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 hardwired 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, the absorption of nutrients, shaping the mucosal immune response and the synthesis or modulation of a plethora of potentially bioactive compounds. Thus, diet-induced microbiota alterations may be harnessed in order 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 concerning these person-specific host, microbiome and diet interactions. In this Review, we describe the latest advances in understanding diet–microbiota interactions, the individuality of gut microbiota composition and how this knowledge could be harnessed for personalized nutrition strategies to improve human health.

The microbiota modulates the pathogenesis, progression and treatment of diseases, ranging from metabolic disorders to neurological diseases1–4. 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 that strongly influences the composition of the microbiota in adulthood4,5. Although early life events — including the mode of birth, type of feeding and complementary diet6,7 — have strong effects on the microbiota, it does retain some degree of flexibility and can be modulated through exposure to a variety of environmental factors8 (BOX 1). Of these, diet is the key determinant of the microbiota configuration, through modulation of the abundance of specific species and their individual or collective functions9–11. 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 influence mostly being determined by the environment rather than genetic background, and thus is potentially more amenable to intervention12,13.

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, which encompasses the secretion of digestive enzymes and other molecules to the gut, as well as immune regulation in response to the bacterial colonization of body surfaces14,15. These three systems are highly interconnected and interdependent.

In the same manner as personalized medicine, personalized nutrition approaches aim to identify key microbiome features that predict the 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, the microbiome and dietary exposures interact in shaping dietary responses.

In this Review, we explore how diet shapes the microbiota, how dietary–microbiome crosstalk may affect disease development and progression, and how this information could be harnessed in the design of tailored diets. We also highlight the current limitations,
challenges and unknowns in decoding these complex multi-factorial networks to gain a better understanding of the 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 the human gut microbiota composition, genetics are outweighed by environmental factors. Several population-based studies have revealed diet as a dominant determinant of inter-individual microbiota variation.

**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 (FIG. 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 of 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) than the dry-season microbiome. 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 fibre is consumed, Bacteroidetes (complex carbohydrate digesters) are more abundant, whereas Actinobacteria, which specialize in degrading specific types of fibres, are depleted.

Another important factor driving dietary changes and subsequent microbiome alterations is urbanization [FIG. 1b]. Urbanization is associated with changes in composition, loss of diversity and loss of particular species, such as *Treponema*24. Non-westernized populations such as the Hadza consume primarily raw or wild foods, resulting in a gut microbiota with higher diversity than in Western populations, whose diet derives almost entirely from commercial agricultural products13,14,22,23. A rural diet leads to enrichment in Bacteroidetes (including the genera *Prevotella* and *Xylanibacter*), allowing rural populations to maximize energy intake from fibres, which is concordant with a depletion in Firmicutes. 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*22. Importantly, in comparison to the simpler and more homogeneous diets in rural areas, urban environments offer a large variety of foods, which leads to greater inter-individual variability of gut microbiomes25,27. In addition to the dietary changes, urbanization is associated with antibiotic use, pollution and improved hygiene, thus further contributing to increase in the variability of gut microbiota in 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. As has been shown in many human intervention studies28–30, 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 entire animal-based or plant-based diet is consumed29, or within a fortnight when the diet fibre and fat contents are modified30. 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 day28. On the other hand, mild changes in some nutritional components do not easily 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, in a highly person-specific manner30. It is important to note that, besides diet, individual gut microbiota configuration is affected by many other factors, including age, sex, medications and ethnicity6,13,31. 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 responsiveness32.

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 Proteobacteria13,25. More specifically, the increase in body fat percentage in mice fed a high-fat diet was positively associated with *Lactococcus* and...
Metabolic derangements
Pathological states in which the host metabolism is dysregulated, which are associated with a clustering of metabolic disorders, including obesity, hypertension, insulin resistance, impaired glucose tolerance and dyslipidemia.

Butyrate
A short-chain fatty acid produced by bacteria in the gut from complex carbohydrates.

Enterotype
Proposed classification of human microbiomes into three different types, depending on which bacterial genus is most prevalent: Bacteroides, Prevotella or Ruminococcus.

Saccharolytic microorganisms
Microorganisms that break down sugar to acquire energy.

**Fig. 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 a high-fat, high-protein, low-fibre diet leads to decreased α-diversity (intra-individual gut microbiota richness), increased β-diversity (inter-individual gut microbiota diversity) and declined abundance or even the extinction of Prevotella and Treponema species, with lower butyrate levels.

**Table: Metabolic derangements**

<table>
<thead>
<tr>
<th>Pathological state</th>
<th>Metabolic disorder</th>
<th>Example</th>
</tr>
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<tbody>
<tr>
<td>Obesity</td>
<td>Metabolic syndrome</td>
<td>Fat storage, insulin resistance</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Cardiometabolic syndrome</td>
<td>High blood pressure, heart disease</td>
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<tr>
<td>Insulin resistance</td>
<td>Type 2 diabetes</td>
<td>High blood glucose, fatigue</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>Metabolic syndrome</td>
<td>High blood sugar, kidney disease</td>
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**Box 1: Butyrate**

Butyrate is a short-chain fatty acid produced by bacteria in the gut from complex carbohydrates.

**Box 2: Enterotype**

Enterotypes are proposed classifications of human microbiomes into three different types, depending on which bacterial genus is most prevalent: Bacteroides, Prevotella or Ruminococcus.

**Box 3: Saccharolytic microorganisms**

Saccharolytic microorganisms are those that break down sugar to acquire energy.

In healthy individuals, even short-term moderate changes in dietary saturated fat levels result in substantially different individual microbiota responses. Moreover, a higher baseline of microbial diversity is associated with less change in the gut microbiota in response to dietary fat, supporting the notion that higher diversity offers greater resilience to dietary perturbations, whereas lower diversity is less optimal.

A similar effect is observed in the gut microbiota composition, with substantial interindividual variation in species composition and abundance. The source of protein affects the gut bacteria, as has been shown in rats fed meat-derived proteins and non-meat-derived proteins (casein and soy). In humans, a long-term animal protein-rich diet is associated with the Bacteroides enterotype. 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 (including Roseburia species, Eubacterium rectale and Ruminococcus bromii). 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.

A-Diversity (intra-individual) 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, changes are also highly variable between individuals, without strong population-level trends. 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.

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. Dietary fibre impacts human gut microbial ecology, resulting in high abundance of Bacteroidetes (Prevotella species). 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; therefore, Hadza hunter-gatherers eating grain-depleted diets and human adults consuming a grain-reduced diet 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 Ruminococcaceae, Roseburia species and Eubacterium rectale. 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. 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. In contrast to
**Prebiotics**
Foods, or compounds found in food, that induce the growth of bacterial species that are beneficial.

**Emulsifiers**
Substances found in food, used to prevent the separation of emulsions in order to achieve the desired textures of food.

**Probiotics**
Live microorganisms (bacteria or yeast) found in dietary supplements or food.

**Faecal microbiota transplantation (FMT)**
Process of transferring faecal matter from one or many individuals to another in order to affect the microbiome of a recipient.

**Barley kernel-based bread (BKB)**
Bread that is made from barley kernels, leading to high resistant starch and non-starch polysaccharide content.

Dietary fibre, digestible simple sugars, which are prevalent in the Western diet, inhibit the colonization of commensal *Bacteroides thetaiotaomicron* in the murine gut and promote the development of obesity.

Although response to fibre has a common signature with the population, heterogeneous and highly personalized shifts in the human microbiota have also been detected in response to carbohydrates, including dietary fibre, resistant starches, and carbohydrate-containing prebiotics. Consumption of a high-fibre weight-stabilization or weight-loss diet in obese individuals affects the intestinal microbiota composition with significant interindividual variation. Although faecal butyrate levels generally increase upon indigestible carbohydrate consumption, the response also varies widely among individuals. The microbiome response to dietary carbohydrates can be predicted from the baseline microbial diversity. This dietary intervention is less efficient in improving clinical phenotypes in individuals with lower microbial gene richness. 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 exhibit greater gut microbiota responses to anulin-type fructan prebiotic than those with low fibre intake, highlighting the importance of considering habitual dietary patterns when aiming to modulate gut microbiota through dietary interventions.

Various dietary additives, including emulsifiers, artificial sweeteners and probiotics, 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). Mechanistically, dietary emulsifiers induce low-grade inflammation in mice by increasing lipopolysaccharide and flagellin levels, which may lead to inflammation-associated colon carcinogenesis.

Many non-caloric artificial sweeteners, like saccharin, sucralose and aspartame, were demonstrated to shape gut microbiota composition in both animals and humans. Although they are 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, and sucralose consumption to disrupted lipid metabolism as well as intestinal inflammation. In preliminary findings in some 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. More importantly, personalized responses to non-caloric artificial sweeteners in human individuals have been observed in both short-term 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 effects of probiotics on the human gut microbiome have reported inconclusive and contradictory results. Probiotic intervention with *Lactobacillus* species significantly modulated the faecal microbiota only in some individuals, whereas a systematic review of randomized controlled trials in healthy adults 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 by host features. 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. Despite this, the efficacy of probiotics in 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 that dietary interventions elicit in host metabolism are person-specific, and that this heterogeneity stems from unique microbiota signatures, in addition to host physiology. 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) consumption were associated with a higher abundance of *Prevotella* species, suggesting that *Prevotella* has a role in the individuality of BKB-induced metabolic improvement. 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. 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, as well as a greater reduction in body fat, suggesting a predictive role of *A. muciniphila* in assessing response to dietary interventions.

Individuals can be classified into responders and non-responders on the basis of the outcomes of dietary interventions. For example, in childhood inflammatory bowel syndrome (IBS), individuals who respond to a
low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet have higher proportions of Bacteroidaceae, Erysipilotrichaceae and Clostridiales species, with a greater capacity for saccharolytic metabolism, whereas non-responders harbour higher levels of bacteria belonging to the genus Turicibacter. Similarly, relative to non-responders, individuals who 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 by a lower abundance of taxa belonging to Bacteroides.

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 glycaemic response (PPGR) to identical foods was 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 exhibited relative contributions to the 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 resulted in consistent gut microbiota alterations and a lower PPGR. The levels of contribution of the microbiome and of discrete clinical and laboratory features to the predictability may vary and merit further examination in diverse populations. This personalized approach to predicting the PPGR to food was recently validated in a non-diabetic population in the United States. More recently, a large-scale twin study revealed high interpersonal variability in postprandial responses (glycaemic, insulinaemic and lipaemic responses) to diets, highlighting that even genetically similar twins respond differently to identical meals. This suggests that, rather than genetic make-up, non-genetic factors, including gut microbiome, host metabolism, meal timing, nutritional content 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 developed to optimize one’s gut microbiome and improve 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. 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. 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.

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. 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 reverse high-fat diet-induced obesity. In addition to the effect on metabolic disease, the microbiome altered by intermittent fasting also leads to certain protections from multiple sclerosis in both mouse models and patients. The role of gut microbiota in mediating the beneficial effect of intermittent fasting on other diseases, as well as the personalized aspects of this intervention, warrants further investigation.

**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 the bacteria in the small and large intestines differ, because they depend on their niche and on 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. The metabolites originating from the metabolic reactions in the gut can affect human physiology in both positive and negative ways. Different microbiomes have different potentials for producing certain metabolites, depending on the metabolic health of the host.
Nonalcoholic steatohepatitis (NASH). A form of nonalcoholic fatty liver disease, characterized by at least 5% hepatic steatosis, with histological liver inflammation and hepatocyte injury.

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 to eliminate those that lead to toxic or harmful metabolites.

**Food component digestion.** The 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 break them down or because 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 the colon, mediate the digestion of a wide variety of carbohydrates⁹⁶-⁹⁷. Although many carbohydrate degradation enzymes are shared between bacterial species and are present in the majority of humans, some functionalities evolve only in particular populations where they provide a specific function. For example, porphyranases and agarases produced by the 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 them⁹⁸,⁹⁹.

Identifying CAZymes often involves searching metagenomes using the sequence information of known enzymes, but it is essential to use phenotypic assays to identify and characterize novel enzyme families⁹⁰,⁹¹. 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 the presence of different energy sources, bacteria may express genes for the production 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 as signalling molecules⁹²-⁹⁷. SCFAs are among many other compounds that the microbiota produces. The wide spectrum of molecules that are synthesized by the microbiota have 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 definition, are not synthesized by the host, but rather, they need to be supplemented. Food is the main source of vitamins and their precursors; however, when 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 estimates of their contributions to daily intake vary substantially, ranging from, on average, 0.078% for pantothenate (vitamin B₃) to 86% for pyridoxine (vitamin B₆)¹⁰⁹. The capacity of the 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 age¹¹⁰. Because potential for the synthesis of vitamins differs between microbiota, the dietary needs for different vitamins will vary among individuals.

Bacteria also have the capacity to detoxify and eliminate harmful molecules by metabolizing them. *Oxalobacter formigenes, Enterococcus faecalis* and several *Bifidobacteria* species degrade the dietary compound oxalate, a major risk factor for kidney stones¹¹¹,¹¹². 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. Note that the bacteria that encode the enzymes necessary for this conversion are, on average, present in higher abundances in populations of omnivores than in vegetarians or vegans¹¹³,¹¹⁴. Ongoing studies are aiming to test whether 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, some members of microbiota convert dietary ethanol into toxic acetaldehyde¹¹⁵,¹¹⁶; synthesize the tumour-associated polyamine N₁,N₁₂-diacetylspermine¹¹⁷; produce phenylacetate from phenylalanine, which contributes to the development of nonalcoholic steatohepatitis (NASH)¹¹⁸; or create the tyrosine derivative 4-ethylphenylsulfate, which has been implicated in the development of autism-like behaviours in a mouse model¹¹⁹.

The synthesis of many compounds is complex and cannot easily be analysed, as many bacteria participate in the necessary conversions, and multiple products arise. For example, the 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

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were reviewed recently\textsuperscript{119,120}. The physiological effects of these indole derivatives include modulation of immune responses through aryl hydrocarbon receptor signalling\textsuperscript{21-24}, regulation of barrier function through the pregnane X receptor (PXR)\textsuperscript{25}, and regulation of insulin secretion through glucagon-like peptide 1 (REF.\textsuperscript{126}), and it has been suggested that these compounds may have antioxidative and anti-inflammatory properties\textsuperscript{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 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 the deconjugation of taurine and glycine and through dehydroxylation. This leads to an expansion of bile acid pool heterogeneity\textsuperscript{128-131}. The detergent properties of bile acids aid fat digestion and absorption by the delivery of lipids, lipid-soluble vitamins and other hydrophobic compounds to the brush border of the intestine\textsuperscript{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 that regulate metabolism in virtually all tissues\textsuperscript{133,134}. Glucose and glucose 6-phosphate absorption is regulated by bile acids through FXR signalling\textsuperscript{135}. Differences in the composition of the bile acid pool between humans with different microbiota and different diets may lead to differences in FXR and GPBAR1 signalling and in the absorption of dietary components, but to date there are no in-depth studies of these topics.

**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 and high in fibre, with a low glycaemic index. These diets are not always effective, and as they are very restrictive, many patients find it difficult to follow them. There is strong evidence for the role of the microbiome in weight gain, which has been 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\textsuperscript{136,137}. A high diversity of bacterial species in the gut is associated with better metabolic health and leanness\textsuperscript{138-140}. 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 of the mechanisms by which a dysbiotic microbiota contributes to metabolic derangements\textsuperscript{138-140}. In patients undergoing surgeries such as vertical banded gastroplasty or Roux-en-Y gastric bypass, the gut bacterial consortium change drastically, and it has been suggested that the beneficial effects of these interventions are at least partially mediated by microbiota alterations\textsuperscript{141,142}. This 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\textsuperscript{139,141}. 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, solely from the metagenomic data, whether a specific microbiota has a high or low energy harvest capacity and whether it induces obesity. Currently, the conclusions of studies associating microbial signatures with obesity, or with any other phenotype, are often contradictory, because of their relatively small sample sizes and high inter-individual variability, but in studies with 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\textsuperscript{99,142}. Furthermore, the administration of *A. muciniphila* in mice ameliorates high-fat diet-induced weight gain\textsuperscript{7}, and it has been suggested that increases in *A. muciniphila* abundance as a result of metformin treatment contribute to the improvement in metabolic parameters of individuals taking this drug\textsuperscript{143}. Interestingly, pasteurized *A. muciniphila* is even more potent than live *A. muciniphila* in reducing the metabolic derangements associated with obesity. Mechanistic studies have shown that the *A. muciniphila* membrane protein Amuc_1100 binding to TLR2 is partially responsible for improvements in gut barrier function and metabolic parameters\textsuperscript{144,145}. These studies propose using *A. muciniphila* as a probiotic to facilitate metabolic health, and prebiotics are a potential way to increase *A. muciniphila* abundance.

**Modulation of host immunity.** The second most studied aspect of the microbiota-derived molecules is their effects 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\textsuperscript{2147}. The integrity of the mucosal barrier is regulated by the microbiome through indole-induced PXR signalling\textsuperscript{122}, through IL-22 (REF.\textsuperscript{148}), and through modulation of the production of mucus by goblet cells\textsuperscript{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\textsuperscript{150}. Furthermore, LPS can also cross the gut barrier transcellularly in chylomicrons\textsuperscript{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 signalling via TLR4 result in metabolic derangements. In mice, the levels of LPS in the blood can be reduced by antibiotic treatment, but a similar approach in obese humans did not yield therapeutic results.

**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 is at higher risk, due to genetics or lifestyle; and enhancement of performance and the achievement of various physiological goals, as is needed, for example, in sports (Fig. 4).

The diet may be designed rationally or by using machine-learning or artificial intelligence pipelines. The first approach includes 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 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 family history of atherosclerosis, one would test the microbiome for the levels of TMAO-producing bacteria and enzymes, check the level of TMAO in the blood and, on the basis of 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 is sufficient to predict responders and non-responders in some cases, but when addressing complex traits, machine-learning methods are more likely to perform better. Machine-learning methods require training a model on data sets of microbiome and clinical features and of the physiological responses to diet, to learn the effect of a specific food on physiology. This approach has the advantage that it does not require prior knowledge and understanding of the complex mechanistic interactions related to the microbiota, 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 to 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. 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 the blood, or of several molecules at the same time, will be the 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 so as 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 a few of them describe mechanisms by which these three entities act on each other. Furthermore, the mechanisms of these interactions are commonly concluded from experiments performed in mice, which is a suboptimal model for human physiology. Studies in humans are challenging because of vast individual variability, lack of control over microbiome composition and difficulties in complying with the 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 characterization of the microbiome are sensitive to sample storage conditions, methods of DNA extraction and sequencing library preparation protocols. Standardization of microbiome characterization is lacking at all steps of the process, starting from the 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 the genes encoded in the microbiome, and for most of them we predict their function on the basis of sequence similarity. Even in *Escherichia coli*, the most thoroughly studied bacterium, the function of ~35% of genes is still unknown\(^1\), and for other bacteria, especially those that are 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 thus disregard the cross-feeding network that is formed by the gut microbiota and the responses from the host. The identification of metabolites using mass spectrometry also has limitations, originating from sample preparation and extraction, the method used, and the analysis for molecule identification\(^1\).

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 to predict the cumulative impacts these factors on the desired outcomes. Using these models provides no understanding of why particular foods, amidst the background of a particular microbiota, give one response and not the other, but given a good training data set, the algorithm is able to identify key parameters and to predict physiological responses. Moreover, the nature of the training data set may limit the applicability of such approaches across cultures, by disregarding regional microbiome variability or disease state. Furthermore, personalized nutrition studies are performed in Western populations and are much embedded in Western food culture, making it difficult to translate their findings to other societies where different products are consumed. Last but not least, designing an optimal diet is not the only component necessary to reach an individual’s goals — nutritionists and psychologists are still necessary in order to ensure compliance and support. Such a comprehensive approach comes with a relatively high cost, and it will be vital to assess whether the benefits for the patient in the long term are significant enough for such treatments to be covered by public health care.

These limitations notwithstanding, the latest advances in microbiome research bode well for the future, with respect to the generation of large and comprehensive data sets and the use of computational tools to design diets that will regulate particular clinical parameters. The long road will necessitate an enhanced understanding of the mechanistic underpinnings of personalized diets and simplification of the approach to enable its scaled-up utilization by large populations, but the approach nonetheless holds the promise of allowing us to rationally harness nutrition in preventing and treating human disease.

Published online: 20 September 2019

This study shows how healthy individuals respond to dietary fat and protein consumption in a highly individualized pattern.


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Acknowledgements

The authors thank the members of the Elinav lab and the members of the Division of Microbiome and Cancer, DKFZ, for discussions and apologize to researchers whose work was not included due to space constraints. A.A.K. was a recipient of EMBO Long Term Fellowship 2016–1088 and support from the European Union’s Horizon 2020 research and innovation programme under Marie Sklodowska-Curie Grant Agreement No. 747114. D.Z. is the recipient of a European Crohn’s and Colitis Organization (ECCO) Fellowship and is supported by the Ken Program of the First Affiliated Hospital, Sun Yat-sen University. E.E. is supported by Yael and Rami Ungar, the Leora M. and Harry B. Helsmey Charitable Trust, the Adelis Foundation, the Pearl Weinsel Merlo Scientific Progress Research Fund, the Lawrence and Sandra Post Family Foundation, the Daniel Morris Trust, the Park Avenue Charitable Fund, the Hanna and Dr. Ludwik Warsaw Cancer Research Fund, the Howard and Nancy Marks Charitable Fund, the Aliza Mousaieff Estate of Malka Moskowitz, the Estate of Myron H. Ackerman, the Estate of Bernard Bishin for the WIS-Clalit Program, Donald and Susan Schwarz, grants funded by the European Research Council, the Israel Science Foundation, Israel Ministry of Science and Technology, Israel Ministry of Health, the Helmholtz Foundation, the Else Kroener Fresenius Foundation, the Garvan Institute, the European Crohn’s and Colitis Organisation, Deutsch-Israelische Projektkooperation and the Welcome Trust. E.E. is the incumbent of the Sir Marc and Lady Tania Feldmann Professorial Chair, a senior fellow of the Canadian Institute of Advanced Research (CIFAR) and an international scholar of the Bill and Melinda Gates Foundation and the Howard Hughes Medical Institute (HHMI).

Author contributions

All authors researched the data for this article, made substantial contributions to discussion of the content, and wrote, reviewed and edited the manuscript before submission.

Competing interests

E.E. is a paid consultant at DayTwo and BiomX. All other authors declare no competing interests.

Peer review information

Nature Reviews Microbiology thanks A. Gaweit and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher’s note

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