Gut microbiome and its potential link to personalized nutrition

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Diet is increasingly appreciated to have a tremendous impact on many aspects of the host's biology in health and disease. Dietary content and timing are also central in shaping the gut microbiome, and contribute to its taxonomic and functional diversity. Regardless, current dietary recommendations remain largely non-personalized, and feature disappointing long-term efficacy in treating obesity and its complications. Personalized nutrition aims to utilize inter-individual host and microbiome variations in generating data-driven personalized dietary recommendations. While personalized nutrition has yielded encouraging and potentially clinically applicable results across several cohorts, host–microbiome interaction networks driving such crosstalk and the mechanisms mediating their metabolic impact remain elusive and merit further studies. Herein, we summarize the latest advances in utilizing diet-microbiota interactions towards the development of personalized nutrition, while focusing on the prospects, challenges and unknowns in integrating this promising new data-driven approach into human precision health.

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Introduction

Diet plays a significant role in shaping an individual-specific commensal microbiota composition and function [1–3]. Importantly, several host physiological responses to dietary interventions, such as postprandial glycemic response, also vary across individuals [4]. These personal variations have led to the consideration that host and microbiome features may contribute to the inter-individual variability in response to environmental factors such as diet [5••]. Recent efforts have utilized individualized host and microbiome datasets, in striving to develop personalized nutritional recommendations, thereby setting the framework towards the advent of precision nutrition in a variety of health contexts [6,7,8•]. Such attempts are focused on the proof-of-concept design of customized nutritional recommendations, based on host and microbiome data as modulators of glycemic responses [9] and lipid levels [10] in response to food consumption. Notably, validation of the aforementioned personalized approaches and microbiome contributions across populations and clinical scenarios may hold promise in impacting human health and risk of disease in a much larger context, such as in diabetes [11••], cardiovascular disease [12] and cancer [13], as well as metabolic syndrome and obesity [14], among others. While the mechanisms by which nutrition-microbiome crosstalk may impact disease pathogenesis remain elusive to date in most cases, increasing number of studies highlight microbiome-modulated metabolites as possible local and systemic modulators of host physiology [12,15] and disease processes [16]. Future research is needed to further decode the complex mechanisms driving such crosstalk. In this short review, we focus on summarizing key aspects of the potential roles of the gut microbiome and host features (Figure 1), as possible inputs enabling the construction of personalized nutrition approaches. We highlight recent findings, questions, and unknowns in utilizing the growing understanding of diet-microbiome interactions, and the large personalized data that they represent, towards integration into nutritional recommendations impacting human health.

Targeting the gut microbiome for personalized nutrition

A multitude of environmental factors play major roles in shaping the human gut microbiota community structure [5••]. Among them, diet is considered a pivotal determinant of personalized microbiome composition and function [17]. The impact of different dietary components, including fatty acids, proteins, carbohydrates, and additives on human gut microbiome structure and function (Figure 1a), has been reviewed in detail elsewhere [18]. Additionally, the gut microbiome can dynamically change with seasonal dietary cycling [19], immigration-related dietary shifts [20] and timing across a 24-hour period [21].

Increasing evidence has begun to shed light on the previously underestimated individualized microbiome

Figure 1
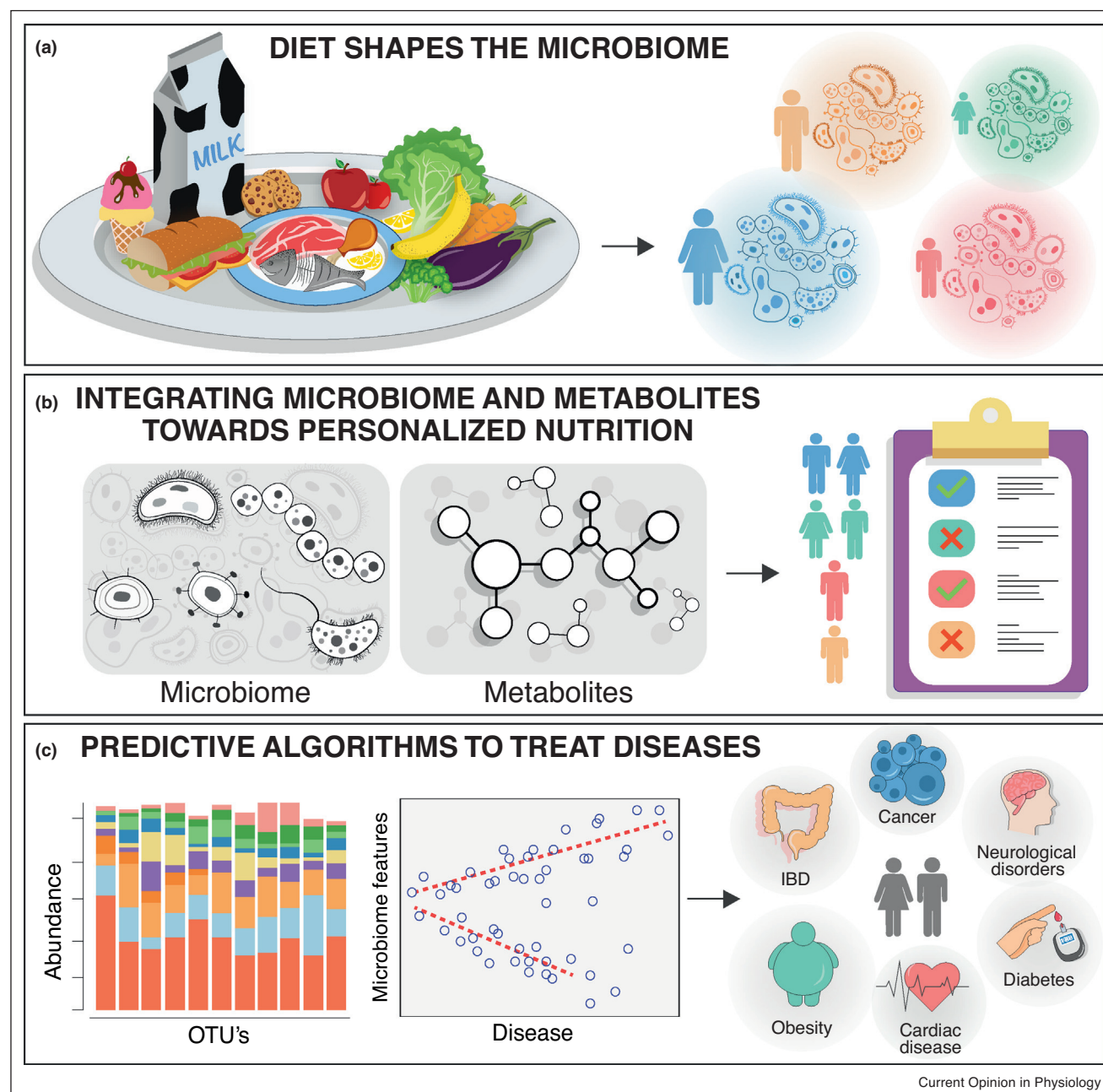
Schematic representation of the main concepts regarding the gut microbiome and its link to personalized nutrition. **(a)** Diet shapes the commensal microbiota in a person-specific manner. **(b)** Combining the microbiome with the gut-derived metabolites towards personalized nutrition approaches. **(c)** Using the microbiome composition and function as a tool to predict personalized host's responses to dietary interventions in order to treat nutrition related diseases.

responses to nutritional intervention. In a study conducted in healthy subjects, a four-week dietary intake of different concentrations of saturated fat and proteins, resulted in alterations of fecal microbial taxa abundance in a person-specific fashion [22]. Interestingly, people featuring a higher microbiome richness (α-diversity) at baseline, exhibited greater resilience to such dietary

interventions, reflected by lower β-diversity between the baseline and experimental diets [22]. In another report, short-term intake of dietary fiber in healthy adults led to person-specific fecal microbiome changes [23]. Specifically, elevated microbial richness at baseline was associated with higher abundance of *Prevotella* and *Coprococcus* species, increased levels of caproate and

valerate, as well as less microbiota shifts upon fiber intake [23]. Consumption of dietary-resistant starches among different individuals led to substantial inter-subject variations in fecal bacterial species [24] and butyrate levels [25]. Moreover, the fecal microbiota compositional responses to non-digestible carbohydrate [26] and galacto-oligosaccharides [27] were also noted to be person-specific in the studied participants. On the other hand, non-caloric artificial sweeteners (NAS), the most commonly used food additives, shape the gut microbiome structure and function in both mice and humans, and impact postprandial glycemic responses in some, but not all humans [28]. Importantly, human NAS responder and non-responder subsets were suggested to feature differential glycemic responses to food, and could be identified based on individualized microbiome patterns [28]. Likewise, consumption of the probiotic *Lactobacillus paracasei* DG, induced individual-specific alterations in fecal *Clostridiales* and butyrate production, depending on the initial intestinal microbial ecology [29]. Notably, such personalized probiotic engraftment in human gut mucosa was predictable by combining the baseline host and microbiome features [30•]. For instance, the stable colonization of the probiotic *Bifidobacterium longum* AH1206 occurred only in 30% of individuals, which was associated with low pre-treatment resident *B. longum* levels and underrepresented microbiome-related carbohydrate utilization genes [31]. These personalized microbiome responses to dietary exposure may be also important in the context of disease. In obese men, the compositional and functional changes of the individual's gut microbiota under a weight-stabilization or weight-loss diet varied significantly from person to person, which was negatively correlated with their microbial diversity [32], and relying on an individual's baseline microbiome composition [33]. Inter-individual microbiome responses to obese-related dietary interventions is also associated with specific bacterial species at baseline, in both males and females [34]. Collectively, a growing body of evidence suggests that previously underappreciated dietary response patterns may be driven, to some extent, by individualized microbial configurations and host traits, and these may be harnessed towards rational and data-driven predictions of dietary combinations uniquely impacting the individualized microbiome and metabolic responses.

Host and microbiome-based predictions of personalized dietary responses

Growing evidence suggests that nutritional intervention elicits person-specific microbiome responses, and such personalized responses may be associated with baseline microbiome signatures [22,23,33]. Integrating gut microbiome-related data, together with other personalized host datasets, in predicting personalized responses to diet is increasingly regarded as meaningful and feasible (Figure 1b). Indeed, in healthy subjects, personal glycemic responses to different types of bread could be simply predicted by pre-intervention microbiome data [35]. For instance, a bacteria from the genus *Prevotella*, was identified in high abundance, and associated with improved glucose metabolism upon consumption of barley kernel-based bread [36]. Likewise, metabolic improvements induced by short-term consumption of a whole grain-based diet were correlated with substantial changes in the abundance of *Eubacterium rectale* before and after intervention [37].

A proof-of-principle study has applied simple regression models to successfully predict both host and microbiota responses to a weight-control diet in obese patients, using the pre-treatment abundance of fecal bacterial species, mainly derived from *Firmicutes*, as predictors [34]. In another report, reduced microbial gene richness was suggested to feature a promising predictive power for the efficacy of dietary intervention in overweight individuals, represented by metabolic and inflammatory improvement [38]. Notably, in a large cohort consisting of 800 overweight/obese subjects in Israel, the high inter-individual variability in postprandial glycemic response could be accurately predicted by incorporating microbiome features and host characteristics, including anthropometrics and dietary habits by using machine-learning algorithms. Utilizing this personalized prediction modality, a small cohort of pre-diabetic individuals following a predicted 'good diet', featured a significant improvement in glycemic responses to food already after a week of personalized nutritional intervention [9]. Implementation of personalized nutrition to improve this typical metabolic syndrome, has been successfully validated in a 327-person cohort in the Midwestern US [39]. Following these studies, identification of specific bacterial taxa and functions that are potentially associated with personalized host responses to various diets, may provide more precise microbiome-oriented targets in personalized nutrition. For example, an obese cohort receiving a calorie restriction diet suggested that the baseline abundance of a mucin-degrading bacterium, *Akkermansia muciniphila*, was associated with improved metabolic outcomes [40]. Notably, in a recent longitudinal study comprising 1098 individuals, the overall baseline microbiome composition enabled prediction of multiple cardiometabolic markers (fasting and postprandial glucose, triglycerides and insulin levels), with two bacterial species, *Prevotella copri* and *Blastocystis spp.*, being the most reliable predictors of favorable postprandial glycemic responses [41•]. Another study showed that the baseline gut microbiota outperformed other host intrinsic factors in determining the dieting-induced individual weight loss, with higher abundance of *Blautia wexlerae* and *Bacteroides dorei* being the strongest predictors for weight loss [42]. Besides the metabolic syndrome, the concept of personalized nutrition and its link to gut microbiome has gained increasing attention in potentially being applicable in other microbiome-associated diseases. For instance, in

childhood inflammatory bowel syndrome, the efficacy of a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet was associated with pre-treatment microbiome markers, including enriched bacterial species possessing higher saccharolytic metabolic capacity and carbohydrate metabolism [43], as well as higher levels of fecal metabolites such as L-urobilin [44]. Pediatric Crohn's disease patients receiving exclusive enteral nutrition (EEN) treatment, demonstrated that the gut microbiota and microbiota-associated metabolites before EEN, differed between responders and non-responders to this nutritional intervention [45]. More importantly, the pre-treatment fecal bacterial species and functions were predictive of sustained remission following EEN [46], suggesting the potential of personalized EEN in the treatment of inflammatory bowel disease [43]. Whether diet-induced alterations in the gut microbiome contribute to such personalized responses warrant further investigations.

Diet-derived microbial metabolites as potential disease-modifying therapies

Mechanisms by which diet-microbiome changes may impact host physiology may include microbiome-based immune modulation [47], effects on gut barrier function [48,49], and modulation of thousands of potentially bioactive molecules, termed metabolites (Figure 1b). These small molecules may influx into the sterile host where they can signal to remote cells and organs. Indeed, metabolites produced, modulated, or degraded by gut commensals, such as short-chain fatty acids (SCFA) [50], neurotransmitters [51] and Trimethylamine N-oxide [52], have been shown to feature remarkable biological activity spanning beyond the bacterial colonization niches [53], and may transmit individual dietary responses to the host. Such impacts may be linked to inter-individual microbiome variations and therefore may explain some personalized traits stemming from the microbiome and its nutritional inputs. For example, it has been recently demonstrated that the microbially produced metabolite imidazole propionate is elevated in prediabetic and type 2 diabetic patients, and can directly impair glucose tolerance and insulin signaling [54•]. It has been also shown that this is directly associated with dietary patterns, altered microbial diversity and inflammation [55], suggesting that a shift in the gut microenvironment could contribute to the expansion of imidazole propionate-producing bacteria in the gut [54•]. Likewise, it was observed that prolonged consumption of SCFAs derived from dietary soluble fibers, specifically inulin, are fermented by the gut bacteria, contributing to hepatocellular carcinoma in mice [56]. Interestingly, Shimizu et al. claimed that SCFAs supplementation (i.e. acetate, propionate and butyrate), induces a protective effect against high-fat-diet-induced obesity in mice, without altering gut microbial composition [57], thus, suggesting that utilization of SCFA-promoting functional foods or 'precision probiotic'

approaches may combat obesity and related metabolic disorders. Furthermore, it has been recently suggested that the production of potentially disease-modifying metabolites by the gut microbiome, could explain the association between the gut and the central nervous system, since they are able to permeate the blood-brain barrier and consequently influence brain function [58••]. Even more provocatively, use of specific diets with claimed antiaging affects [59], or ketogenic diets possibly impacting neurodegeneration [60], memory deficits [61] and seizures [62] may involve the microbiome. These merit further validation, mechanistic elucidation and controlled human experimentation. Likewise, further studies are needed to decode downstream mechanisms by which microbes sense and react to specific food-derived compounds, and their downstream impact on the host, mediated either by local modulation of the gut milieu, or system immune-induced and metabolite-induced effects. Such mechanistic insights may shed light on the molecular basis driving personalized nutrition and its suggested effects on human physiology.

Challenges and open questions

Despite growing evidence suggesting a contributing role of the gut microbiota in predicting the personalized host response to dietary interventions, the precise weight of gut microbiome-associated features to such predictions, in comparison to other personalized host-related features, and what are the instances in which these sets of data could be integrated or redundant, merit further large-scale studies. Additionally, deciphering the mechanisms driving interactions between nutritional signals, gut microbiome, and the host is proving to be a complex and daunting task. First, multiple host-related factors, apart from diet, including physiological and lifestyle features are likely considered as strong modulators of microbiome composition and function [63], and downstream host physiology and disease patterns. These are often entangled and confound dietary patterns and need to be carefully and mechanistically dissected in future studies [64]. Second, reproducibility across cohorts might be hindered due to divergences in sampling, computational analysis and sequencing methods, as well as region-specific microbiome signatures in different populations, dietary habits, and seasonal dietary dynamics. These technical and additional confounders need to be considered and adjusted when deciphering the role of gut microbiome in personalized nutrition. Third, illuminating the mechanisms by which personalized diet-microbiota interplay influences the host physiology, requires integration of multi-omics strategies not only limited to microbiome analyses but in combination with proteomics, metabolomics, transcriptomics and epigenomics. Furthermore, it is worth to analyze the cost-effectiveness when implementing personalized nutrition interventions, since financial challenges in low-income

populations need to be considered given the relatively high cost and advanced technology needed (e.g. smartphones for dietary assessment, software tools development, sequencing platforms). Simplifying sample processing, data collection and analytical processes may improve accessibility to large populations potentially benefiting from such rational data-driven nutritional approach. Finally, predictive nutritional responsiveness approaches need to be validated across ethnic and geographical localities, of populations not yet represented by published studies. One such important initiative, recently declared by the National Institutes of Health, aims at collecting multi-omic information from 10 000 individuals across the US, in generating a large, multi-ethnic dataset enabling the testing and refining precision nutritional approaches aimed at targeting metabolic disease [65].

Other research directions related to personalized nutrition are beginning to be explored, but are currently often challenged by lack of continuous physiological and disease readouts. We expect that with the advent of medical wearables new opportunities will arise to integrate nutrition and personalized human responses as modulators and predictors of human responses that span beyond the few currently explored metabolic readouts. Such capacities may enable potential applications of personalized nutrition in the non-metabolic setting, such as inflammatory, neurodegenerative and cancer-related disorders (Figure 1c). Moreover, in addition to nutritional content, dietary timing (also termed chrono-nutrition [21]) also likely impacts the gut microbial ecology and downstream host responses in a highly individualized manner. Future large-scale population studies are required to identify potential microbial and clinical predictors of person-specific responses to timed feeding, using advanced machine-learning algorithms and accurate validation methods.

Finally, we strongly believe that personalized nutrition may constitute just one of precision microbiome-based interventions to be potentially integrated into human clinical medicine in years to come. Other promising modalities may include whole microbiome replacement through microbiome transplantation (fecal and vaginal [66]), the use of 'precision probiotics' [67] tailored to the individual as a basis for supporting preventive medicine to improve human health; precision editing of the gut microbiome by use of bacteriophages; the use of bio-engineered bacteria; and therapies based on individualized metabolite supplementation or inhibition. All of these modalities are at their infancy development phase, and face significant hurdles and challenges towards implementation in humans. However, we are hopeful that some of these microbiome-based modalities, together with personalized nutrition, may prove useful in impacting human disease in a safe, effective and evidence-based manner.

Author contribution
All authors performed an extensive literature research, contributed substantially to discussion of the content, wrote and edited the manuscript.

Conflict of interest statement
EE is a salaried scientific consultant for DayTwo and BiomX.

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