZeneca, Eli Lilly, Orion, Pfizer, Roche, Sanofi Aventis, UCB, Biogen, Genentech, Bristol Myers Squibb (BMS), GSK and Merck Sharp and Dohme (MSD); acknowledges consultancy for MSD, Takeda, Polaroid Therapeutics, Janssen and BMS; and has received honoraria for development and/or delivery of education from Takeda, Ferring, Janssen, Dr Falk, Lilly and Nordic Pharma. HRTW has received fees from Takeda, Pfizer and Tillotts Pharma. GH has received grant funding from Ferring and Pfizer, honoraria from AbbVie and Ferring. All other authors declare that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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