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The promise of the gut microbiome as part of individualized treatment strategies

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Abstract

Variability in disease presentation, progression and treatment response has been a central challenge in medicine. Although variability in host factors and genetics are important, it has become evident that the gut microbiome, with its vast genetic and metabolic diversity, must be considered in moving towards individualized treatment. In this Review, we discuss six broad disease groups: infectious disease, cancer, metabolic disease, cardiovascular disease, autoimmune or inflammatory disease, and allergic and atopic diseases. We highlight current knowledge on the gut microbiome in disease pathogenesis and prognosis, efficacy, and treatment-related adverse events and its promise for stratifying existing treatments and as a source of novel therapies. The Review is not meant to be comprehensive for each disease state but rather highlights the potential implications of the microbiome as a tool to individualize treatment strategies in clinical practice. Although early, the outlook is optimistic but challenges need to be overcome before clinical implementation, including improved understanding of underlying mechanisms, longitudinal studies with multiple data layers reflecting gut microbiome and host response, standardized approaches to testing and reporting, and validation in larger cohorts. Given progress in the microbiome field with concurrent basic and clinical studies, the microbiome will likely become an integral part of clinical care within the next decade.

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Author contributions

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Competing interests

P.C.K. serves on the advisory board of Novome Biotechnologies and is an ad hoc consultant for Otsuka Pharmaceuticals, Pendulum Therapeutics and IP group. The other authors declare no competing interests.

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Inter-individual variability in disease presentation, treatment response and adverse effects of treatment presents a major challenge for the effective management of disease and patient safety. This realization is foundational to precision medicine, which in its simplest form can be described as identifying the right treatment for the right patient without trial and error using an individualized approach. Initial paradigms into the realm of precision medicine have focused on subtyping patients based on host genetics and a range of clinical and laboratory features, for instance, the genetic make-up of tumour tissue[1]. This process has led to substantial improvements in predicting the efficacy and toxicity of therapies[2]. However, the host genome represents only part of the genes of the superorganism as the genetic and chemical diversity of the microbial communities in and on our body is greater than that encoded in the human genome[3]. As individuals harbour a unique and widely variable gut microbiome it is not surprising that it contributes to the heterogeneity in disease phenotype as well as to treatment response[4].

An aspect that differentiates the gut microbiome from human genetics is that it represents a dynamic component of our health, continuously interacting with both host and environmental factors through complex networks. Although a potential challenge, the plasticity of the gut microbiome also offers a unique opportunity, making it an appealing target for precision medicine[5–8]. Several categories and levels of microbiome-based therapeutics currently exist, with variable specificity in targeting the microbiome. Faecal microbiota transplantation (FMT), the least targeted approach, involves the transfer of faeces in its entirety from one individual to another to attempt to repopulate the gut with ‘healthy’ microbiota[9]. Probiotics (live microorganisms that have presumed health benefits with adequate administration) have potential for targeted therapy, although most current formulations used in clinical practice lack the required specificity[10]. Prebiotics are compounds that are selectively digested to stimulate the growth or activity of beneficial organisms, thus with much potential for the personalization of therapy[11]. Synbiotics, which are a mixture of microorganisms and substrates that are selectively utilized by the host to achieve some health benefit, offer even further space for the personalization of microbiome-related therapeutics[12]. Besides supplementing specific compounds in their purified form, the dietary intake of foods known to be rich in prebiotic compounds is another possible avenue for shifting microbiota populations. The accumulating data on specific microbiota-driven mechanisms underlying disease pathogenesis, prognosis and treatment outcomes has led to the investigation of a multitude of additional approaches, including but not limited to engineering bacteria to perform specific functions, small-molecule drugs and biologic agents that alter microbial function or its interaction with the host, and native or engineered phages to alter microbial composition and function[13,14].

In this Review, we summarize the current evidence in support of using the gut microbiome as a tool for precision medicine and suggest future work needed to incorporate the microbiome as a tool for individualized treatment or interventions. We selected six broad disease groups that have a relatively strong level of evidence for a role for the gut microbiome. Although there are exciting developments in every disease group, the level of promise and maturity when considering clinical impact varies among the different disease groups (FIG. 1; Supplementary Fig. 1). We discuss the disease states from the highest to the lowest maturity of knowledge for clinical practice. Within each section, we aimed to

provide information on known taxonomic associations and microbiota mechanisms within the condition, currently used microbiome-directed therapeutics, the role of gut microbiome in predicting treatment response and toxicities, and finishing with an outlook on novel microbiome therapeutics. Given the current differences in evidence between these disease states regarding the gut microbiome, this organization is not entirely uniform across sections. Instead of providing an exhaustive overview of the gut microbiome in each disease state, we aimed to highlight studies that are relevant to the field of precision treatment and synthesize the current status and maturity of this rapidly developing field. The Review provides convincing evidence to support incorporation of the microbiome in clinical practice whilst acknowledging the challenges and outlining a path to get closer to this goal.

Infectious disease

The mechanisms involved in antibiotic-induced disruption of the gut microbiome in facilitating opportunistic and nosocomial infections are a topic of intense interest. We use the example of *Clostridioides difficile*, which is the most common nosocomial diarrhoeal infection[15], to highlight microbiome and pathogen-specific features that might explain the inter-individual variability in clinical outcomes. Recurrent *C. difficile* infection (CDI) has been a central focus of microbiome research from the advent. CDI most commonly follows antibiotic use and, paradoxically, the first-line treatment of CDI also consists of antibiotics[16]. Although antibiotics are quite effective at the population level, subsets of patients either fail therapy or CDI might recur after successful treatment, which could be related to host features, such as advanced age, or to the use of medications, such as proton pump inhibitors[17], combined with features of the specific pathogens in context of the gut microbiome.

In addition to host factors, disruption of gut microbiota has been found to be a key factor underlying CDI. Those with CDI were found to have an elevated relative abundance of *Enterococcus*, *Veillonella*, *Lactobacillus* and Gammaproteobacteria species and lower levels of *Bacteroides*, Lachnospiraceae and Ruminococcaceae species in comparison to healthy individuals as controls[7,18]. Moreover, when modelled in germ-free mice, alterations in the gut microbiome driven by a range of host factors increased susceptibility to CDI as a result of elevated amino acid availability, which is a favoured nutrient niche of *C. difficile*[19]. Similarly, other studies using mouse models have identified loss of microbiota-derived inhibitory factors as well as an increase in open nutrient niches in CDI, which include decreases in levels of short-chain fatty acids (SCFAs) (specifically valerate) and the secondary bile acid deoxycholic acid and increased levels of the organic acid succinate, sialic acid and amino acids[20–23]. These microbiome-driven factors that increase susceptibility to CDI vary among individuals and not every individual that develops CDI exhibits all of these abnormalities.

In addition to the gut microbiome, strain to strain variability of *C. difficile*, such as variation in toxin production, metabolism and biofilm formation capacity, might contribute to different outcomes. A study using whole-genome sequencing of ~400 clinical isolates from patients with CDI found that the majority of disease recurrences are caused by the same strain as the initial infection, which suggests that strain-specific features that

enable persistence in the gut might be relevant for recurrent disease[24]. The organization of *C. difficile* into multicellular biofilms could allow persistence as biofilms can provide a physical barrier against antibiotics and can interfere with clearance from the gastrointestinal tract[25]. Hence, diagnostic tests that incorporate whole-genome sequencing along with the metabolic milieu in the gut and the specific microbial taxa will likely provide greater resolution when considering individualized treatment approaches.

The current approach for treating multiple recurrent CDI or treatment failure involves FMT, which has been remarkably effective in treating recurrent CDI, irrespective of the route of administration, the degree of engraftment or specific features of the donor gut microbiome[26]. The primary feature that predicts FMT failure is continued antibiotic use[27]. Despite its efficacy, there are concerns about the long-term safety of FMT, which are now being investigated in a long-term registry[28]. In addition, the question remains as to how to best screen for donor stool. Should this screening be conducted using metagenomics or pathogen whole-genome sequencing to identify the antibiotic resistance profile or is culture or PCR-based screening for pathogens sufficient? The usefulness of a whole-genome sequencing-based approach is illustrated by two clinical trials with cases of bacteraemia with extended-spectrum β-lactamase-producing *Escherichia coli* linked to donor stool[29]. This safety concern of FMT is especially relevant for immunocompromised patients.

Beyond FMT, the gut microbiome has also been found to be predictive of treatment outcomes in CDI. At the taxonomic level, the pre-treatment abundance of Ruminococcaceae, Rikenellaceae, *Bacteroides* and *Faecalibacterium* has been associated with a positive response to antibiotics in CDI and higher levels of Clostridiaceae, Lachnospiraceae, *Blautia*, *Coprococcus*, *Streptococcus*, *Bifidobacterium*, *Ruminococcus* and *Actinomyces* were associated with non-response in a study including 88 patients with CDI[30]. Some of these taxa also predicted the risk of recurrent infection[30], whereas other taxa have been associated with an overall inability for *C. difficile* to colonize the gut31 (FIG. 2).

The increased understanding of microbiome-driven mechanisms underlying CDI and the prognostic role of the gut microbiome in treatment outcomes, combined with uncertainty regarding long-term risks of FMT, have led to a surge in microbiota-based diagnostics and therapeutics for CDI. The most advanced among these are defined microbial consortia, which showed promise in phase II clinical trials[32] and have now been reported to be successful in phase III clinical trials[33,34]. In addition, there are several approaches utilizing specific bacteria and/or metabolites, prebiotics, and phages that are in early stages of investigation. These narrow range treatment modalities will likely allow for more personalized therapeutics based on host and host microbiome features, potentially further increasing the efficacy and decreasing the risk surrounding treatment of CDI[35]. This progress provides optimism for the development of future, more precise microbiota-based treatment strategies in CDI (TABLE 1).

Cancer

The gut microbiome can inform the field of personalized cancer biology from four different perspectives: inhibiting cancer development, identifying novel treatments, optimization of

existing treatments and cancer diagnostics. In regard to cancer development and identifying novel treatments, these issues relate to imperfect functioning of the gut microbiome–immune system axis, which contains both immune inhibitory and immune stimulatory roles for the gut microbiota and the tumour tissue itself[36]. The optimization of existing treatments relates to reducing adverse effects and predicting response to cancer therapies that range from chemotherapy and radiation therapy to new immunotherapy approaches. Here, the role of the gut microbiome in metabolizing drugs as well as affecting immune cell and cytokine levels can result in changes in therapeutic response and in the development of adverse effects.

Microbiome links to cancer

Mechanistic knowledge of the gut microbiome–immune system axis can be explored both to intercept cancer development and to identify novel treatments. Cancer development and disease progression can be influenced through the oncogenic effects of microorganisms and their products, modulating circulatory metabolite levels that might promote or inhibit tumour growth, and inducing pro-inflammatory and immunosuppressive effects[37,38]. Localized alterations of microbiota have been identified in association with the development and degree of progression of cancers involving organs that harbour commensal organisms (colorectal, cervical, lung, head and neck)[37]. The mechanistic connection between the gut microbiome and cancer is most evident in colorectal cancer[39]. The intricate relationship between microorganisms and their metabolites with the gut mucosa can lead to changes in mucosal permeability increasing localized exposure to a wide array of potential carcinogenic compounds and potentially leading to a chronic inflammatory state[39]. Another example of a mechanistic link is the presence of *E. coli* strains that carry the pathogenicity island *pks*, which encodes genes to synthesize the genotoxic secondary metabolite colibactin and could be used to predict colon cancer risk[40]. Outside of defined mechanistic features, differences in gut microbial composition and functional attributes have been associated with malignancy in organs with less direct contact[37]. For example, a study involving 68 patients with pancreatic cancer suggests that the abundance of *Pseudoxanthomonas*, *Saccharopolyspora* and *Streptomyces* in tumour tissue is associated with long-term survival after surgical resection in comparison to those with poorer outcomes[41]. These protective effects were transferred via faecal transplantation in a mouse model, suggesting FMT as a potential treatment modality that needs further consideration broadly, at least in adjunctive form[41].

Microbiome and cancer therapeutics

The response to both chemotherapy and immunotherapy can be influenced by the gut microbiome in regard to both efficacy and toxicity[42]. This relationship can be due to synergistic effects in antigen presentation, the induction of inflammatory responses and the chemical modification of drugs[42]. For example, cyclophosphamide, a widely used alkylating agent that induces DNA crosslinks, in part imposes its antitumour effects by modulating the immunological pathways[43,44] linked to the generation of specific T helper 17 (T_H17) responses after bacterial translocation to secondary lymphoid organs in a mouse model[45]. In a mouse study on the type 1 immune response-inducing CpG-oligodeoxynucleotides and the DNA crosslinking agent oxaliplatin, therapeutic efficacy was reduced in the presence of antibiotics, which was attributed to reduced tumour necrosis factor (TNF) production by tumour-associated myeloid cells[46]. This antibiotic-induced reduction of oxaliplatin

efficacy is likely multifactorial given that its therapeutic effect is partly driven by the production of reactive oxygen species by the gut microbiota[46]. Finally, the microbial metabolism of gemcitabine by the action of bacterial cytidine deaminases to generate 2′,2′-difluorodeoxyuridine can reduce its therapeutic effect[47].

In addition to chemotherapeutic agents, there is increasing evidence for the importance of the gut microbiota in determining the effectiveness of cancer immunotherapy. In humans, reduced progression-free survival and overall survival has been associated with the use of antibiotics with immunotherapy in multiple cancer types (non-small-cell lung cancer, renal cell cancer and urothelial carcinoma)[48,49]. This finding has been further investigated using animal models that suggest a role of immune-mediated mechanisms in these negative effects of antibiotics. The efficacy of ipilimumab, a CTLA4 inhibitor, was improved in mice when the *Bacteroides* species *B. fragilis* and *B. thetaiotaomicron* and *Burkholderiales* were present at increased abundance, which was linked to the upregulation of IL-12-dependent T_H1 immune responses[50]. In a mouse model of colon cancer, efficacy of CTLA4 blockade was enhanced in the presence of *Bifidobacterium pseudolongum* through immune activation from increased translocation of inosine facilitated by the decreased mucosal barrier function resulting from treatment[51]. IL-12 has also been found to play a role in CCR9+CXCR3$^+$CD4$^+$ cell recruitment to epithelial tumours in mice, which in turn has been associated with an elevated abundance of *Akkermansia muciniphila* in the human gut microbiome[48]. The effect of PD1 and PDL1 checkpoint inhibitors against melanoma can be enhanced in mice with increased abundance of *Bifidobacterium* species[52]. Interestingly, *Bifidobacterium* species might even have anti-melanoma effects in the absence of conventional therapy as its abundance pre-treatment in the same mouse population was associated with tumour growth suppression[52]. This effect is thought to be related to the upregulation of dendritic cell function, leading to enhanced activity and accumulation of CD8$^+$ T cells in the tumour microenvironment[52]. The efficacy of PD1 inhibitors in treating melanoma was also enhanced in the presence of a higher abundance of *Bifidobacterium longum*, *Collinsella aerofaciens* and *Enterococcus faecium* in a study of 42 patients with metastatic disease[53] whereas, in a separate human cohort of 43 patients with melanoma, increased microbiome diversity was associated with improved cancer survival after PDL1 and PD1 therapy[54]. Specifically, Ruminococcaceae, Firmicutes, *Eubacterium* sp., Clostridia, Clostridiales and *Faecalibacterium prausnitzii* were enriched in patients who were responsive compared with those who were non-responsive (FIG. 2).

The toxicity of chemotherapeutic agents can be a major factor dictating their ability for use. Drug metabolism can be altered by the gut microbiota in several ways, including by competitive inhibition, direct metabolic effects of gut microorganisms and altered host expression of genes involved in metabolic pathways, as seen with the downregulation of xenobiotic detoxifying genes in germ-free mice[55,56]. Specifically, the toxicity of anticancer agents, such as 5-fluorouracil (5-FU), irinotecan and sorafenib, has been attributed to gut microbial metabolism. The toxicity of the DNA replicator 5-FU when co-administered with the viral DNA polymerase inhibitor sorivudine in a rat model results from reduced metabolism of 5-FU induced by the microbial product of sorivudine transformation, bromovinyl uracil (BVU)[42,57,58]. Knowledge of the specific biochemical pathways responsible for the formation of BVU could help predict this toxicity to inform

alternate treatment options or the development of specific inhibitors of BVU formation. Administration of the topoisomerase inhibitor irinotecan is commonly hindered by the development of severe diarrhoea[42], linked to bacterial β-glucuronidase-mediated reactivation of inactive irinotecan metabolites[59]; antibiotic treatment has been shown to decrease production of the active irinotecan metabolite in vitro60, administration of a probiotic cocktail that lowers β-glucuronidase activity improves diarrhoea in patients with colon cancer and small-molecule inhibitors of glucuronidases have shown promise in preclinical mouse models[59,61,62]. The tyrosine kinase inhibitor, sorafenib, is another agent whose toxicity might be related to gut microbial activity as both diarrhoea and hand–foot syndrome following sorafenib administration in patients with hepatocellular carcinoma were associated with specific microbial taxa[63] (FIG. 2). Specifically, an abundance of *Veillonella*, *Bacillus*, *Enterobacter*, *Faecalibacterium*, *Lachnospira*, *Dialister* and *Anaerostipes* were protective against hand–foot syndrome, with abundance of *Butyricimonas* and lower levels of *Citrobacter*, *Peptostreptococcus* and Staphylococcaceae associated with less development of diarrhoea. The mechanism underlying this effect might be diminished by enterohepatic recycling of the medication and its metabolites[63]. A study of patients with metastatic renal cell carcinoma treated with other tyrosine kinase inhibitors (pazopanib and sunitinib) showed improvement in treatment-induced diarrhoea when treated with FMT from healthy donors versus placebo, further implicating these alterations in the microbiome in relation to this adverse effect[64]. The development of activity-based protein probes to identify the specific microbial pathways responsible for xenobiotic metabolism holds promise as a diagnostic tool and might enable better stratification of treatments[65].

Novel therapeutics could use bacterial strains or purified pathogen-associated molecular patterns that function as Toll-like receptor (TLR) agonists to trigger local immune responses in patients with low levels of TLR stimulation[37]. In addition, levels of faecal and circulatory microbial metabolites that can affect tumour growth (SCFAs, secondary bile acids, vitamins and polyamines) could be used to assess metabolic health status before treatment and, in turn, influence a next generation of biotherapeutics, perhaps in combination with dietary intervention[37]. A range of immune cell subsets (T_H17 cells, T regulatory (T_{reg}) type 1 cells, cytotoxic T lymphocytes, $CD4^+$ cells, $CD8^+$ cells) and cytokine abundances (TNF, IL-12, IL-22 through aryl hydrocarbon receptor (AHR) signalling) are affected by changes in the gut microbiota and might be modulated to influence cancer immunosurveillance. Measurements of such markers can also lead to the assessment of immune health of the patient and provide a target for intervention. These approaches will require detailed personalized multi-omic studies on large cohorts before they can be embraced in the clinic.

The studies thus far provide strong support for a role of the gut microbiota in both the heterogeneity of cancer phenotypes and response to cancer therapy. However, data from human studies are largely associative and still need to be replicated across cohorts. The mechanistic data are obtained primarily from animal studies, raising some concern about translational validity. Despite these concerns, the outlook remains optimistic and integration of the microbiome as a component of treatment strategies in cancer seems inevitable (TABLE 1).

Metabolic disease

Obesity

The number of children and adults with overweight or obesity is growing, with over 40% of adults in the USA now meeting criteria for obesity[66]. A major challenge in tackling obesity is the complexity of mechanisms resulting from the interplay of genetics, gut microbiome, diet and environment, which result in physiological changes contributing to obesity.

Microbiome links to obesity.—A meta-analysis published in 2016 of curated human microbiome studies found a small but statistically significant association between obesity and lower within-sample alpha diversity metrics of richness and evenness[67]. Besides alpha diversity, an elevated Firmicutes to Bacteroidetes ratio in obesity has been reported in early microbiota studies both in mouse models and human studies[68–72] but was not replicated in this meta-analysis[67]. Despite the lack of robust compositional markers, a role for gut microbiome in obesity is supported by transplantation experiments showing that germ-free mice colonized by stool from monozygotic twins discordant for obesity exhibit the metabolic phenotype of the donor[73]. This premise is further strengthened by the observation that weight gain induced by a high-fat diet compared with a low-fat plant polysaccharide diet in humanized mice (germ-free mice colonized with stool from healthy human) can be transmitted to recipient germ-free mice by just transplanting faecal samples from these humanized mice without requiring continued feeding of a high-fat diet[74]. This finding suggests that the microbiome is important in propagating the obesity phenotype even if it was initiated by other causes. Several mechanisms underlying obesity have been attributed to the gut microbiome such as an increased efficiency of energy extraction from diet, influencing satiety and energy intake, systemic inflammation, and insulin resistance[75–78].

The lack of consistent compositional markers in obesity suggests substantial functional redundancy. Indeed, there is less redundancy at the functional level as shifts in several different microbial community configurations can drive changes in production of an array of bioactive factors such as SCFAs, bile acids and lipopolysaccharides (LPS), all of which have been implicated in obesity[79]. SCFAs play a role in hormonal signalling, such as that of serotonin and peptide YY release, which play a role in satiety, implicating involvement of the gut–brain axis in driving obesity[80]. Although there have been major advances in the understanding of microbiome-driven mechanisms underlying obesity, we do not yet have sufficient resolution to stratify individuals with obesity based on underlying microbiome-based mechanisms. With accumulating evidence in this area, one can easily envision the microbiome-based stratification of individuals to be part of future personalized strategies for obesity management[81]. The efficacy of probiotics as a therapeutic regimen for obesity has been suggested in animal models but the results of clinical trials in humans have been mixed and, given the lack of consistency in probiotic formulations used, their role remains unclear at this point[82]. With regard to the use of prebiotics therapeutically, again there have been encouraging findings in animal models but there is yet to be any clear crossover into humans in clinical trials in terms of durable weight loss[83].

Microbiome and obesity therapeutics.—The main therapeutic approaches in the management of obesity are diet, medications (such as glucagon-like peptide 1 (GLP1) agonists, orlistat and phentermine) and bariatric surgery. Diet can affect the gut microbiota both in the short and long term, with alterations occurring in response to brief dietary changes[84]. More importantly, the therapeutic effect of diet is also dependent on an individual's microbiome[84,85]. In simplifying the gut microbiome to 10 microbial strains in germ-free mice it was demonstrated that dietary modifications alter the colonization pattern of the gut and its fermentative capabilities[86]. One approach to dietary modification in individuals with obesity is increasing the consumption of fruits, vegetables and low-energy density foods whilst concomitantly reducing the intake of foods with high nutrient density; however, the response to such an intervention is quite variable. A pilot study in 26 individuals with overweight or obesity found that a high predicted abundance of glycoside hydrolases in the gut microbiota prior to such a dietary intervention was associated with <5% body weight loss following volumetric dietary intervention, suggesting a potential role for the baseline gut microbiome in predicting outcome[87]. These findings are in line with inter-individual variability in glycaemic response and lipaemia following meals, which has been attributed to the gut microbiome[88–90]. Increased calorie intake has been associated with rapid alteration of the gut microbiome in humans within 3 days in a population of 21 healthy individuals, including individuals with normal (between >18.5 and <25) and high (≥30) BMI, showing an increased relative abundance of Firmicutes and depletion of Bacteroidetes[91]. These changes were associated with increased energy harvest as evidenced by reduced stool caloric content. Hence, reducing caloric intake might exert a beneficial effect by modifying the microbiome in subsets of individuals with obesity[76,77,92]. The relative abundance of gut bacteria, such as *Eubacterium ruminantium* and *Clostridium felsineum*, has also been associated with increased microbiome plasticity in response to several variable dietary interventions in a group of 78 individuals with obesity[93]. Together, these studies suggest that the concept of some foods being 'healthy' for everyone is too simplistic and that dietary choices based on gut microbiome metrics might be beneficial in regard to weight management[94].

Few studies have examined the gut microbiome in the context of pharmacological and surgical treatments against obesity. However, the GLP1 agonist liraglutide, which increases insulin release and delays gastric emptying in the setting of elevated blood glucose levels, was found to increase the Firmicutes to Bacteroidetes ratio in rats and might therefore drive weight loss, at least in part, through secondary changes in the gut microbiome[95]. Having prior Roux-en-Y gastric bypass surgery (a bariatric procedure used to manage patients who fail lifestyle modifications and medications) was associated with a reduced relative abundance of Firmicutes and higher levels of facultative anaerobes, such as Proteobacteria, at 15 months post-surgery[96]. These changes could play a role in weight loss. An alternative surgery — sleeve gastrectomy — was effective in reducing inflammation and shifted the gut microbiome of 23 patients with pre-surgical obesity closer to that of healthy individuals used as controls, with corresponding recovery of microbially determined plasma glutamate levels as a biomarker of obesity[97]. Whilst most of the findings need to be validated in larger cohorts and tested in mechanistic models, these studies highlight the utility of microbiome analysis in assessing the efficacy of currently available obesity therapies.

In terms of microbiome-based therapeutics, *A. muciniphila* is a promising candidate for the treatment of metabolic syndrome and obesity. The consumption of *A. muciniphila* was protective against weight gain in mice owing to improved intestinal barrier function, diminished endotoxemia and improved glucose tolerance through the activation of TLR signalling as a result of an outer membrane protein[98]. Pilot data in 32 people suggest the safety and efficacy of *A. muciniphila*, with modest weight loss and improvement in laboratory markers of obesity over 3 months[99]. Similarly, *Christensenella minuta*, noted to be one of the most heritable microbial species and specifically associated with leanness in humans, was also found to be effective in treating obesity in an animal model[100] and a randomized controlled trial in humans is planned to start soon[101]. Although we highlight some ongoing efforts to target the microbiome to decrease intestinally derived inflammatory signals, the alteration of nutrient signalling and modulation of the gut–brain axis can also prove to be effective strategies. These novel approaches of targeting microorganism– host interactions will likely be an important part of preventing and treating obesity[102] (TABLE 1).

Insulin resistance or diabetes

Because of the effect on circulatory metabolites and immune status, the gastrointestinal tract and associated gut microbiome can be viewed analogously to an endocrine organ. As such, it is involved in glucose metabolism by affecting insulin signalling.

Microbiome links to altered glycaemic control.—Several studies provide cross-sectional taxonomic changes in the gut microbiome in diabetes with a shift towards a lower abundance of butyrate-producing organisms and overall microbial diversity but findings have not been consistent amongst studies[103–105]. However, a clear relationship between the gut microbiome and insulin resistance has been elucidated with FMT from donors with metabolic syndrome leading to decreased insulin sensitivity in germ-free mice in comparison to FMT from those with Roux-en-Y gastric bypass[106]. This was further supported in another human study where insulin sensitivity in individuals with obesity was improved after FMT from lean donors prior to the intervention[107]. This highlights the potential therapeutic benefit from microbiota-directed therapies in carefully selected patients for whom a shift in the gut microorganisms may lead to more substantial clinical benefit[107]. A randomized clinical trial in humans showed that increased diversity and abundance of a select group of SCFA-producing strains promoted by dietary fibres led to improvement in haemoglobin A_{1c} levels, which was attributed to increased glucagon-like peptide[108]. However, other potential SCFA producers were diminished or unchanged, suggesting that not all SCFA producers are created equal and a more targeted restoration of specific microorganisms may be more beneficial. Future studies like this will help identify specific groups of bacteria that are not just capable of a function but in fact work synergistically to restore a key function. Together, these studies support the link between the gut microbiome and diabetes and highlight the promise of using the gut microbiome to optimize therapy (TABLE 1). The mechanisms underlying the role of gut microbiome in insulin resistance or type 2 diabetes mellitus (T2DM) overlap with those identified for obesity, such as low-grade inflammation, changes in gastrointestinal permeability with possible endotoxemia, and decreased SCFA production and absorption, which is consistent with the concept of

metabolic syndrome. The changes in SCFAs can in turn affect the production of various metabolic hormones, such as GLP1 and peptide YY, which play a role in insulin secretion[77]. In addition, elevated branched-chain amino acid (BCAA) levels owing to an altered ratio of microbial BCAA biosynthesis and BCAA degradation have been associated with early insulin resistance in human studies and might be driven by *Prevotella copri* and *Bacteroides vulgatus*[109]. Colonization with *P. copri* was also associated with insulin resistance in a conventional mouse model[109]. Another microbial metabolite, imidazole propionate, was found to be elevated in patients with T2DM and can directly impair glucose tolerance and insulin signalling[110]. These studies highlight how microbiota-derived circulatory metabolites can drive the pathogenesis of diabetes.

Patients with T2DM are primarily managed with diet and medications (such as metformin, sulfonylureas and GLP1 agonists), although they might eventually require insulin replacement therapy and/or surgery. The current approach is to try treatment options sequentially even though there are substantial differences in how individuals respond to each of the treatments and some patients might not respond to diet or medications[111]. The microbiome offers an important avenue for optimization to determine whether a treatment strategy is better suited to an individual. A seminal study conducted in Israel in 800 non-diabetic individuals outlined the potential for developing personalized dietary recommendations based on an elegant machine learning approach using a combination of measurements, including microbiome and host features as well as blood glucose response to varying diets[88,89] (FIG. 1; Supplementary Fig. 1). A subsequent study validated this approach in a US Midwestern population of 327 individuals without diabetes and confirmed that an individual's microbiome can predict changes in blood glucose in response to different meals[112]. Interestingly, carbohydrates as a group were still associated with increased glycaemic response, but this approach identifies the major offenders within carbohydrates at an individual level, allowing them to restrict specific carbohydrates rather than a blanket low carbohydrate diet, which often has low adherance[94]. Another study found that an individual's microbiome can not only predict changes in blood glucose but also changes in triglycerides in response to different meals[90].

Microbiome and diabetes therapeutics.—One of the most commonly used medications for the treatment of diabetes is metformin, which suppresses liver glucose production, increases insulin sensitivity, and enhances muscle and liver glucose uptake[113]. Metformin efficacy seems to be dependent, at least in part, on the microbiome. Metformin administration in both animal and human studies leads to an increased abundance of *A. muciniphila* as well as several bacterial species associated with the production of SCFAs (for example, *Blautia* and *Butyricicoccus*)[114,115] (FIG. 2). *A. muciniphila* can improve glycaemic control through ileal goblet cell proliferation, a decrease in gastrointestinal permeability with lower endotoxemia and stimulation of TLR signalling as seen in mouse models[114,116]. The SCFA butyrate is linked to improved energy metabolism in rodents through its beneficial effects on skeletal muscle, brown fat tissue and pancreatic β-cells[117]. In addition, the SCFA propionate suppresses hepatic gluconeogenesis and reduces appetite and body weight in rodent models[118,119]. The most common adverse effects of metformin are related to gastrointestinal discomfort such as pain, bloating and nausea. A study

including 27 healthy men without diabetes found that abundance of specific genera (*Sutterella*, *Allisonella*, *Bacteroides* and *Paraprevotella*) in stool prior to initiating metformin was associated with the development of gastrointestinal adverse effects120 (FIG. 2). This finding suggests that, in addition to a role in metformin efficacy, the gut microbiota might also contribute to its gastrointestinal intolerance. Hence, microbiome-based stratification could enable the selection of patients likely to have a favourable response and tolerate therapeutic doses. Data supporting a role for the gut microbiome in other diabetes therapies are sparse but a decrease in the abundance of the phylum Firmicutes upon administration of the GLP1 agonist liraglutide in mice was associated with improvement in glycaemic control[121].

Given the data supporting the connection between metformin administration and increased abundance of *A. muciniphila* and butyrate-producing microorganisms, a multicentre, double blind, randomized placebo-controlled trial studied the administration of these microorganisms in probiotic form in 76 patients with T2DM[122]. There was a promising trend towards better glycaemic control in those who received a combination therapy synbiotic (*A. muciniphila*, *Clostridium beijerinckii*, *Clostridium butyricum*, *Bifidobacterium infantis*, *Anaerobutyricum hallii* and inulin) versus placebo, although the small population and short follow-up (12 weeks) leave it unclear whether this approach might be beneficial in the long-term for T2DM[122]. Trials to expand on this finding and studies using similar targeted microbiome approaches for diabetes management should help to push treatment of this condition further into precision medicine in the future.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a considerable morbidity associated with metabolic syndrome given the progression to cirrhosis and end-stage liver disease if left unchecked. The gut microbiome is closely linked to the liver through the gut–liver axis[123] and detoxification of microbial products is an important function of the liver.

Microbiome links to NAFLD.—Gut microbiota alterations and their consequences observed in metabolic syndrome, such as elevated Firmicutes to Bacteroidetes ratio, increased energy harvest capacity, increased intestinal permeability and low-grade inflammation, have also been reported in NAFLD[124–126]. The role of the microbiome in NAFLD is supported by the development of steatosis in gnotobiotic mice after the transfer of faeces from human donors with NAFLD[127]. Other microbiome-mediated mechanisms implicated in NAFLD include microbial bile acid modification and associated effects on liver farnesoid X receptor (FXR) signalling, endotoxemia, and production of uraemic toxins such as methylamines and p-cresyl sulfate[126]. Although, by definition, NAFLD is not associated with alcohol consumption, the current definition does not account for endogenous production of ethanol. *E. coli* and other Enterobacteriaceae from the phylum Proteobacteria are able to endogenously produce ethanol; thus, the high metabolic activity of these microorganisms in the gut could conceivably result in elevated levels of ethanol contributing to steatosis in patients considered to have NAFLD[128,129]. Although extreme cases (referred to as auto-brewery syndrome) are rare, prolonged low levels of ethanol from microbial production might still be a contributing factor[130].

Microbiome and NAFLD therapeutics.—Metformin, which is commonly used to treat T2DM[98,114,115], is also used in management of NAFLD, with animal studies supporting the efficacy of metformin in this setting[131] and human data showing improvement in liver function tests but not in histological response[132]. As outlined earlier, a successful response to metformin seems to be driven, at least in part, by the gut microbiome. The mechanistic connections between NAFLD and the gut microbiome have led to studies exploring potential microbiota-based therapeutics. FMT has shown promise in animal studies[133–135] and preliminary human data also suggest improvement of hepatic steatosis and abnormal intestinal permeability after FMT[136,137]. Ongoing clinical trials will better clarify the efficacy and safety of these procedures[138,139]. Probiotic administration has also shown some promise with regard to improving steatosis and markers of liver inflammation. However, the composition of these probiotic formulations have been variable, complicating their clinical recommendation at this point[140–143]. A study in germ-free mice colonized with faeces from two cytolysin-positive patients with alcoholic hepatitis showed therapeutic benefit with bacteriophages that target cytolytic *E. faecalis*[144] and it remains to be seen whether similar approaches might also be useful in NAFLD. Other novel microbiome therapeutics focused on alleviating sources of liver toxicity from the microbiota seem promising but are in an early stage (TABLE 1).

Cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death in the USA and continues to rise on a global level, growing by 12.5% between 2005 and 2015 (REF.[145]). It is estimated that 90% of CVD is preventable through improved lifestyle and diet[146]. CVD has been repeatedly linked to endotoxemia, increased intestinal permeability and low-grade inflammation, all of which can be driven by the gut microbiome[147].

Microbiome links to CVD

An early advance in the field of gut microbiome research was the identification of elevated plasma levels of the metabolite trimethylamine-*N*-oxide (TMAO) as a risk factor for CVD[148–150]. TMAO is produced in the liver by action of flavin monooxygenase 3 using the bacterial metabolite trimethylamine (TMA) as a substrate. TMA originates from the bacterial conversion of choline, phosphatidylcholine or L-carnitine[148,151]. The mechanistic role of TMAO based on animal studies suggests it is likely a major driver of atherosclerotic plaques[152] and high plasma L-carnitine levels are associated with decreased event-free survival from cardiovascular events only when there is a concurrent increase in TMAO levels, suggesting that TMAO is the likely driver of cardiovascular risks in humans[148,153]. The mechanisms by which TMAO contributes to CVD include its effect on foam cells and endothelial cells, vascular inflammation, atherosclerotic lesions, fibrosis, and enhanced platelet aggregation and thrombosis[154]. Specific gut microorganisms, including *Proteus mirabilis*, *Proteus penneri* and *Escherichia fergusonii*, are known to produce TMA in vitro and in animal models[155,156]. However, because of considerable inter-strain diversity, the abundance of the genes responsible for TMA production, namely *cutC/D* or *cntA*, in the human gut microbiome might have larger predictive promise than levels of specific taxa[152,157].

In addition, atherosclerotic CVD in humans was also linked to a reduced functional capacity for microbial fermentation of the gut microbiota as well as to an elevated abundance of the bacterial taxa Enterobacteriaceae and *Streptococcus*[158]. Other microbiota-derived metabolites that correlate with lowering of blood pressure are the SCFAs acetate and butyrate[159,160]. A reduced abundance of SCFA producers, such as *Eubacterium rectale*, *Dorea longicatena*, *Clostridium clostridioforme* and *F. prausnitzii*, has been associated with the development of heart failure in humans[159,160].

Diet is one of the mainstays of prevention and treatment of CVD and, as microbial metabolism of dietary components has a mechanistic role in the pathogenesis of CVD, the gut microbiome might be partly responsible for the effectiveness of dietary interventions. Both a Mediterranean diet and high-fibre diet seem to be protective against CVD and a case–control study in 396 patients with myocardial infarction (MI) and 843 healthy individuals as controls found that absence of *P. copri* was associated with an 18% lower risk of MI after a Mediterranean diet whereas carriage of *P. copri* was associated with a non-significant increase in MI following a Mediterranean diet[160–162.] Adherence to a Mediterranean diet has also been associated with an increased abundance of several gut microorganisms known to metabolize fibre and produce SCFAs such as *F. prausnitzii*, *Eubacterium eligens* and *Bacteroides cellulosilyticus*[162]. The benefit from increased fibre consumption might be related to increased production of the SCFA acetate by fibre-degrading microorganisms or their interaction partners. Acetate is involved in regulation of the transcription factor Egr1, which in turn regulates cardiac inflammation, fibrosis and hypertrophy in mice[163]. In addition, elevated abundance of the butyrate producer *Clostridium sphenoides* prior to various dietary interventions has been associated with a greater decrease in cholesterol levels in individuals with obesity and may also be relevant for CVD93. Contrasting the Mediterranean and high-fibre diets, consumption of a Western diet (high intake of fatty and/or processed meats, saturated fats, salt, sugar and refined grains)[164] is associated with an increased risk of CVD, which might be linked to a decreased abundance of gut microorganisms such as *Bifidobacterium* and *Eubacterium* spp.[163]. Interestingly, the TMAO precursors choline, phosphatidylcholine and L-carnitine are prevalent in animal protein, which is a characteristic component of the Western diet. However, the consumption of animal protein such as red meat might only be harmful in a subset of individuals who harbour microorganisms that can generate TMA or other metabolites.

Microbiome and CVD therapeutics

The efficacy and toxicity of several drug treatments directed at CVD is associated with the gut microbiome. A key example of this aspect is the presence of cardiac glycoside reductase genes in *Eggerthella lenta* that inactivate digoxin, an important drug in the treatment of cardiac arrhythmia that acts through inhibition of the Na+/K+/ATPase at the myocardium[165] (FIG. 2). It is likely that this bacterial enzyme activity is due to substrate promiscuity rather than a process evolved in response to environmental exposure of digoxin. This finding provides an example of how the chemical diversity of the gut microbiome can lead to crosstalk with the metabolism of human-designed drugs[166]. As digoxin has a narrow therapeutic window, determining the presence of this bacterial metabolic pathway before starting treatment could enable more accurate dosing and minimize adverse effects.

Interestingly, the genes responsible for digoxin inactivation are repressed in the presence of considerable amounts of the amino acid arginine and a high-protein diet reduced digoxin inactivation in a mouse model[165].

Statins, which work through competitive inhibition of HMG-CoA reductase, are the most commonly used medications for CVD-associated hyperlipidaemia, with nearly half the US population aged between 40 and 75 years having an indication for their use[167]. Interestingly, there is substantial inter-individual variability in response to statins as measured by varying decreases in LDL cholesterol levels[168]. This variability might originate from the gut microbiome as more robust treatment responses were seen in individuals[169,170] and animal models[171–174] with higher gut microbial diversity. In addition, having elevated levels of Proteobacteria was associated with decreased efficacy of simvastatin in a study of 100 individuals with total cholesterol levels of 160–400 mg/dl showing variable LDL response[170]. The efficacy of a different statin, rosuvastatin, was also decreased in the presence of higher levels of Cyanobacteria and Lentisphaerae combined with lower levels of Firmicutes and Fusobacteria in a population of 64 patients with hyperlipidaemia[174] (FIG. 2). These studies suggest that statin treatment response can be predicted based on an individual's gut microbiome. A study published in 2020 found the Bacteroides 2 (Bact2) enterotype, which is associated with obesity, to be less prevalent in patients treated with statins[175], which suggests that statins have a microbiome-shaping effect. Whether this finding can be used to predict therapeutic outcomes and direct therapeutic choices in the future remains to be seen.

Given the accumulating evidence in support of the role of gut microbiome in the pathogenesis of CVD, it is not surprising that there are several ongoing clinical trials investigating the role of probiotics in CVD. Two examples include the comparison of the antimicrobial rifaximin and the probiotic *Saccharomyces boulardii*[176] and the effect of *Lactobacillus acidophilus* on inflammation in patients with heart failure[177]. Such interventional trials provide a valuable opportunity to study potentially beneficial microbiome rearrangements based on longitudinal information on the gut microbiome collected from patients following treatment. Based on some of these highlighted findings, there seems to be a place for next-generation microbial therapeutics that can drive specific functions such as acetate production or improved barrier function. An alternate approach is the development of small-molecule inhibitors of specific microbial pathways such as the recently described inhibitors of TMA-producing enzymes[152,156]. These inhibitors might enable more precise therapeutic interventions and can be specifically directed towards patients with high TMAO levels and functional gene levels that indicate a high TMAO production capacity[156,178].

In general, the recognition that the gut microbiome plays a role in CVD pathogenesis and treatment is an important advance that opens up novel avenues for disease recognition, stratification and treatment (TABLE 1).

Autoimmune or inflammatory disease

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune condition that results in chronic inflammation of the joints. Several studies have described alterations in the gut microbiota in patients with RA and these alterations vary with the stage of disease[179].

Microbiome links to RA.—One consistent finding in the literature is that members of the genus *Prevotella* are associated with progression of disease (*P. copri*) as well as with disease amelioration (*Prevotella histicola*) in RA, highlighting that different species and/or strains within the same genus can have divergent effects on host physiology[180,181]. Hence, it is important to resolve the taxonomic differences at the species or strain level and not to generally label an entire genus as being beneficial or harmful. The potential role of *P. copri* in the pathogenesis of RA is based on findings in both human and rodent studies. In in vitro studies and in mice, *P. copri* has been shown to increase T_H17 responses, which are in turn associated with increased arthritic bone erosion[182]. In humans, *P. copri* 16S rDNA has been found within the synovial fluid of RA-affected joints[183]. Although *P. copri* seems to be an important determinant of RA, its levels are reported to be highly variable over time in healthy individuals[184]; hence, longitudinal studies coupled with assessment of host phenotypes are needed to better understand its role in RA. In addition to the gut microbiome, specific periodontal bacteria and periodontal disease have been associated with an increased risk of RA in humans and mouse models of arthritis. *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* have both been associated with an increase in autoantibodies against citrullinated peptides and might contribute to the autoimmunity in RA[183].

Microbiome and RA therapeutics.—In addition to a role in pathogenesis, the gut microbiota might also play a role in determining response to medications commonly used for RA. These include disease-modifying agents, such as methotrexate and hydroxychloroquine, and anti-inflammatory agents such as sulfasalazine and nonsteroidal anti-inflammatory drugs (NSAIDs). Host factors and genetics have failed to provide a predictive model for response to methotrexate but a higher gut microbial diversity has been associated with methotrexate treatment[185–187]. A study in 26 drug-naive patients with new-onset RA found distinct microbial taxa and their genes in methotrexate responders and non-responders[188]. A microbiome-based model developed using machine learning techniques predicted the lack of response to methotrexate in a validation cohort of 21 patients with a high degree of accuracy (AUC 0.84). This finding was attributed to the direct metabolism of methotrexate by gut microbiota given that methotrexate levels following incubation of the drug with distal gut microbiota from patients was predictive of the clinical response[188]. In another study, the impact of methotrexate treatment on specific microbial taxa and pathways in mouse models led to decreased immune activation and thus decreased disease activity[189]. These studies suggest that microbial metabolism of methotrexate by gut microbiota may play a role in efficacy of the medication and the effect of methotrexate on the reduction of disease activity is itself driven by modulation of the gut microbiome. Methotrexate, which suppresses immune function through competitive inhibition of dihydrofolate reductase, has

been associated with a reduced abundance of *Enterobacteriales*[185] but there remains a lack of clarity as to whether this finding has any effect on medication response[185]. However, it does further suggest that methotrexate affects the gut microbiome structure and that the microbiome-informed prediction of response to methotrexate could be explored further to guide treatment. The differential gut microbial metabolism of methotrexate itself to inactive or inaccessible forms that remain within bacterial cells is a possible mechanism by which the gut microbiome alters methotrexate efficacy[190]. Gut microorganisms also play a role in the toxicity of methotrexate; *Bacteroides fragilis* gavage has been found to be protective against intestinal mucositis, an adverse effect seen in about one-third of patients with methotrexate administration[191], following methotrexate treatment in mice[192]. The efficacy of hydroxychloroquine, which inhibits immune activation via reduced TLR signalling and CD154 expression[193], has been associated with gut microbial alpha diversity with a higher pre-treatment diversity favouring greater efficacy, but it is unclear whether it is simply the higher microbial diversity or the increased abundance of specific bacteria that are responsible for this effect[186]. As with methotrexate, there have been alterations in the gut microbiome associated with the TNF inhibitor etanercept but again without a defined relationship to efficacy in current studies[185].

The 5-aminosalicylic acid prodrug sulfasalazine is converted into its active metabolite following acetylation by the enzymatic action of gut microbiota and, as a result, its efficacy is dependent on the gut microbiota[194,195]. Adverse events related to NSAIDs and paracetamol might be related to the gut microbiota. The activity of bacterial β-glucuronidase can lead to toxicity of NSAIDs and inhibitors of this enzyme decrease NSAID-induced enteropathy in mice[196,197]. In principle, the measurement of β-glucuronidase activity can help identify individuals who should either avoid NSAIDs or are candidates for co-treatment with specific small-molecule inhibitors of β-glucuronidase. Certain bacteria can produce p-cresol, which competes with paracetamol for enzyme binding in the liver and can lead to production of the hepatotoxic compound NAPQI[198] (FIG. 2). Thus, p-cresol levels might be used to guide paracetamol dosing to avoid hepatotoxic adverse effects.

The potential contribution of gut microorganisms to the pathogenesis of RA has led to the exploration of probiotics as a potential therapeutic option. These efforts are primarily focused on modulation of the immune system to counteract changes seen in RA rather than a strategy to potentially replace missing microorganisms or mechanisms. *P. histicola* decreased the incidence and severity of arthritis in susceptible HLA-DQ8 mice by the suppression of antigen-specific T_H17 responses and by stimulating increased transcription of IL-10 (REF.[181]). Administration of *Lactobacillus casei* was associated with decreased pro-inflammatory molecules (IL-1β, IL-2, IL-6, IL-12, IL-17, IFNγ, TNF and COX2) by CD4+ T cells in mouse models of collagen-induced arthritis[199]. In humans, *Bacillus coagulans* has been studied as a potential adjunctive therapeutic option in 45 adults with RA, with administration leading to improved self-assessment of pain and disability and lower inflammatory markers than placebo[200]. The differential effect of microbial species on the immune system suggests that immune marker-based subtyping of RA could help select patients most likely to respond to specific microbiota-based therapeutics (TABLE 1).

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic inflammatory condition that includes Crohn's disease and ulcerative colitis. The heterogeneous nature of IBD subtypes in terms of disease phenotype, susceptibility, progression and response to treatment has inspired attempts at subtyping them beyond just clinical presentation. The focus has been on host genes and the immune response but the exposome and the microbiome are increasingly being recognized as important determinants of inter-individual variability in IBD.

Microbiome links to IBD.—A central role for gut microbiota in IBD is based on observations such as disease remission following faecal diversion, higher disease burden in areas of the gastrointestinal tract with elevated levels of bacteria, improvement in subsets of patients following antibiotic treatment, and IBD-specific changes in gut microbiota composition and function[201–204]. Furthermore, enhancement of inflammatory pathways associated with IBD, such as IL-17, was observed after colonization of mice with stool from patients with IBD, highlighting its role in disease[184,205].

Both Crohn's disease and ulcerative colitis are characterized by dramatic shifts in microbial community structure with the most consistent finding being increased relative abundance of the phylum Proteobacteria and, specifically, the family of Enterobacteriaceae. Abundances of specific species have been linked to Crohn's disease (*E. coli*, *Campylobacter* species and *Mycobacterium avium*)[204] and the depletion of specific butyrate-producing bacteria is associated with both Crohn's disease and ulcerative colitis pathogenesis[206,207]. Adherent-invasive *E. coli* has also been identified in the ileal mucosa of patients with Crohn's disease with an associated increase in TNF secretion but it is unclear whether this bacteria is disease inducing or its presence is a consequence of underlying disease factors[208–211]. Overall, these community shifts represent an increase in facultative anaerobes, such as Proteobacteria, at the expense of obligate anaerobes[211,212]. The majority of studies outlined here focus on the luminal microbiome, which, while important in IBD pathogenesis, has lower discriminatory power than the mucosa-associated microbiome in identifying IBD[213].

The overall expansion of Enterobacteriaceae in IBD is likely due to changes to the nutritional landscape of the gut such as elevated host production of *N*-acetyl ethanolamine signalling lipids, which can be exploited by Enterobacteriaceae[214–216]. In addition, bacterial nitrogen metabolism is linked to Enterobacteriaceae expansion though the production of ureases[217] and the availability of nitrate in an inflammatory environment, which can fuel anaerobic respiration of Enterobacteriaceae[218]. An increased abundance of Proteobacteria might not necessarily be the inciting event in IBD and could result from a combination of host genetic predisposition as well as dietary and environmental exposures. However, Proteobacteria do contain highly immunogenic LPS, which in itself can trigger an inflammatory response. This feedforward mechanism might serve to perpetuate inflammation and allow Proteobacteria to thrive while at the same time excluding bacteria such as *F. prausnitzii*, which does not fare well in an inflammatory milieu[212,219]. This hypothesis is supported, in part, by the observation that IBD treatment with TNF inhibitors is associated with restoration of a more diverse gut microbiome in paediatric patients with Crohn's disease[213]. Besides LPS, several other bacterial components and metabolites have

also been implicated in IBD such as higher levels of polyamines and ATP and lower levels of secondary bile acids and butyrate[184].

The microbiome and IBD therapeutics.—The gut microbiome also plays a role in predicting the response to existing IBD treatments. A higher pre-treatment gut microbial alpha diversity is associated with a higher likelihood of remission following treatment with the anti-integrin therapy vedolizumab (α4β7 antagonist), suggesting a potential role for microbial metabolism in determining efficacy[220] (FIG. 2). Similarly, specific gut microbiome signatures have been associated with disease recurrence after discontinuation of the anti-TNF treatment infliximab[221] (FIG. 2). As the current clinical practice is typically to continue biologic therapies long after achieving remission[222], such signatures might allow the selection of patients who could be weaned off therapy. Given the variability in response to biologic medications as well as the cost and morbidity involved, the ability to predict response and persistent remission with microbiome analysis could streamline management of IBD.

These observations have fuelled the development of microbiota-based therapies for treatment of IBD ranging from probiotics and FMT to specific bacterial compounds or metabolites[223]. *F. prausnitzii* is one example of a possible probiotic as the reduced abundance of *F. prausnitzii* in postoperative specimens of patients with Crohn's disease is associated with increased disease recurrence after resection[207]. *F. prausnitzii* has been shown to prevent acute colitis by reducing the secretion of inflammatory cytokines[224,225], suggesting it has anti-inflammatory effects, which might be a result of its ability to produce butyrate or through an independent effect on the immune system[226]. In the future, postoperative profiling of the microbiome could enable the identification of individuals who might benefit from therapeutic strategies such as *F. prausnitzii* probiotics[223].

Similarly, the efficacy of FMT in IBD has been linked to specific features in the donor microbiome. Abundances of the family Lachnospiraceae and the genus *Ruminococcus* are associated with response, suggesting a role for specific microbial taxa or metabolites in determining response and offering a possible explanation for the variability in response seen in other FMT trials to date[227]. As we continue to learn more about the role of the gut microbiome in IBD, sub-phenotyping based on the gut microbiome might better stratify patients in terms of predicting progression as well as response to specific treatments and could lead to the development of individualized therapeutic strategies targeting the gut microbiome (TABLE 1).

Allergic and atopic diseases

The critical role of the gut microbiota in immune education makes it an important player in allergic and atopic diseases. The microbiota is most vulnerable during early stages of life and changes during this time can have a long-lasting effect on the immune system. Hence, most microbiome studies in allergic and atopic diseases have focused on early life, with the goal of determining how diet, allergen exposure and microbiome composition of the newborn baby can drive allergic diseases and identify specific targets that can be modulated to prevent these diseases. This potential window of intervention is suggested by

the observation that atopy in early life is a risk factor for the development of food allergy and eventually asthma in later life[228]. This link suggests a shared underlying mechanism classically linked to CD4 T_H2 hyperactivation combined with reduced levels of dendritic cell-induced T_{reg} cells, all of which are affected by the microbiome. While the field is still in its infancy, we highlight some areas in which personalized microbiome changes might be relevant.

Food allergies

Food allergies are likely driven by a complex interplay between genetics, diet and the commensal microbiota[229,230]. In humans, distinct gut microbiota changes have been reported in cohorts with different types of food allergy such as those against eggs, peanuts, soy, wheat and milk[231–233]. However, the lack of consistency among studies makes it challenging to interpret these changes[227,234,235]. The role of the gut microbiota is supported by the observations that germ-free mice are sensitive to anaphylactic responses to foods, antibiotics increase allergen sensitization, and transplantation of gut microbiota from healthy infants can protect against food allergies in mice[236]. In the latter FMT study, the bacterial species *Anaerostipes caccae* was found to be protective against food allergy response to cow milk. Another FMT study found that bacteriotherapy with the bacterium *Subdoligranulum variabile* or a consortium of *Bacteroides* strains was found to be protective to peanut allergy in mice[237]. Specifically, the T_{reg} cell pathway MyD88–RORγt was found to be important in protecting against food allergies in mice and was identified to be deficient in infants with food allergies[237]. T_{reg} cell subsets are induced by the microbial metabolite butyrate[238] but butyrate was not found to be responsible for the observed effects in this study[237].

Besides immune education, the microbiome could be influencing the effective dose of an allergen by either production or degradation. Specific strains of milk-fermenting probiotics, such as *Lacticaseibacillus rhamnosus*, improved tolerance to milk, supporting a potential role in allergen degradation[239,240]. Thus, by assessing the capacity of the microbiome to degrade foods, we might be able to predict the spontaneous resolution of an allergy or identify individuals who might benefit from microbiota-based therapies.

Atopy and asthma

Disruption of the gut microbiota in early life, such as that associated with caesarean section delivery and growing up in a ‘clean’ environment with decreased microbial exposure, has been associated with an increased risk of developing atopy and asthma[241–243]. Although there are no consistent human microbiota signatures associated with atopy and asthma[229,244–254], microbial metabolites might be directly involved in disease development. Circulating levels of the SCFA propionate originating from the gut was found to reduce inflammation in the lung in a manner dependent on free fatty acid receptor 3 (FFAR3) and dendritic cell functioning in mice[255]. Microbial metabolites might be specifically involved in T_H2 reprogramming and hyperactivation, even though not all individuals with asthma have elevated T_H2 levels[256]. A microbial metabolite involved in asthma development, the linoleic acid derivative 12,13-diHOME, was identified through a series of metabolomics and microbial genetics studies[257]. Birth cohorts with an elevated asthma risk were found to have increased faecal levels of 12,13-diHOME, which was linked to reduced anti-inflammatory

cytokine and T_{reg} cell levels in the lungs, indicating hampered immune tolerance[257]. The bacterial epoxide hydroxylase enzyme responsible for the production of 12,13-diHOME may be inhibited as a therapeutic strategy in the subset of patients with elevated enzyme levels.

The supplementation of breast or formula milk with specific strains or communities has been attempted with the aim of reducing the risk of development of atopy or asthma later in life. One such example is the use of *L. rhamnosus* GG, which led to an increase in microbial species thought to promote immune tolerance in infants at high risk of developing asthma, although the progression to asthma development and severity of disease later in life was not clearly assessed[258]. In addition, *Acinetobacter lwoffii* and *Lactococcus lactis* strains isolated from farm cowsheds possessed strong allergy-protective properties in mice and could be explored in human cohorts[250]. To better understand the temporal mechanisms underlying the role of gut microbiota in the development of allergic and atopic disease, longitudinal birth cohorts that track clinical outcomes are necessary. Overall, these studies can inform future efforts aimed at personalizing treatment strategies in allergic conditions based on the gut microbiome (TABLE 1).

Future perspectives

There has been much focus on cause-and-effect when considering the microbiome in health and disease, but it is clear that the gut microbiome can contribute to a disease even if it is not the inciting factor. In fact, the gut microbiome is rarely the sole driver of disease and needs to be considered in the context of systems biology involving host genetics, host physiological responses and the environment. We need to understand where the gut microbiome lies in the complex regulatory framework that predisposes an individual to a disease state. Although the gut microbiome has been associated with many diseases, it has been difficult to quantify the relative amount of this contribution compared with other variables such as host (epi)genetics, proteome or transcriptome. A major challenge in delineating the contributions of different host and microbiome factors is due to the difficulty of separating the effect of host and environmental factors on the microbiome from their effect on host biology independent of the microbiome. Vujkovic-Cvijin et al. investigated an array of lifestyle, physiological and dietary factors that might work to confound microbiome-related studies owing to the vast inter-individual variability[259]. Studies like this one not only help to further the understanding of the microbiome in relation to health and disease but also how to improve the quality of future work to better move towards understanding the power of the microbiome in precision medicine and individualized treatment. Multi-omics approaches in defined model systems, such as gnotobiotic animals, can also help unravel such contributions from different data layers.

Future studies in large cohorts of well-phenotyped patients will need to be multidimensional, incorporating host and microbial multi-omics as well as the exposome to better understand the relative contribution of the gut microbiome and other data levels to a disease state or treatment efficacy. These studies should also encapsulate the temporal and interpersonal variation by using longitudinal sampling. Longitudinal data analysis has been shown to reduce variation as compared with cross-sectional studies[260,261] and can be used to make

causal links. As an example, the variation that underlies treatment response can be identified through longitudinal monitoring of treatment-naive cohorts to identify relevant microbiome and host factors that could underlie treatment variability. This approach combined with intelligent in vitro and ex vivo approaches can identify novel factors responsible for therapeutic response, adverse effects and drug metabolism[5,262]. Such studies will also enable us to determine whether the gut microbiome could potentially serve as a readout of other host-associated factors such as diet, genetics, age, and lifestyle and potentially simplify machine learning algorithms for disease classification and treatment stratification (FIG. 3).

As noted already, describing entire genera as being beneficial or harmful can be misleading and higher resolution techniques should be used when profiling individual microbiomes. A good example of such dichotomy is *Prevotella*, which has been hailed both as the ‘poison’ as well as the elixir in RA. Microbial functions might be more relevant targets given the generally stronger associations of microbial metabolite levels to disease compared with taxonomic abundances. In addition, functional characteristics of the microbiome are more conserved among individuals. It might therefore be that ‘missing microbial functions’ is a more useful concept for precision treatment than the popularized ‘missing microbes’ concept[263]. At the same time, it is important to note that more than one microbial function can underlie a disease state, as seen regarding susceptibility to CDI[24,25,264–266]. Hence, future therapies need to be based on better mechanistic understanding and address a missing function or functions, realizing that there might be different functional abnormalities in different individuals.

As we see continued strong momentum in the field with an increasing number of studies, it can be tempting to run before we can walk. We need to be careful and realize that we are still in the early stages of investigation and there remain major challenges to address before we can translate knowledge of the microbiome into accessible measures that can be used in the clinic to benefit patients. Some of these challenges include a lack of validation of microbiome-based markers across large clinical cohorts, lack of standardization in processing and analysis of microbiome data, and a lack of individualized understanding of microbiome-related mechanisms in different disease states. Despite these shortcomings and challenges, the rapid pace of the field and progress made over the past decade brings optimism that the microbiome will be a part of clinical practice sooner rather than later. We can start to envision how the microbiome can be incorporated in personalized treatment strategies and move beyond the approach of a continuum of treatment strategies for all patients to selecting the best strategy for each patient.

Conclusions

In this Review, we highlight the major advances in our understanding of the role of the gut microbiome in the development, progression and treatment of different disease states. Together, this evidence clearly highlights the gut microbiome’s promise in precision medicine and individualized treatment. While there has been major progress, scientific rigor and the strength of findings supporting a role for the gut microbiome vary between disease states as summarized in this Review (FIG. 1; Supplementary Fig. 1). Although the majority of human studies have focused on compositional analysis to identify microbial

biomarkers of response, deeper mechanistic understanding will be required to develop precision therapeutics and stratify treatments. Overall, the field has realized this need and has shifted towards studying the functional aspects of the microbiome. Although a non-targeted ecosystem-based approach shows benefit in CDI, the efficacy of such untargeted measures might not extend to multifactorial chronic diseases in which a multitude of mechanisms are at play.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key poins

- The gut microbiome, with substantially greater genetic diversity than the host, is an important factor in determining the variability in disease development, progression and treatment response.
- Tremendous progress has been made in characterizing the microbiome and its influence on biology.
- Stratifying to species or strain level is important as microorganisms within the same genus might have a differing effect on the same disease process; the same organism might also have different effects on separate disease processes, making the definition of a universal ‘healthy’ microbiota based on composition alone difficult.
- To incorporate the microbiome in the clinic, large patient cohorts with multidimensional and longitudinal analyses are needed to understand the contribution of the microbiome on disease development, progression and treatment in the context of systems biology.
- The gut microbiome is an important component in personalized medicine; most of the progress has been in metabolic and cardiovascular disorders as well as in cancer therapies.
- The gut microbiome is influenced by numerous factors (including age, diet and host genetics) and hence serves as a readout for those factors, simplifying the input for machine learning-based models in clinical practice being developed to predict disease outcomes or treatment response.

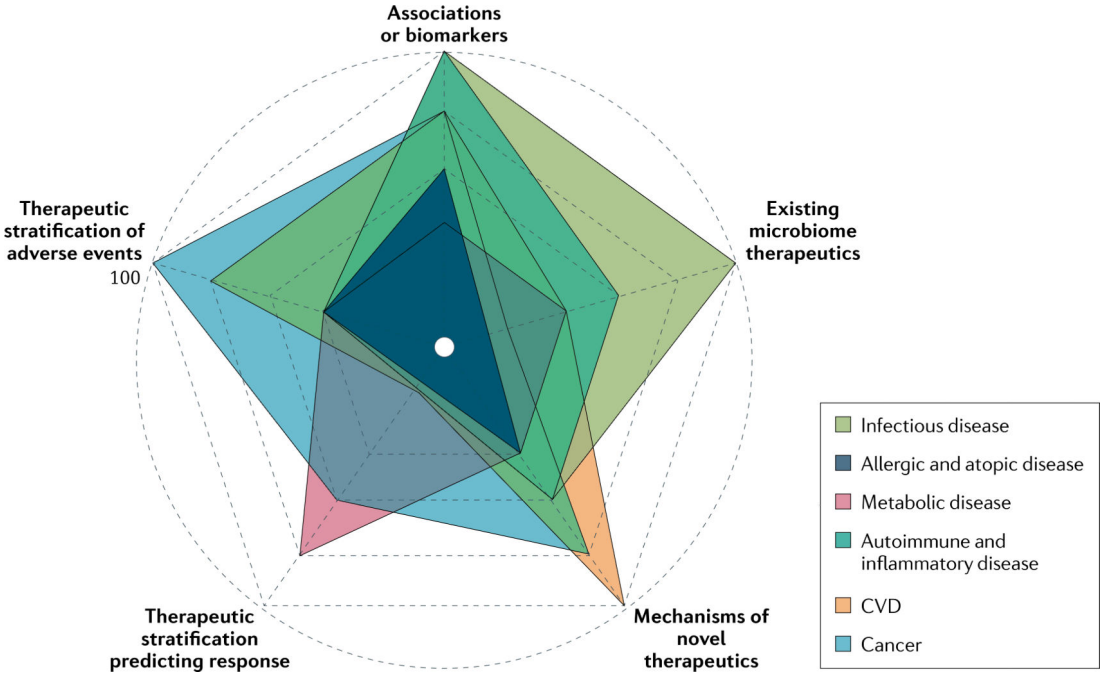

Fig. 1 |. Maturity of the gut microbiome as a precision medicine tool.

The advance in microbiome science, while overall remarkable, has been uneven across different disease states. In this figure, we outline the maturity of the microbiome field with regard to advancement to clinical practice in individual disease groups based on a review of available literature in humans. We consider the following parameters within each disease group: presence of robust taxonomic associations or biomarkers; the existence of microbiome therapeutics; knowledge on actionable microbiome mechanisms; use of microbiome in therapeutics stratification; and use of microbiome in prediction of adverse therapeutic effects. A maximal scale of 100 is defined as findings that are currently used in the clinic and the minimal scale of 0 indicates that no progress has been made in this specific aspect. See Supplementary Fig. 1 for each individual disease in a separate plot. CVD, cardiovascular disease.

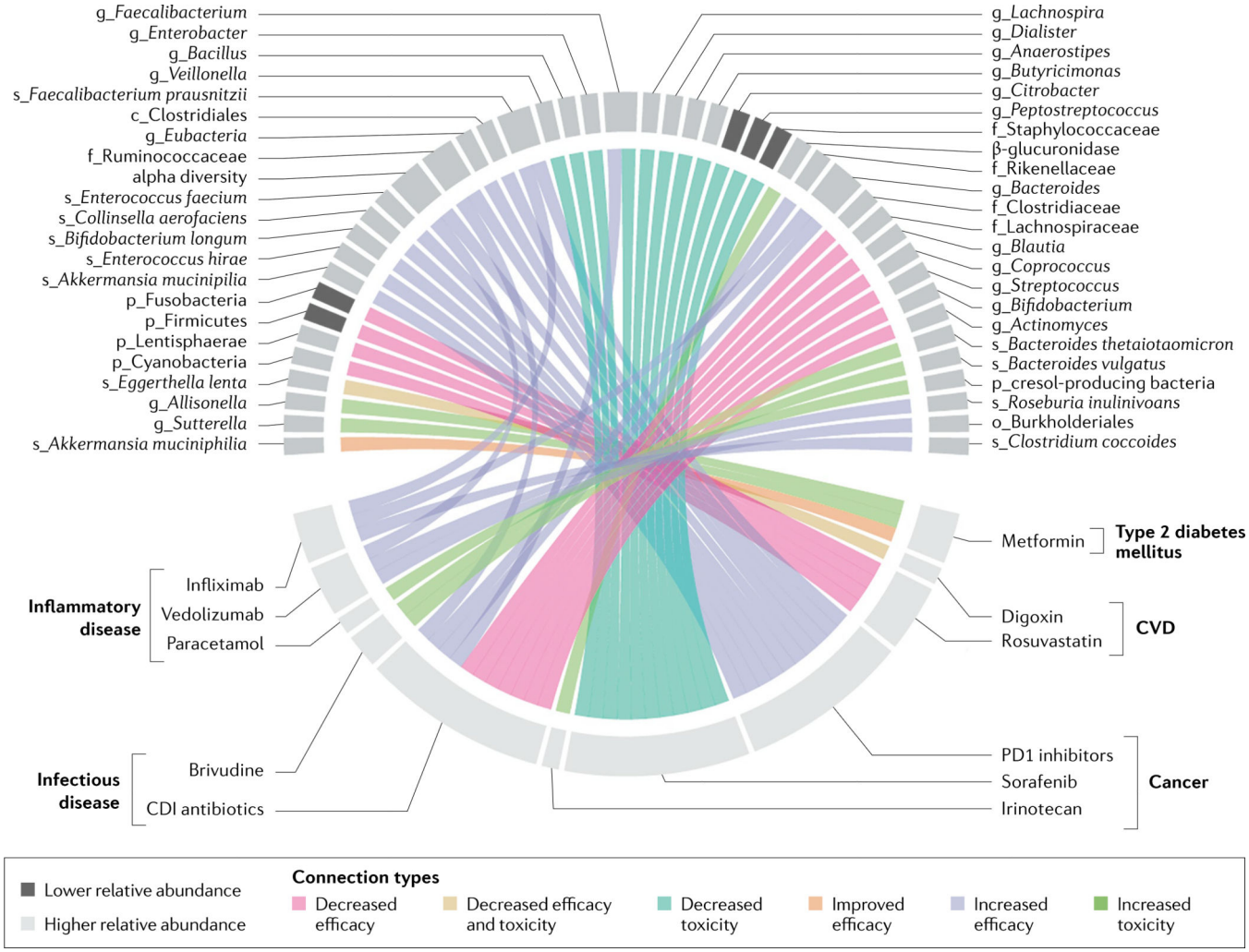

Fig. 2 |. association between the gut microbiome and medication therapy.

Associations between the specific microbial taxa and the efficacy or toxicity of commonly used medications. Only human studies are included and we do not account for differences in the level of confidence in the findings based on association alone or additional biological validation. Prefix indicates phylogenetic level (p_phylum, o_order, f_family, g_genus, s_species). There are a multitude of other medications for which in vitro or animal data suggest associations with outcomes and we expect this field to expand rapidly. CDI, *Clostridioides difficile* infection; CVD, cardiovascular disease.

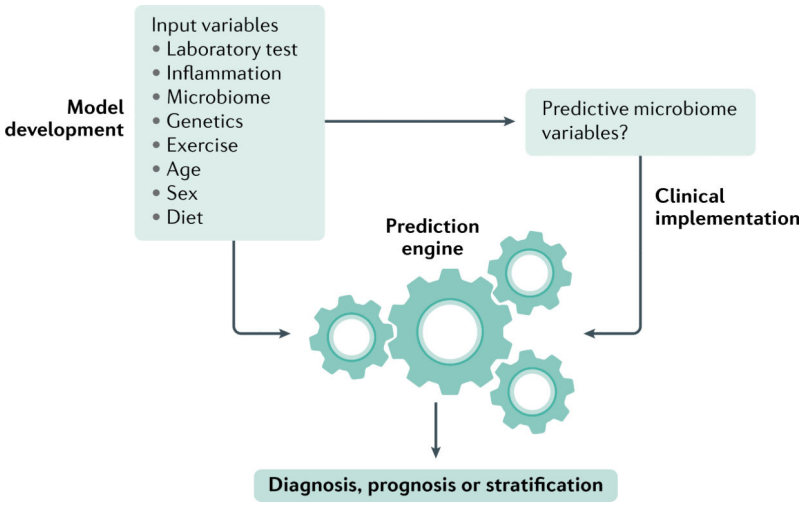

Fig. 3 |. the gut microbiome as a readout of host variables in prediction models.
Computational prediction models using artificial intelligence and machine learning hold great promise for the optimization of clinical management. The predictive value of these models depends on the training data, which ideally includes a range of host measurements (left panel). However, determining all these parameters for every patient might be prohibitive in cost and time. As the gut microbiome responds to most of the lifestyle factors it could serve as a valuable abstracted readout that is simple to access and measure. The most relevant microbiome features could be identified in the comprehensive large-scale training cohort (left), allowing the use of the microbiome alone as a predictor of clinical outcomes.

Table 1 |

Current status and outlook for the gut microbiome in disease

Disease category	Current status	Outlook
Clostridioides difficile infection	The gut microbiome is an important determinant of susceptibility and response to treatment in *C. difficile* infection[7,18–23,30,31]; strain-specific differences in *C. difficile* might determine the ability to evade antibiotic treatment[24,25,264–266]	Although FMT has been effective in treating recurrent *C. difficile* infection, studies with defined microbial communities have shown promise and could replace FMT[32–34]
Cancer	Gut microbiota composition can serve as a diagnostics tool to detect early-stage cancer[37,40]; the gut microbiome can affect cancer development through the production of metabolites and modulation of immune states[36,38,41]; the gut microbiome can mediate effectiveness and toxicity of chemotherapy and immunotherapy[42,45–64]	Novel microbial therapeutics (prebiotics, probiotics, bacterial metabolites) targeting cancer or adverse effects of therapy seem promising[37]; new tools, such as activity-based protein profiling, can serve as diagnostics for predicting efficacy and adverse events[65]
Obesity	The gut microbiome is an important determinant of efficacy of dietary, medication and surgical interventions[84–93]; poor agreement between studies regarding obesity-related microbiome changes has made sub-phenotyping difficult[67–72]	Novel microbiome therapeutics show promise in trials[82,98–102]; clinical studies are needed to validate the stratification of existing therapies based on the microbiome
Type 2 diabetes mellitus	Gut microbiota composition can predict glycaemic response to food[90,103–109,112]; microbial products (SCFAs, BCAAs) play a part in glucose tolerance[77,110]; efficacy and adverse effects of medications for diabetes are driven in part by the gut microbiome[120,121]	Next-generation microbial therapeutics composed of multiple synergistically acting bacteria hold promise for treatment in diabetes[122]; microbiome-guided dietary and drug therapy can help improve management of diabetes[88,89]
NAFLD	The gut–liver axis can result in deleterious changes in the liver from microbiota-related mechanisms[126]; endogenous production of ethanol by bacteria might contribute to steatosis[128–130]	Bacteria and bacteriophage-based therapeutics show promise in liver disease and are an area of ongoing investigation[133–144]
Cardiovascular disease	The association between cardiovascular disease and the microbiome is more related to the functional output of microbiome (metabolites) rather than taxonomic changes[148,149,151,152,155–157,159,160]; the gut microbiome mediates effectiveness of both dietary and medication-based interventions[93,160–163,165–167,169–175]	Novel mechanism-based therapeutics targeting bacterial metabolism are on the horizon[152,156]
Rheumatoid arthritis	Specific gut and oral bacteria are associated with the development of rheumatoid arthritis[179–183]; the gut microbiome is an important determinant of efficacy of anti-inflammatory drugs to treat rheumatoid arthritis[185,186,188–190,194]	Microbial therapeutics with immune-modulating properties have shown promise in preclinical studies[181,199,200]
IBD	Feedforward mechanism between the microbiota and host might perpetuate inflammation in IBD[184,204–215,217–219]; sub-phenotyping based on gut microbiota can enable better stratification to predict disease progression and treatment response[220,221]	Microbial therapeutics based on underlying mechanisms and identifying microbiome features that determine success of FMT are active areas of investigation[216,223–227]
Allergic and atopic diseases	The effect of the gut microbiota early in development is an important risk factor for the development of allergic and atopic diseases, exact mechanisms remain elusive[228,233–235,241–243]	Microbial therapy holds promise in allergic conditions by shifting the community to an immuno-tolerant state and degrading allergens[237,239,240,250,255,257,258]

BCAAs, branched-chain amino acids; FMT, faecal microbiota transplantation; IBD, inflammatory bowel disease; NAFLD, non-alcoholic fatty liver disease; SCFAs, short-chain fatty acids.