

Personalized Nutrition: Are We There Yet?

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ABSTRACT

The human genome has been proposed to contribute to interpersonal variability in the way we respond to nutritional intake. However, personalized diets solely based on gene-nutrient interactions have not lived up to their expectations to date. Advances in microbiome research have indicated that a science-based generation of a personalized diet based on a combination of clinical and microbial features may constitute a promising new approach enabling accurate prediction of dietary responses. In addition, scientific advances in our understanding of defined dietary components and their effects on human physiology led to the incorporation and testing of defined diets as preventive and treatment approaches for diseases, such as epilepsy, ulcerative colitis, Crohn disease, and type 1 diabetes mellitus. Additionally, exciting new studies show that tailored diet regimens have the potential to modulate pharmaceutical treatment efficacy in cancer treatment. Overall, the true therapeutic potential of nutritional interventions is coming to light but is also facing substantial challenges in understanding mechanisms of activity, optimization of dietary interventions for specific human subpopulations, and elucidation of adverse effects potentially stemming from some dietary components in a number of individuals.

Key Words: microbiome, microbiota, nutrigenomics, nutrition, personalized

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The impact of diet on health and disease has been studied for decades and is believed to span a variety of human pediatric and adult disorders, particularly diseases related to the cardiometabolic syndrome, such as obesity, type 2 diabetes (T2D), and nonalcoholic fatty liver disease and their cardiovascular complications (1). Indeed, changes in our nutritional habits over the past few decades have been associated with a vast increase in the prevalence of these diseases. Concomitantly, a clear rise has been observed in childhood obesity prevalence that is associated with the appearance of comorbidities in children that were previously “reserved” for adults, such as T2D and dyslipidemia that if not addressed early will lead to later cardiovascular disorders (1). However, decades of nutritional advice from national and international health organizations has not alleviated this global

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What Is Known

- Individuals feature different responses to diet, associated with their unique microbiome, life-style, and genetics.
- Microbiome alterations have been associated with numerous diseases.
- Dietary interventions may impact human disease, possibly through modulation of the microbiome.

What Is New

- We summarize the most recent achievements in personalized nutrition in children.
- We describe how nutritional interventions can potentially improve the efficacy of pharmaceutical interventions.
- We emphasize the importance of utilizing microbiome-diet interactions in formulating personalized dietary interventions.
- We highlight challenges currently limiting full-scale utilization of microbiome data in optimizing precision medicine and diet.

epidemic. This is in part because of noncompliance with nutritional advice provided, but it is mainly because of recommendations being generalized and applicable only on a population level. This is exemplified by the age-old advice against consumption of dietary fat because of its association with cardiovascular disease that was recently refuted (2). Several recent studies demonstrate that a single dietary paradigm may not fit all and that no single silver bullet can address specific clinical manifestations of human disease on a population level (1). Responses to diet are heterogeneous among different individuals, and it is now clear that this heterogeneity is driven in part by our individual genetic background and our gut microbiome composition (1,3). This insight is sparking a growing interest in the role and potential of personalized nutritional interventions. Technological advances are allowing not only a more intricate understanding of the mechanisms at play driving disease but also in the underlying mechanisms acting to ameliorate disease (1,3). With growing knowledge on the personalized impacts of dietary components, the field is entering an exciting era in which diet may be added as a potential measurable and reproducible additive to the therapeutic arsenal in ameliorating clinical parameters of complex diseases but also improving the efficacy of pharmaceutical treatments.

VARIABILITY IN INTERPERSONAL RESPONSES TO DIET

Nutrigenetics

Technological advancement in genome sequence analysis, resulting in the completion of the human genome project almost 2

decades ago, broadened our understanding of the underlying factors shaping our physiology and the extent to which genomic subtleties or interindividual differences impact heterogeneity in our responses to environmental stimuli, especially dietary exposures. Genotypic variation contributes to phenotypic interpersonal heterogeneity in response to nutrition, including glucose levels, cholesterol levels, blood pressure (4), and metabolism of amino acids (5). Nutrigenetics is an aspect of personalized nutrition that aspires to personally tailor nutrition, based on individual genotypic characteristics. Classic cases of such tailored interventions include familial monogenic metabolic diseases where personalized dietary interventions can have a direct and dramatic impact on the lives of affected children. For example, the National Health Service (NHS) in the United Kingdom screens for 6 familial metabolic diseases: phenylketonuria (PKU), medium-chain acyl-CoA dehydrogenase deficiency (MCADD), maple syrup urine disease (MSUD), isovaleric acidemia, glutaric aciduria type 1 (GAT1), and homocystinuria (6). The NHS implements personalized nutrition strategies including a diet low in Phenylalanine (PKU) and diet restricted in protein, particularly leucine for isovaleric acidemia (Fig. 1).

In more genetically complex childhood disorders, such as celiac disease (CD) featuring a strong genetic component associated with HLA-DQ2/DQ8 haplotypes (7), preventive dietary interventions are much more controversial. Some studies suggest that introducing gluten between 4 and 6 months of age may create an ‘immune tolerance’ that may prevent or delay enteropathy development (7), but others fail to observe that the time of gluten introduction influences CD development (7). Meta-analysis studies sound a cautionary note with regard to both gene-nutrient interactions described in the literature that were not found to be

reproducible (8) as well as towards commercialization of claimed gene-nutrient interactions insufficiently evidence-based (9–11).

Microbiome-based Dietary Approaches

The indigenous microorganisms residing on and within the human body, collectively known as the microbiome, may play essential roles in immune system development, modulation of immune responses, and host metabolism (12). Alterations in the habitual compositional structure of microbiome communities have been associated with numerous diseases, such as inflammatory bowel disease (IBD) and manifestations of cardiometabolic disease (13). In contrast to the rigid compositional structure of our genome, our microbiome is characterized by a plasticity predominantly influenced by environmental factors rather than the host’s genetic background (14). Diet constitutes the foremost environmental factor orchestrating the gut microbial composition and functional potential, making it an attractive and relevant tool to induce microbiome changes for therapeutic purposes. Dietary behavior has an impact on numerous diseases including cardiovascular diseases (CVDs) (15), IBD (16), diabetes mellitus (17), cardiometabolic disease (18), liver disease (19), and cancer (20,21). In parallel, these diseases have been associated with a dysbiotic gut microbiome (22–29).

Dietary modulation of the microbiome composition is brought about by the macronutrient and micronutrient content of food consumed. This is exemplified by Hadza hunter-gatherers of Tanzania who display a seasonal compositional shift with the cyclic loss and reappearance of numerous taxa attributed to seasonal shifts in food availability (30). Conversely, lack of seasonality in

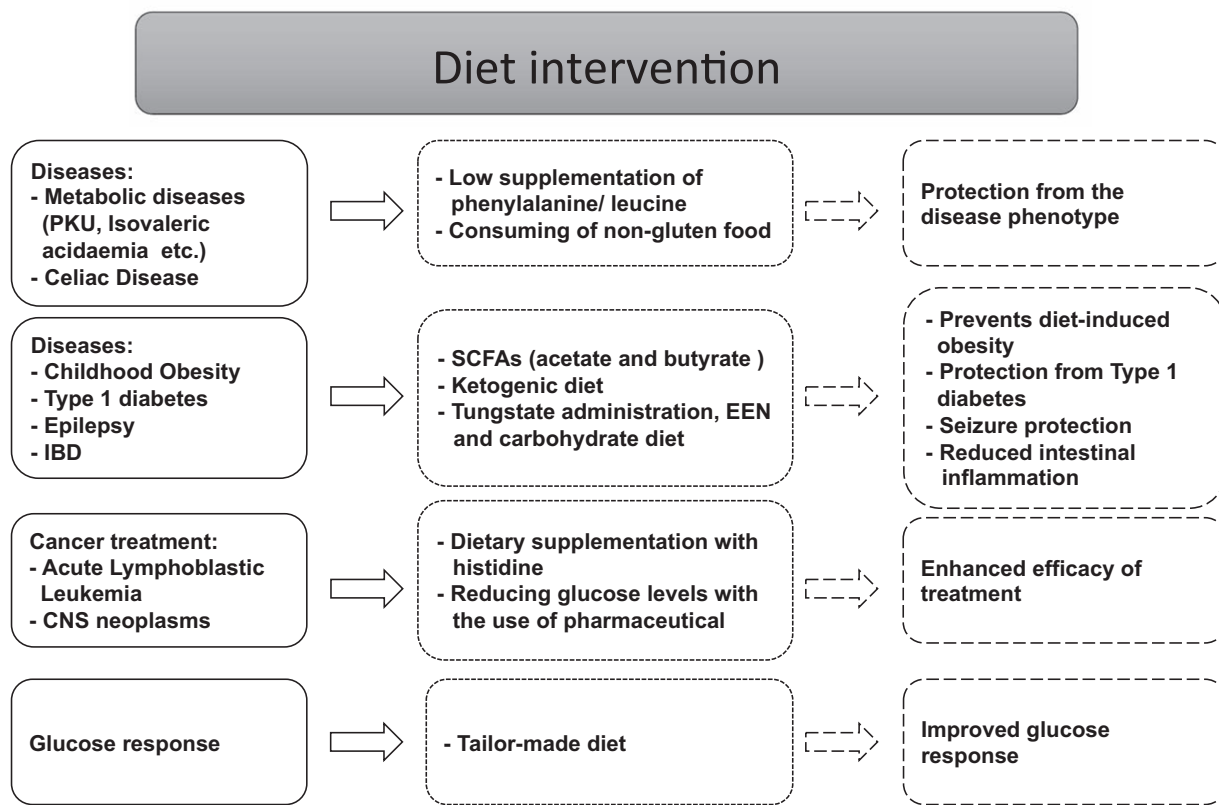


FIGURE 1. A scheme depicting representative indications, potentially utilizing a combination of genomic, clinical and microbiome features, in improving personalized human care.

particular food types can lead to permanent loss of taxa groups. This is exemplified by the reduced level of microbiota-accessible carbohydrates (MACs) in western diets resulting in reduced microbial richness that is permanent within a few generations and cannot be reconstituted by reintroduction of MACS (31). Diets consisting exclusively of animal or plant products that were implemented for short periods of time have been shown to result in microbiome compositional changes (32). In this context, diets based on animal products resulted in higher abundance of bile-tolerant microorganisms (such as the genera *Alistipes* and *Bilophila*), and diets based on plant products led to increased abundance of the phylum Firmicutes that have the ability to metabolize dietary plant polysaccharides (32). Detectable changes can be astonishingly rapid as described by Mardinoglu et al (33) who showed that implementing a diet with reduced carbohydrates can confer microbiome compositional changes within 24 hours, resulting in reduced abundance of bacteria that degrade fiber (33). Through all the examples of microbiome amenability to alterations via micronutrient availability, resilience to alterations remains an open issue and may stem from the degree or type of dietary intervention. Acute dietary alterations confer extensive microbiome changes, demonstrated by a study where participants exclusively ate boiled white rice for a period of a week. Conversely, microbiome displays a potential resilience to less dramatic dietary interventions, such as consuming industrially produced white bread versus artisan style sourdough bread (32).

MICROBIOME-ASSOCIATED DIETARY INTERVENTIONS IN HUMAN DISEASE

In the following section, we present some recent examples demonstrating the powerful potential that microbiome-based dietary interventions may hold in enhancing the efficacy of treating human disease.

Childhood Obesity

Childhood obesity is a global epidemic associated with risk factors for cardiovascular disease, insulin resistance, musculoskeletal disorders, and even some cancers (34–37). Similar to adults, significant differences in gut microbiome composition were observed in obese adolescents compared with normal weight adolescents (38). These differences have shown significant causal effects in obesity and insulin sensitivity (39–41). In parallel, diet showed the ability to shape the gut microbiome (42). For example, short-chain fatty acid (SCFA)-producing bacteria were more abundant in the gut of rural African children (high-fiber diet) compared with the gut of European children (western diet) (42,43). As a dietary intervention, SCFAs, such as butyrate prevented diet-induced obesity and insulin resistance (44).

Type 1 Diabetes

Type 1 diabetes (T1D) is an autoimmune disorder destructive to the human pancreas, mainly affecting children or young adults. A significantly lower microbiome diversity was shown in T1D compared with healthy controls (45). Microbiota-derived SCFAs, mainly acetate and butyrate, are reported to be protective against T1D. Butyrate increases the abundance of Regulatory T cells (Tregs), whereas acetate alters the surface phenotype of B cells resulting in a reduced number of the autoimmune T effector cells (46). Acetate and butyrate represent a link between diet, gut microbiome, and immune cells in the development of T1D. Bacteroidetes phylum produces acetate, whereas members of the Firmicutes phylum, including *Clostridium* species, 'preferentially' produce butyrate (46).

Epilepsy

In approximately 30% of patients with epilepsy, seizures cannot be brought under control by medications (refractory epilepsy). For these patients, alternative nonpharmacological options are considered, including the ketogenic diet (KD) that is a diet high in fat and low in carbohydrates. In a relevant randomized control trial carried out on children and adolescents with refractory epilepsy, KD showed its effectiveness in seizure protection (47) (Fig. 1). Insights into the underlying mechanism promoting the neuroprotective effects of KD were described recently, indicating an important role of the gut microbiome in mediating seizure-protective effects of the diet (48). A KD implemented on mouse models of epilepsy resulted in enrichment of the species *Akkermansia muciniphila* and *Parabacteroides* genus that confer seizure protection. Interestingly, supplementing mice on a control diet with these 2 bacterial species results in seizure protection. Furthermore, Olsen et al described modulation of circulating metabolites that together result in a modulation of brain metabolism. Specifically, a reduction in systemic gamma-glutamylated amino acids and increased hippocampal GABA/glutamate levels that together associate with seizure protection (48).

Inflammatory Bowel Disease

Gut microbiome has been shown to be associated with IBD, although the precise mechanisms of its impacts on the pathogenesis of IBD remain elusive. One targeted dietary intervention strategy described by Zhu et al (49) was aimed at altering specific components of the microbiome in colitis and was based on the observation that gastrointestinal inflammatory diseases are characterized by a dysbiotic gut microbiome and blooming of facultative anaerobes of the *Enterobacteriaceae* family. The authors developed their strategy around the identification of molybdenum-cofactor-dependent metabolic pathways that were associated with inflammation-associated dysbiosis (50) and were found to be present only during periods of inflammation. Targeting of the blooming *Enterobacteriaceae* by oral treatment with tungstate to selectively reduce molybdenum-dependent anaerobic metabolism (49) resulted in a reduction of intestinal inflammation in colitis mouse models (49).

An important aspect of managing pediatric patients with Crohn's disease includes addressing the restoration of adequate nutritional intake of patients. To this end, exclusive enteral nutrition (EEN) represents a first line therapy treatment strategy that can lead to remission rates of up to 80% in pediatric Crohn's disease cases (51). Overall, EEN leads to marked improvements in numerous clinically relevant parameters through multiple suggested effects including gut permeability modulation, alteration in local and systemic inflammation, and microbiome compositional alterations (51). An association between microbiome compositional changes and Crohn's disease has been established in numerous studies (52–54), thereby highlighting the microbiome as a prime target for interventions including dietary interventions. EEN has been shown to result in marked gut microbiome changes (55), and dysbiotic gut communities in Crohn's disease patients can be used as predictors of sustained remission following EEN (56). Although EEN shows great promise in alleviating Crohn's disease clinical symptoms, it is highly restrictive and difficult to maintain in the long-term. Approaches utilizing solid food-based diets in Crohn's disease feature some preliminary signs of potential impact on disease course (57,58); however, further studies are clearly needed to understand the mechanistic aspects of dietary interventions and their refining.

Cancer

Acute lymphoblastic leukemia (ALL) is a common cause of cancer and death among children. A fundamental component of chemotherapy for pediatric ALL is the drug methotrexate (59). Although methotrexate is widely used, its high toxicity often necessitates premature treatment termination. The amino acid histidine catabolism pathway has been linked to methotrexate sensitivity. Histidine catabolism depletes cellular resources of tetrahydrofolate, increasing sensitivity to methotrexate. Furthermore, expression level of the gene *HAL*, the histidine catabolism pathway rate-limiting enzyme, is associated with ALL patient survival (60). Experiments in mice showed that dietary supplementation with histidine resulted in an increase in the histidine catabolism pathway flux and in turn increased leukemia sensitivity to methotrexate (60) (Fig. 1). These observations present new opportunities in ALL treatment where *HAL* expression may be used as a predictor of treatment responders. Additionally, supplementation of histidine through diet could increase methotrexate efficacy and provide the opportunity to reduce dose levels, and therefore, toxicity with obvious benefits to the patients (60).

Another compelling example of nutritional interventions potentially impacting cancer was recently shown in central nervous system neoplasms in which mutations of the gene *PIK3CA* are often found (61). As PI3K is also involved in glucose homeostasis, a recent report by Hopkins et al (62) shows that using PI3K inhibitors lead to hyperglycemia, and the resulting glucose-insulin feedback compromises PI3K inhibition and overall treatment efficacy. Reducing glucose levels with pharmaceuticals led to enhanced efficacy of treatment in preclinical models. Involvement of the gut microbiome in these dietary effects merits further studies.

PERSONALIZING DIET BY INTEGRATION OF MICROBIOME AND CLINICAL FEATURES

Microbiome-dependent, interindividual variability in responses to dietary intake have been recently demonstrated in numerous studies (32,63,64). Noncaloric artificial sweeteners were shown to induce glucose intolerance in some individuals but not in others through personalized alterations in microbiome composition (32). The postprandial glycemic response has been shown to be modulated in a microbiome-dependent manner (32). Implementation of a machine-learning algorithm incorporating gut microbiome compositional characteristics in addition to multiple clinical parameters predicted postprandial glycemic responses on a personal level. Importantly, this approach in turn was successfully implemented in personalized nutritional interventions improving postprandial glucose responses (32) (Fig. 1). The relevance of this personalized predictive model was further validated on another cohort of 327 individuals recruited from Minnesota and Florida in the USA (65). Interindividual postprandial glycemic responses were further reported in a study where individuals consuming artisanal sourdough bread were compared with those consuming industrially prepared white bread (64). The preconception of artisanal sourdough bread being a healthy option over industrially prepared white bread was challenged after it was found that participants responded in a personalized manner to each bread. Furthermore, machine-learning algorithms implemented that utilized microbiome compositional characteristics were able to predict each participant's postprandial glycemic response to the particular type of bread (64). In another study, a continuous glucose-monitoring approach detecting blood glucose levels through time revealed interindividual variations in regulation of blood glucose. Even individuals considered nondiabetic by traditional laboratory one-off testing had glucose levels fluctuating into the diabetic range (63). In this

study, the authors were able to develop individualized glucose fluctuation patterns and classify these into individual "glucotype" patterns to be used for early detection of T2D risk (63). A recent study suggested that prescriptive and personalized diet (CD-TREAT) for IBD patients could have similar effect as EEN. CD-TREAT replicated the EEN changes in the microbiome and decreased gut inflammation (66).

Personalized interventions have been further suggested for probiotic supplementation (67). Individuals were found to display a person-specific probiotics' colonization efficiency. Probiotics' colonization ability could be predicted based on the individual's microbiome composition before initiation of probiotic intervention. This presents an important opportunity for personalized probiotic supplementation (67).

CHALLENGES IN MICROBIOME- AND PERSON-TAILED DIETARY APPROACHES

Microbiome-based interventions feature multiple challenges. For example, microbiome composition has been shown to be influenced by ethnicity (68) and geography (69). He et al (69) found that the gut microbiome composition in individuals from the Guangdong province of China was explained mainly by the geographic location in the province. Only segregation based on geographic locality (compared with individuals across the study) enabled an accurate microbiome-based machine-learning prediction of metabolic outcomes. Likewise, a study following 6 ethnic groups living in Amsterdam revealed that variations in microbiome composition were explained to a greater extent by ethnicity than by factors, such as diet or metabolic disorder indicators (68).

Host gene-nutrient interactions and their effect on metabolic health need to be studied in large population-based cohorts, such as the Framingham Heart study (USA) (70), UK Biobank cohort study (UK) (71), and the China Kadoorie Biobank Study (72) to investigate the environmental and genetic determinants modulating these interactions. Likewise, the contribution of host genome features on personalized nutrition preferences merits future large-scale investigation (73,74).

Other challenging aspects of personalized nutrition include its high expenses currently making it prohibiting to a large proportion of the population (75), limitations associated with human compliance, and the need of refinement and validation in multiple ethnicities through the conduction of clinical trials.

CONCLUSIONS AND PROSPECTS

Dietary behavior has a crucial influence on both health and disease. The initial excitement on the utilization of host gene-diet interactions to formulate personalized diet interventions has somewhat subsided, given a lack of reproducible evidence of the impact of this approach. However, combining person-specific clinical features with data extracted from their unique microbiome may enable a more accurate delineation of individualized nutritional responses. Interestingly, nutritional interventions are also showing promise in improving the efficacy of pharmaceutical interventions. Nonetheless, multiple challenges do remain that need to be overcome in implementing such approaches in wider populations, understanding underlying mechanisms of nutritional modulation, ensuring that personalized diets include all the necessary micronutrients, and improving long-term compliance to these interventions. Given these limitations, personalized nutrition may hold promise in our future as a science- and measurement-based approach that will improve metabolic health and possibly impact the course of obesity, cardiometabolic disease, and potentially other 'multi-factorial' disorders.

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