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Diet–microbiota interactions and personalized nutrition

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Abstract

Conceptual scientific and medical advances have led to a recent realization that there may be no single one-size-fits-all diet, and that differential human responses to dietary inputs may rather be driven by unique and quantifiable host and microbiome features. Integration of these person-specific host and microbiome readouts into actionable modules may complement traditional food measurement approaches in devising diets that are of benefit to the individual. Although many host-derived factors are hard-wired and difficult to modulate, the microbiome may be more readily reshaped by environmental factors such as dietary exposures and is increasingly recognized to potentially impact human physiology by participating in digestion, absorption of nutrients, shaping of the mucosal immune response, and synthesis or modulation of a plethora of potentially bioactive compounds. Thus, diet-induced microbiota alterations may be harnessed to induce changes in host physiology, including disease development and progression. However, major limitations in 'big data' processing and analysis still limit our interpretive and translational capabilities of these person-specific host, microbiome and diet interactions. In this Review, we describe the latest advancements in understanding diet–microbiota interactions, the individuality in gut microbiota composition and how this knowledge could be harnessed for personalized nutrition strategies to improve human health.

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Introduction

The microbiota modulates pathogenesis, progression, and treatment of diseases, ranging from metabolic disorders to neurological diseases[1,2,3]. Reshaping host–microbiota interactions through personalized nutrition is a new therapeutic avenue for both disease control and prevention. Gut microbiota composition and function is shaped from infancy when the individual is colonized by bacteria from caregivers and the surrounding environment, a process which strongly influences the composition of the microbiota in adulthood[4,5]. Although early life events, including the mode of birth, type of feeding and complementary diet[6,7] have strong effects on the microbiota, it does retain some degree of flexibility and can be modulated through exposure to a variety of environmental factors[8]. Of these, diet is the key determinant of microbiota configuration, through modulation of the abundance of specific species and their individual or collective functions[9,10,11,12]. Furthermore, the effects of a particular diet on individuals in the population differ from person to person, and may be influenced by a combination of host and microbiome features, the latter mostly determined by the environment rather than genetic background, and thus is potentially more amenable to intervention[13,14].

Collectively, three chemically- and biologically-complex systems function together and influence each other to determine an individual's dietary responses: diet, which consists of thousands of different chemical molecules and varies between individuals not only in composition, but also in timing and regularity of consumption; the microbiota, which comprises several hundreds of bacterial strains that form an ecological network with more or less favourable states; and host physiology and metabolism that encompasses secretion of digestive enzymes and other molecules to the gut, and immune regulation in response to bacterial colonization of body surfaces[15,16]. These three systems are highly inter-connected and inter-dependent.

In the same manner as personalized medicine **[G]**, personalized nutrition approaches aim to identify key microbiome features that predict a response to particular food components which can then inform the design of a diet leading to favourable outcomes. The main challenge in harnessing the potential of microbiome-informed personalized nutrition is to identify how the host, their microbiome and dietary exposures interact in impacting dietary responses.

In this Review we explore how diet shapes the microbiota, how the dietary–microbiome cross-talk may affect disease development and progression, and how this information could be harnessed to design tailored diets. We also highlight current limitations, challenges and unknowns in decoding these complex multi-factorial networks in gaining a better understanding of environmental, microbial and genetic integration of person-specific responses to food.

Dietary influences on the microbiota

One of the desired outcomes of a dietary intervention is to change the composition of the bacterial consortia in the gut from a disease-associated to a more homeostatic state. Although twin studies have indicated a role of host genetics in shaping human gut microbiota composition, it is outweighed by environmental factors[13,17]. Several population-based studies have revealed diet as a dominant determinant of inter-individual microbiota variation[18,19].

Environmentally-driven dietary fluctuations alter the gut microbiota

The cyclic changes in human gut microbiota due to seasonal variation in diet, especially for people living in traditional societies, is a prime example of how potent diet is in shaping the microbiota (Figure 1a). In the community of Hadza hunter-gatherers in Tanzania, more frequent berry foraging and honey consumption in the wet season result in significantly lower abundances of the phylum Bacteroidetes (particularly the family *Prevotellaceae*) than in the dry season, when hunting becomes the dominant activity. Consistently, the wet-season Hadza gut microbiome possesses remarkably fewer genes encoding plant, animal and mucin carbohydrate-active enzymes (CAZymes) compared to the dry-season microbiome[20]. Hutterites, an isolated, communal-living population in North America, consume more fresh vegetables and fruit during summer and more frozen or canned food during winter. This dietary variation between seasons is thought to partly explain the microbial differences detected in their stools between seasons. In the summer, when more fib is consumed, Bacteroidetes (complex carbohydrate digesters) is more abundant, whereas Actinobacteria, which are specialized in degrading specific types of fibres, are depleted[21].

Another important factor driving dietary changes and subsequent microbiome alterations is urbanization **[G]** (Figure 1b)**.** Urbanization is associated with changes in composition, loss of diversity and loss of particular species, such as *Treponema*[22]. Non-Westernized populations such as the Hadza consume mainly raw or wild foods resulting in a gut microbiota with higher diversity compared to Western populations, whose diet derives almost entirely from commercial agricultural products[8,13,22,23]. A rural diet leads to enrichment in Bacteroidetes (including genera *Prevotella* and *Xylanibacter*), allowing rural populations to maximize energy intake from fibres, which is concordant with a depletion in Firmicutes[24]. Strikingly, the loss of diversity seen in westernized populations was also found to occur in individuals who migrated from developing nations to the United States as early as six to nine months after arrival. In the guts of these immigrants, the Western-associated genus *Bacteroides* started to displace the non-Western-associated genus *Prevotella*[25]. Importantly, in comparison to simpler and more homogenous diets in rural areas, urban environments offer a large variety of foods, which leads to greater inter-individual variability of gut microbiomes[26,27]. In addition to the dietary

changes, urbanization is associated with antibiotic use, pollution and improved hygiene, thus further contributing to the increase in variability of gut microbiota in the Western societies.

Personalized microbiota responses to dietary components

Changes in dietary macronutrients, including fat, protein and carbohydrates, lead to significant shifts in the human gut microbiota[28]. As shown in many human intervention studies[10,28], the diet-induced alterations of gut-associated microbial communities can occur in a rapid and reproducible manner. Specifically, short-term extreme changes in diet are sufficient to alter the microbiome, for example, within four days when an entirely animal[10] or plant based diet was consumed[10] or within a fortnight when the diet fibre and fat contents were modified[28]. In humanized gnotobiotic mice, shifting from a low-fat, plant polysaccharide-rich diet to a high-fat, high-sugar diet alters the microbial community structure and metabolic pathways within a single day[29]. On the other hand, mild changes in some nutritional components are not easy to disrupt the resilience of the gut microbiome, for example, the consumption of different varieties of bread leads to a minor alteration in gut microbiota composition, and in highly person-specific manner[30]. It is important to note that, besides diet, individualized gut microbiota configuration is affected by many other factors, including age, sex, medications and ethnicity[8,13,31]. By exerting effects on the microbiota, these individual traits further confound the effect of diet in shaping the gut microbiota, making it more complex to evaluate the collective responsiveness[32].

Dietary fat strongly affects gut microbiota composition and function, which in turn influences host metabolism. A high saturated fat and low fibre diet in mice results in a decrease in Bacteroidetes and an increase in Firmicutes and Proteobacteria[33,34,35]. More specifically, the increase in body fat percentage in mice fed a high fat diet was positively associated with *Lactococcus* and *Allobaculum* species but was negatively associated with *Akkermansia* species[36]. It should be noted that the translational potential of dietary fat–microbiome cross-talk in rodent studies to humans is limited. This is possibly due to the known divergences in dietary composition and complexity, fat-induced metabolic derangements **[G]** and microbiome configurations between rodents and humans[37,38]. In humans, a high intake of dietary fat (mainly saturated fatty acids) is associated with reduced microbiota richness and diversity in both adults and infants[39,40]. A recent intervention study showed that a high-fat diet in heathy adults is associated with increased levels of *Alistipes* and *Bacteroides* species, a decrease in *Faecalibacterium* spp., and elevation of the faecal cometabolites p-cresol and indole, which are associated with cardiovascular and metabolic disorders[41]. The modulation of gut microbiota by other dietary fat types remains unknown. Current evidence suggests that in

healthy humans, the consumption of omega-3 polyunsaturated fatty acids (PUFAs) leads to an increased abundance of several butyrate **[G]**-producing bacteria, in line with the known anticancer and anti-inflammatory effects of omega-3 PUFAs[42].

Changes in dietary fat intake lead to alterations in gut microbiome composition in a highly person-specific manner. In healthy individuals, even short-term moderate changes in dietary saturated fat levels result in substantially different individual microbiota responses[43]. Moreover, a higher baseline of microbial diversity is associated with less change in the gut microbiota in response to dietary fat[43], supporting the notion that higher diversity offers greater resilience to dietary perturbations, whereas lower diversity is less optimal.

Similar to fat, protein content in food influences the gut microbiota composition with substantial inter-personal variation in the species composition and abundance. The source of protein affects the gut bacteria, as showed in rats fed meat-derived proteins and non-meat-derived proteins (casein and soy)[44]. In humans, a long-term animal protein-rich diet is associated with the Bacteroides enterotype **[G]** [45]. A short-term animal protein-rich diet consistently increases the level of bile-tolerant bacterial species (including *Alistipes*, *Bilophila* and *Bacteroides*) while decreasing the abundance of saccharolytic microorganisms **[G]** (including *Roseburia* spp., *Eubacterium rectale* and *Ruminococcus bromii*)[10]. By contrast, consumption of a plant protein diet, based on glycated pea proteins, significantly increases the levels of commensal lactobacilli and bifidobacteria, and elevates short chain fatty acid (SCFA) production in humans[46].

Alpha (intra-individual) diversity is a predictor of the extent of microbiota composition change upon the short-term consumption of different protein sources (red meat, white meat and nonmeat sources) in healthy subjects. Importantly, the changes are also highly variable between individuals without strong population level trends[43]. Similarly, sulfur-containing amino acids in the diet do not significantly impact the abundance of intestinal sulfate-reducing bacteria (*Desulfovibrio* and *Bilophila* species) on the population level, whereas personal responses in microbial community structures and functions do exist and are maintained over time[47].

The effect of carbohydrates on the gut microbiota is complex, depending on their types and amounts. In humans, the long-term consumption of complex carbohydrates has been shown to promote the *Prevotella* genus[45]. Dietary fibre impacts human gut microbial ecology resulting in high abundance of Bacteroidetes (*Prevotella* spp.) [23,24]. Specific bacteria can grow on certain types of carbohydrates and therefore diet can select for or eliminate particular species. For example, bifidobacteria are selectively efficient degraders of arabinoxylans present in

wheat and other grains[48], therefore Hazda hunter-gatherers eating grain-depleted diets[23] and human adults consuming a grain-reduced diet[49] have fewer bifidobacteria in their microbiota. In overweight people, diets that are high in non-digestible carbohydrates result in a significant increase in bacteria within the phylum Firmicutes, including *Ruminococci* spp., *Roseburia* spp. and *Eubacterium rectale*[50]. By contrast, diets poor in fermentable carbohydrates in obese individuals result in a significant reduction of butyrate-producing Firmicutes, and a decline in faecal butyrate levels[51]. In mouse models, dietary fibre deprivation promotes the expansion of colonic mucus-degrading bacteria, thus leading to intestinal barrier dysfunction and susceptibility to mucosal pathogens[52]. In contrast to dietary fibre, digestible simple sugars which are prevalent in the Western diet, inhibit the colonization of commensal *Bacteroides thetaiotaomicron* in murine gut, and promote the development of obesity[53].

Although response to fibre has a common signature within the population, heterogeneous and highly personalized shifts in the human microbiota have also been detected in response to carbohydrates, including dietary fibre[50,54], resistant starches[55], and carbohydrate-containing prebiotics **[G]** [30,56,57]. Consumption of a high-fibre weight-stabilization or weight-loss diet in obese individuals affects the intestinal microbiota composition with significant inter-personal variation[58,59,60]. Although faecal butyrate levels generally increase upon indigestible carbohydrate consumption, the response also varies widely among individuals[61]. The microbiome response to dietary carbohydrates can be predicted from the baseline microbial diversity[58]. This dietary intervention is less efficient in improving clinical phenotypes in individuals with lower microbial gene richness[59]. In addition, prior dietary habits could also potentially influence the gut microbiota response to dietary interventions. For example, healthy individuals with habitual high fibre intake exhibited greater gut microbiota responses to an inulin-type fructan prebiotic compared to those with low fibre intake[62], highlighting the importance of considering habitual dietary patterns when aiming to modulate gut microbiota through dietary interventions.

Various dietary additives including emulsifiers **[G]** , artificial sweeteners and probiotics **[G]** have been shown to induce gut microbiota changes in animal and human studies. Supplementation of dietary emulsifiers in mice results in a reduction in Bacteroidales and an increase in *Ruminococcus gnavus* and other mucolytic bacteria, and such changes in the microbiota are sufficient to drive the development of metabolic syndrome in germ-free mice, as shown by faecal microbiota transplantation (FMT) **[G]**[63]. Mechanistically, dietary emulsifiers induce low-grade inflammation in mice by increasing lipopolysaccharide and flagellin levels, which may lead to inflammation-associated colon carcinogenesis[64].

Many non-caloric artificial sweeteners like saccharin, sucralose and aspartame were

demonstrated to shape gut microbiota composition in both animals and humans[65]. Although considered safe, the contribution of some artificial sweeteners to the development of metabolic or inflammatory disorders through the induction of gut dysbiosis has been shown in some mouse studies, linking saccharin treatment to the development of liver inflammation[66], and sucralose consumption to disrupted lipid metabolism[67] as well as intestinal inflammation[68]. In humans, the consumption of artificial sweeteners is associated with the induction of glucose intolerance through compositional and functional alterations in the intestinal microbiota, and such metabolic effects are transferable to germ-free mice by FMT[69]. More importantly, personalized responses to non-caloric artificial sweeteners in human individuals have been observed in both short- and long-term non-caloric artificial sweeteners consumption studies. These differences in individual responses are possibly due to differences in the intestinal microbiota, but this needs further validation.

Live bacteria, also termed probiotics, represent one of the most widely consumed dietary additives. Studies investigating the effect of probiotics on the human gut microbiome report inconclusive and contradictory results. Probiotic intervention with *Lactobacillus* species significantly modulated the faecal microbiota only in some individuals[70,71], whereas a systematic review of randomized controlled trials in healthy adults[72] and a probiotic intervention study in healthy infants[73] failed to report an effect of probiotic consumption on faecal microbiota composition. Such conflicting results might stem from variations in individual responses to probiotics and probiotic colonization. Indeed, dietary probiotic consumption induces a highly individualized colonization pattern in the gut mucosa of both healthy and antibiotic-treated humans, subsequently influencing the gut microbial community and host physiology in a person-specific manner, which can be predicted by the microbiota prior to treatment and host features[74,75]. Another specific probiotic, *Bifidobacterium longum* AH1206 colonizes the gut persistently in only ~30% of individuals. Its colonization can be predicted as it correlates with low abundance of endogenous *B. longum* and an underrepresentation of carbohydrate-utilization genes prior to treatment[76]. Despite this, the efficacy of probiotics in the modulation of the gut microbiome in health and disease needs further investigation and an individualized approach is merited given the great inter-individual variation in microbiome configurations.

Personalized host response to diet

There is emerging evidence that the changes dietary interventions elicit in host metabolism are person-specific, and that this heterogeneity stems from unique microbiota signatures in addition to host physiology (Figure 2)[14].

The level of one particular bacterial species may be a predictor of the response to a particular

diet. Healthy individuals who showed improved glucose metabolism following barley kernel-based bread (BKB) **[G]** consumption were associated with a higher abundance of *Prevotella* species, suggesting that *Prevotella* has a role in the individuality of BKB-induced metabolic improvement[77]. Similarly, intake of whole grains induced anti-inflammatory responses and blood glucose level changes of different magnitudes in healthy subjects; those with greater improvements in blood IL-6 levels had higher levels of *Dialister* and lower levels of Coriobacteriaceae species in their stools, whereas *E. rectale* was correlated with postprandial glycemic and insulin responses[78]. In overweight and obese adults on a calorie restricted diet, individuals with higher levels of baseline *Akkermansia muciniphila* exhibited a greater improvement in insulin sensitivity and lipid metabolism, and a greater reduction in body fat, suggesting a predictive role of *A. muciniphila* in assessing response to dietary interventions[79.] Individuals can be classified into responders and non-responders based on the outcome of the dietary interventions. For example, in childhood inflammatory bowel syndrome (IBS), individuals that respond to a low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet have higher proportions of *Bacteroidaceae*, *Erysipilotrichaceae* and *Clostridiales* species with a greater capacity for saccharolytic metabolism, whereas non-responders harbor higher levels of bacteria belonging to the genus *Turicibacter*[80]. Similarly, compared to non-responders, individuals that respond to a low fermentable substrate diet in the management of childhood IBS are characterized by higher levels of taxa belonging to the genera *Sporobacter* and *Subdoligranulum* and a lower abundance of taxa belonging to Bacteroides[81].

More accurate personalized prediction methods that differentiate responders from non-responders have been developed by combining baseline microbiome signatures with other important individual traits. In an 800-person cohort comprising overweight or obese non-diabetic individuals in Israel, high interpersonal variability in the postprandial glycemic response (PPGR) **[G]** to identical foods were predicted accurately by gut microbiome, dietary habits, blood parameters and anthropometrics using a machine-learning approach. Different dietary components, age, serum parameters and the microbiome all exhibit relative contributions to personalized predictions, showing either beneficial or non-beneficial but person-specific predictive effects. More specifically, 21 beneficial and 28 non-beneficial microbiome-based features were identified in line with their relative contributions to the algorithm-based predictions. More strikingly, short-term personalized dietary interventions based on these predictions result in consistent gut microbiota alterations and a lower PPGR[14]. The level of contribution of the microbiome and of discrete clinical and laboratory features to the predictability may vary, and merits further examination in diverse populations. This personalized approach to predict the PPGR to food was recently validated in a non-diabetic

population in the United States[82]. More recently, a large-scale twin study revealed high interpersonal-variability in postprandial responses (glycemic, insulinemic and lipemic responses) to diets, highlighting that even genetically-similar twins respond differently to identical meals[83]. This suggests that, rather than genetic makeup, non-genetic factors, including gut microbiome, host metabolism, meal timing, nutritional contents and exercise have a fundamental role in determining the response to food. This further supports the notion that to achieve the same result in different individuals, personalized approaches to diet need to be employed. Nevertheless, such a 'tailored nutritional approach' is in its infancy and more feasible, sustainable personalized nutritional strategies need to be further developed to optimize one's gut microbiome and to improve the host responsiveness.

Interplay between dietary timing, gut microbiota and the host

Time-specific dietary intake, including circadian feeding patterns and intermittent fasting, can impact the gut microbiota and host physiology (Figure 1a). In both mice and humans, the rhythmicity of dietary intake couples with the host circadian clock to shape the daily circadian fluctuation in microbiota composition and function[84,85]. Alterations in feeding patterns can flexibly change the microbiota rhythmicity, for example, a high fat diet dampens the microbial diurnal oscillations in mice, which in turn influences host circadian clock function and metabolism[86,87].

Intermittent fasting (that is, voluntary abstinence from consuming drinks and food during certain periods) has been hypothesized to promote metabolic health through the effects on gut microbiota[88]. In mice, intermittent fasting reshapes the gut microbiota composition and increases the level of the metabolites acetate and lactate, which directly promote adipose tissue browning and reverses high-fat-diet-induced obesity[89]. In addition to metabolic disease, the microbiome altered by intermittent fasting also led to certain protections from multiple sclerosis in mouse models and in patients[90]. The role of gut microbiota in mediating the beneficial effect of intermittent fasting on other diseases, and the personalized aspects of this intervention, warrants further investigation.

Although the gut microbiota can be reshaped by diet, it is worth noting that in a substantial portion of individuals, obesity-induced gut microbiota alterations persist, even after successful dieting. Such persistence can drive faster weight regain and greater metabolic derangement, a phenomenon that can be rescued by FMT or flavonoid-based metabolite treatment in mice[91]. Such lasting effects of past dietary history and reduced microbiota reversibility can also be observed during repeated dietary shifts in mice[92]. Similarly, mice fed a low-fibre diet gradually lose microbial diversity over generations, which is not reversible through the reintroduction of dietary fibres[93]. Such microbiota persistence or extinction after a particular diet should be

considered when designing effective microbiota-targeted therapies.

Microbial influences on host physiology

Ingested food, before it is digested and absorbed into the bloodstream, comes into contact with bacteria. Both the composition and digestive functions of bacteria in small and large intestine differ because they depend on the niche and nutrient availability. Bacteria aid the digestion of food and, in this process, produce a plethora of metabolites that often are not produced by the host (Figure 3). The metabolites originating from the metabolic reactions in the gut can affect human physiology in both a positive and a negative fashion. Different microbiomes have different potentials for producing certain metabolites, depending on the metabolic capabilities and metabolic interactions within the population. Therefore, another personalized diet design strategy is to supply compounds that are precursors of beneficial bacterial metabolites or eliminate those that lead to toxic or harmful ones.

Food components digestion

Gut microbiota partakes in the digestion of food and notably, it digests complex carbohydrates from the diet that would otherwise be unavailable to the host. These molecules are mostly plant cell wall derived polysaccharides and storage carbohydrates. Fibres, such as β-glucan or pectins, are not digested in the small intestine because humans lack the enzymes that digest them or they are not accessible to the action of enzymes (for example, resistant starches)[94,95].

Supplementing the diet with fibre is a relatively common practice in the western world. Designing personalized diets with respect to fibre requires an understanding of the metabolic capabilities of each person's microbiome as some carbohydrates may be digested and beneficial to one person, but undigested and inert in another.

Gut bacteria encode many different CAZymes that, mainly in colon, mediate the digestion of wide variety of carbohydrates[96,97]. Although many carbohydrate degradation enzymes are shared between bacterial species and are present in the majority of humans, some functionalities evolved only in particular populations where they provide a specific function. For example, porphyranases and agarases produced by gut bacteria of Japanese people digest seaweed carbohydrates (which are commonly consumed in Japan, but European populations lack the bacterial species that produce these enzymes and therefore cannot digest them[98,99].

Identifying CAZymes often involves searching metagenomes using sequence information of known enzymes, but it is essential to use phenotypic assays to identify and characterise novel enzyme families[100,101]. Metagenomic analyses are largely limited by insufficient functional annotation of bacterial genes. The fact that a bacterium harbours a gene does not imply that

the gene is expressed. In presence of different energy sources, bacteria may express genes for the digestion of one, a group or several of these enzymes, depending on the environmental context. Moreover, bacteria form a metabolic network and cross-feed each other providing an additional level of complexity. The changes in bacterial composition along the gastrointestinal tract mean that the same bacterium may have a different metabolic profile depending on its niche.

Synthesis and modulation of bioactive compounds

In the process of carbohydrate digestion, bacteria produce SCFAs, including propionate, butyrate and acetate, that have multiple beneficial effects on the host in addition to their roles as energy sources for gut epithelial cells and acting as signalling molecules[102,103,104,105,106,107]. Short chain fatty acids are among many other compounds that the microbiota produces. The wide spectrum of molecules that is synthesised by the microbiota has a variety of effects on human physiology. Depending on the synthetic potential of the microbiota, eliminating or supplying specific substrates leads to changes in the production of particular metabolites. Knowledge of these synthetic pathways could lead to the design of targeted dietary interventions that modulate the levels of these metabolites.

Vitamins, by their definition, are not synthesised by the host, but rather they need to be supplemented. Food is the main source of vitamins and their precursors; however, provided with substrates, gut bacteria can contribute to the synthesis of vitamins (mainly vitamins from the B family and vitamin K)[108]. Microbiota-derived vitamins are not sufficient to support human physiology, and the estimation of their contribution to the daily intake varies substantially, and on average ranges from 0.078% for pantothenate (vitamin B5) to 86% for pyridoxine (vitamin B6)[109]. The capacity of microbiota to produce vitamins is not stable, for example, the number of genes involved in the biogenesis of folate increases with age, whereas those encoding for enzymes of the cobalamin (vitamin B12) synthetic pathway decrease with age[6]. As the potential for synthesis of vitamins differs between microbiotas, the dietary needs for them will be different among individuals.

Bacteria also have the capacity to detoxify and eliminate harmful molecules by metabolising them. *Oxalobacter formigenes*, *Enterococcus faecalis* and several *Bifidobacteria* species degrade the dietary compound oxalate, a major risk factor for kidney stones[110,111]. Thus, individuals who suffer from kidney stone formation could, in addition to avoiding oxalate-rich foods, modulate their microbiota to enrich for efficient oxalate-degrading species.

On the other hand, bacteria can convert L-carnitine, choline and phosphatidylcholine into trimethylamine N-oxide (TMAO), a compound which is associated with the development of cardiovascular diseases. Noteworthy, the bacteria that encode the enzymes necessary for this conversion are on average in higher abundances in populations of omnivores in comparison

to vegetarians or vegans[112,113]. Ongoing studies are aiming to test if cardiovascular diseases can be controlled by TMAO level reduction through a diet low in L-carnitine, choline and phosphatidylcholine, and a gut microbiota low in TMAO producers.

Similarly, other molecules may be avoided in food if their metabolites are deleterious. For example, members of microbiota that convert dietary ethanol into toxic acetaldehyde[114,115]; synthesise the tumour-associated polyamnie N(1),N(12)-diacetylspermine[116]; produce phenylacetate from phenylalanine, which contributes to development of nonalcoholic steatohepatitis **[G]**[117]; and tyrosine derivative 4-ethylphenylsulfate that was implicated in the development of autism-like behaviours in a mouse model[118].

The synthesis of many compounds is complex and cannot easily be analysed as many bacteria participate in conversions and multiple products arise. For example, tryptophan derivatives include several compounds including indole, tryptamine, indoleethanol, indolealdehyde, indolelactic acid, indoleacetic acid, indolepropionic acid, indoleacrylic acid and 3-methylindole. The bacterial species and pathways responsible for the production of these metabolites was reviewed recently[119,120]. The physiological effects of indole derivatives include modulation of immune responses through aryl hydrocarbon receptor signalling[121,122,123,124], regulation of barrier function through the pregnane X receptor (PXR)[125], regulation of insulin secretion through regulation of glucagon-like peptide-1[126], and it was suggested that these compounds may have antioxidative and anti-inflammatory properties[127]. In addition to effects on the host, metabolites also act on bacteria through cross-feeding mechanisms, signalling and quorum sensing; however, these effects remain largely unexplored.

Regulation of food absorption

Bacteria affect human physiology and food absorption by regulating the bile acid pool size and composition. Primary bile acids **[G]** are produced from cholesterol in hepatocytes and are released into the duodenum upon ingestion of food by humans. In the intestine, bacteria convert primary bile acids into secondary bile acids through deconjugation of taurine and glycine, and dehydroxylation. This leads to an expansion of bile acid pool heterogeneity[128,129,130,131]. The detergent properties of bile acids aid fat digestion and absorption by delivery of lipids, lipid soluble vitamins and other hydrophobic compounds, to the brush border of the intestine[132]. Furthermore, bile acids are potent signalling molecules that signal through Farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (GPBAR1) and regulate metabolism in virtually all tissues[133,134]. Glucose and glucose 6-phosphate absorption is regulated by bile acids through FXR signalling[135]. Differences in the composition of the bile acid pool between humans with different microbiotas and diets may lead to

differences in FXR and GPBAR1 signalling as well as absorption of dietary components, but to date there are no in depth studies of these aspects.

Modulation of host metabolism

Metabolic health and weight control are the main targets for dietary interventions. Currently, the practice is to advise individuals to eat foods that are low in calories, high in fibre, with a low glycemic index **[G]**. These diets are not always effective and as they are very restrictive, many patients find it difficult to follow them. There is a strong evidence for the role of microbiome in weight gain and it was demonstrated by transplanting the microbiota from lean and obese humans into mice and observing that an 'obese' microbiota caused mice to gain weight in comparison to the mice that received microbiota from lean donors[136,137]. A high diversity of bacterial species in the gut is associated with better metabolic health and leanness[2,3,79,136]. Another feature of the microbiome from obese humans is a higher ratio of Firmicutes to Bacteroidetes species. Importantly, there are also studies reporting no association between the Firmicutes to Bacteroidetes ratio and obesity, suggesting that there is a need for greater resolution in describing bacterial composition and for further mechanistic understanding on the mechanisms by which a dysbiotic microbiota contributes to metabolic derangements[138,139,140]. In patients undergoing surgeries such as vertical banded gastroplasty or Roux-en-Y gastric bypass, gut bacterial consortia change drastically and it was suggested that the beneficial effects of these interventions are at least partially mediated by microbiota alterations[141,142]. These effect is mediated by changes in energy harvest (that is, the capacity of the microbiota to harvest energy from the diet) and through interaction between bacteria or their components and the host[139,143]. All these observations suggest that diet composition is not the only determinant for weight gain, and that the microbiota is a key factor in regulating energy harvest and metabolism. Nevertheless, it is not trivial to identify whether a specific microbiota has a high or low energy harvest capacity and whether it induces obesity, solely from the metagenomics data. Currently, the conclusions of studies associating microbial signatures with obesity, or any other phenotype, are often contradictory due to relatively small sample sizes and to the high inter-individual variability, but with studies of large cohorts, finding the microbial signatures of different phenotypes and diseases could be within our reach.

Stepping away from correlation to causation may be facilitated by unravelling underlying mechanisms. *A. muciniphila* was found to correlate with body mass index (BMI), fasting glucose and subcutaneous adipocyte diameter[79,144]. Furthermore, administration of *A. muciniphila* in mice ameliorates high-fat diet-induced weight gain[79] and it was suggested that increases in *A. muciniphila* abundance as a result of metformin treatment contributes to the improvement in metabolic parameters of individuals taking this drug[145]. Interestingly, pasteurised *A. muciniphila* is even more potent than live *A. muciniphila* in reducing metabolic

derangements associated with obesity. Mechanistic studies showed that *A. muciniphila* membrane protein Amuc_1100 binding to TLR2 is partially responsible for improvement of gut barrier function and metabolic parameters[144,146]. These studies propose using *A. muciniphila* as a probiotic to facilitate metabolic health and prebiotics are potential way to increase *A. muciniphila* abundance.

Modulation of host immunity

The second most studied effect of the microbiota derived molecules is their effect on the immune system of the gut, barrier function, inflammatory diseases such as inflammatory bowel disease (IBD) and metabolic diseases.

SCFAs produced by members of microbiota such as *Faecalibacterium prausnitzii* nourish gut epithelial cells, promote barrier function in the gut and thus have an anti-inflammatory effect[2,147]. The integrity of the mucosal barrier is regulated by the microbiome through indole-induced PXR signalling[125], through IL-22[148], and through modulation of the production of mucus by goblet cells[149]. In the case of a dysfunctional intestinal barrier, higher amounts of lipopolysaccharide (LPS) enter systemic circulation causing so-called 'metabolic endotoxemia', which results in low-grade inflammation in tissues[150]. Furthermore, LPS can also cross the gut barrier transcellularly in chylomicrons **[G]**[151]. LPS that enters portal circulation first acts on both mesenchymal and immune cells of the liver *via* TLR4 signalling, altering their function, and then the LPS that escapes the liver enters systemic circulation and acts systemically. In adipose tissue, changes in immune function due to LPS signaling *via* TLR4 result in metabolic derangements[152]. In mice, the levels of LPS in the blood can be reduced by antibiotic treatment[150,153], but a similar approach in obese humans did not yield therapeutic results[154].

Microbiota-based personalized nutrition

The future of personalized nutrition spans main or auxiliary therapy in diseases from metabolic diseases and immune diseases of the gut to neurological disorders and cancer; prophylaxis for diseases for which an individual has a higher risk due to genetics or lifestyle; and enhancement of performance and achievement of various physiological goals as needed, for example, in sports (Figure 4).

The diet may be designed rationally or using machine-learning or artificial intelligence pipelines. The first approach would include the identification of particular microbiome signatures and their associated metabolic properties. Such signatures may be simple: the presence or absence of specific species, genes or enterotypes **[G]** in the microbiome, or may be complex and include many different features. Once the population is stratified, the second

step is to identify beneficial foods for all microbiome types and for desired outcomes. For example, for individuals with a history of atherosclerosis in the family, one would test the microbiome for the levels of TMAO-producing bacteria and enzymes, check the level of TMAO in the blood and, based on these data, suggest a diet low in its precursors to those who have high levels of TMAO-producing bacteria and TMAO in the blood.

The first approach is feasible for some measures and it is sufficient to predict responders and non-responders in some cases, but when addressing complex traits, machine learning methods are more likely perform better. Machine learning methods require training a model on datasets of microbiome and clinical features, and the physiological responses to diet to learn the outcome of the effect of a specific food on physiology. This approach has an advantage in that it does not require prior knowledge and an understanding of the complex mechanistic interactions, so it theoretically can be performed for any quantifiable feature.

Perspectives

Microbiota-based nutrition is beginning to be utilized to predict variable clinical phenotypes or guide personalized therapies in metabolic syndrome as well as gastrointestinal disorders. Recent successful efforts in the development of personalized diets regulating blood sugar levels provide hope for further advancements in the control and treatment of disease[14,155]. Furthermore, the healthy population may benefit from personalized dietary programs as a means of disease prevention and weight regulation.

Controlling the levels of specific molecules, such as lipids, vitamins, TMAO and so on in blood or several molecules in the same time will be next step in the development of personalized nutrition. Designing a diet that accounts for several different attributes may be challenging, as particular foods and the microbiota associated with particular metabolites may not correlate. Other approaches to regulate the diet–microbiota axis may include probiotics and prebiotics to alter the composition of the microbiota to achieve better results in combination with personalized diet regimens. Nevertheless, designing personalized diets based on the microbiome remains challenging. Currently, most studies involving interactions between food, the microbiome and human physiology remain correlative and only few of them describe mechanisms by which these three entities act on each other. Furthermore, mechanisms of the interactions are commonly concluded from experiments performed in mice, which is a suboptimal model for human physiology[156]. Studies in humans are challenging, because of the vast individual variability, lack of control over microbiome composition and difficulties in complying to experimental diet regimens. To overcome these issues, human nutrition studies require large cohorts of participants and, to study some metabolic changes, experiments have to last for long periods of time, which is often unrealistic.

Each of these systems (human physiology, microbiota and food) is complex and each comes

with a unique set of technical limitations. Results from the characterisation of the microbiome are sensitive to sample storage conditions, methods of DNA extraction and sequencing library preparation protocols. Standardisation of microbiome characterisation is lacking at all steps of the process, starting from sampling, through different targeted and untargeted sequencing library preparation approaches to data analysis using different quality control guidelines, bacterial genome databases and tools. Furthermore, we know the function of only a fraction of genes encoded in the microbiome, and for most of them we predict their function based on sequence similarity. Even in *Escherichia coli*, the most thoroughly studied bacterium, there are still ~35% of genes for which a function is unknown[157] and for other bacteria, especially those difficult to culture, this number is much higher. Functional studies of bacterial metabolism are usually performed *in vitro* in monocultures, which do not recapitulate the actual environment of the gut, and disregard the cross-feeding network that is formed by the gut microbiota and the responses from the host. Identification of metabolites using mass spectrometry also has limitations originating from sample preparation and extraction, the method used and the analysis for molecule identification[158].

To overcome this complexity, various computational tools are increasingly being utilized. Many of these algorithms are 'black-boxes', which are fed with information such as food composition, microbiome composition and physiological human responses in predicting their cumulative impacts on desired outcomes. Using these models provides no understanding of why particular foods, on the background of particular microbiota, gives one response and not the other, but given a good training dataset, the algorithm is able to identify key parameters and predict physiological responses. Moreover, the nature of the training dataset may limit applicability of such approaches across populations, by disregarding regional microbiome variability or disease state. Furthermore, the personalised nutrition studies are performed in western populations and are very embedded in western food culture, making it difficult to translate to other societies where different products are consumed. Last, but not least, designing an optimal diet is not the only component necessary to reach individual's goals — nutritionists and psychologists are still necessary to ensure compliance and support. Such a comprehensive approach comes with a relatively high cost, and it is vital to assess if the benefits for the patient in long term are significant enough for such treatments to be covered by public health care.

With these limitations notwithstanding, the latest advances in microbiome research bode well for the future in respect of generation of large and comprehensive datasets and using computational tools to design diets that would regulate particular clinical parameters. The long road will necessitate an enhanced understanding of the mechanistic underpinnings of personalized diets, simplification of the approach that would enable upscaled utilization by large populations, but may hold promise in rationally harnessing nutrition in preventing and

treating human disease.

Box 1. Forces shaping the gut microbiome

The arms race between pathogens and the host leads to rapid evolution of the host immune system. These changes in do not leave the microbiota unaffected. In humans, the environment (food composition and timing, antibiotics and other drugs use, weather, hygiene, etc.) is the main force driving variation in the microbiota across individuals[13]. Similarly, the microbiome sampled from two baboon species in Kenya clusters according to environmental factors, such as soil[159]. This suggests that, on average, the genetic differences between humans within a population are too small to outweigh diet as a determinant of microbiome composition. Nevertheless, genetics and the resulting physiological differences may still have a role in shaping the microbiome. When the microbiome of different species of non-human primates or small mammals are analysed, the strongest determinant of differences in the microbiome was evolutionary distance rather than diet, indicating that there are major differences in the gut niche due to genetic factors between these organisms[160,161]. This suggests that genetics has a potentially interesting and important role in shaping the microbiome, and genome-wide association studies (GWAS) could provide evidence for this role. Human genetic variability is associated with microbiome features, such as variability in the genes and regulatory regions that are important for the maintenance of barrier functions[162]. The first GWAS studies have been performed and yielded divergent results, therefore to draw more significant conclusions, larger cohorts and more comprehensive datasets need to be collected and analyzed across populations[163].

Figure legends

Figure 1. Dynamic changes in the microbiome in response to diet.
(a) Dietary timing, including seasonality, circadian rhythmicity and intermittent fasting, shape the gut microbiome composition and function. (b) Changes in dietary patterns following westernization, accompanied by alterations in dietary components, result in remarkable changes in the gut microbiome composition and function. For example, shifting from a low-fat, high fibre diet to high-fat, high-protein, low-fibre diet leads to decreased alpha-diversity (intra-individual gut microbiota richness), increased beta-diversity (inter-individual gut microbiota diversity), declined abundance or even the extinction of *Prevotella* and *Treponema* species, with lower butyrate levels.

Figure 2. Personalized microbiota and host responses to diet.
Diet changes the gut microbiome composition and function in a person-specific manner, which is associated with a pre-intervention microbiome profile. Diet also results in highly individualized variation in host responses (for example, glycemic response), which can be accurately predicted by their unique microbiome signatures. By utilizing both aspects, personalized nutritional strategies can be developed to modify an individuals' microbiome and further improve one's response to a specific diet.

Figure 3. Clinically relevant bacterial metabolites.
Examples are depicted of food components that are catabolized by gut microbiota to physiologically active molecules, which signal to different tissues in the body eliciting either beneficial or detrimental responses.
Dietary fibre is degraded by bacterial enzymes to short chain fatty acids (SCFAs), that in addition to serving as nutrition for enterocytes, act as signalling molecules that bind to GPR41 and GPR 43 on surface of gut epithelial cells and immune cells, regulating the secretion of pro-inflammatory cytokines such as IL18 and through GPL-1 and PYY peptides act on the central nervous system regulation of food intake and energy expenditure. Moreover SCFAs act as histone deacetylase (HDAC) inhibitors in immune cells and adipocytes regulating their transcription through chromatin state. L-carnitine, choline and phosphatidylcholine is

converted by some members of microbiome to Trimethylamine N-oxide (TMAO), which is associated with increase prevalence of cardiovascular diseases.
Amino acid derivatives produced by microbiota also have significant roles in the modulation of host physiology. Indole molecules originating from tryptophan regulate secretion of GLP-1 with PXR signalling and influence immune response through AHR signalling. Tyrosine derived 4-ethylphenylsulfate (4EPS) was implicated in promoting autism behaviours in mice, while phenylacetate, derivative of phenylalanine, as well as acetaldehyde that originates from ethanol were shown to contribute to development of fibrosis and non-alcoholic steatohepatitis.

Figure 4. Microbiota-based diet design.
In designing personalized nutrition, factors to consider in addition to microbiome composition and function include genetics, clinical parameters, lifestyle and particular personal goals of the individual. All or subsets of these features may be used to identify personalized dietary combinations that impact microbiome composition, function and host physiology. The goals of personalized nutrition include, but are not limited to, disease control and prevention and modulation of physiology to achieve particular lifestyle.

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Glossary

- personalized medicine – medical approach in which patients are stratified into groups depending on different factors that contribute to treatment outcomes and then receive tailored treatment predicted to be the most effective
- urbanization – refers to changes from rural to urban areas and encompasses both flux of people from rural areas to cities and growth of urban areas
- metabolic derangements – pathological state in which host metabolism is dysregulated and associated with a clustering of metabolic disorders including obesity, hypertension, insulin resistance, impaired glucose tolerance, dyslipidemia
- butyrate – short chain fatty acid produced by bacteria in the gut from complex carbohydrates
- Bacteroides enterotype - human microbiomes with high prevalence of Bacteroides
- saccharolytic microorganism – microorganisms that break sugar to aquire energy
- emulsifiers – substances found in food, used to prevent separation of emulsions to achieve desired textures of food
- prebiotics – foods or compounds found in food that induce growth of bacterial species that are beneficial
- faecal microbiota transplantation – process of transferring faecal matter from one or many individuals to another in order to affect the microbiome of recipient
- probiotics – live microorganisms (bacteria or yeast) found in dietary supplements or food
- barley kernel-based bread (BKB) – bread that is made from barley kernels leading to high resistant starch and non-starch polysaccharides content
- postprandial glycemic response (PPGR) – the increase of glucose level in the blood following a meal injestion
- nonalcoholic steatohepatitis – a form of nonalcoholic fatty liver disease, characterized by at least 5% hepatic steatosis with histological liver inflammation and hepatocyte injury
- Primary bile acids – amphipathic molecules produced by the hepatocytes and released to the intestine to aid digestion and absorption of lipids
- glycemic index – numeric value on the scale from 0 to 100 that represents average glucose level increase upon consumption of particular food
- chylomicrons - lipoprotein particles composed of cholesterol, triglicerides and phospholipids and carrier proteins that allow transport of fat in the blood
- enterotypes - proposed classification of human microbiomes into three different types depending on which bacteria are most prevalent Bacteroides, Prevotella or

Ruminococcus

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