Addressing the Nutritional Phenotype Through Personalized Nutrition for Chronic Disease Prevention and Management

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ABSTRACT

The primary focus of public health recommendations related to the prevention of food-related chronic disease has been on the adoption of healthy dietary patterns; however, implementation has been challenging. There has been increasing recognition that an individual's diet and environment may impact disease susceptibility by affecting the expression of genes involved in critical metabolic pathways. Precision nutrition (PN) has emerged to translate discoveries about diversity in nutrient metabolism between subgroups and the inter-individual variability in the responses to dietary interventions. The overarching goals of PN are to deliver individualized, actionable dietary therapy based on an individual's nutritional phenotype, created from the integration of genetics, metabolic profile, and environmental factors in order to prevent and treat chronic disease. This review addresses the developments of genome- and omic-driven PN and how they have been used to prevent and treat disease, as well as how they might be integrated into broader clinical practice.

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Behavioral lifestyle modifications, such as improving dietary quality and increasing physical activity (i.e., move more every day), are fundamental to efforts to prevent, manage, and reduce health-related

consequences of chronic disease.[1–4] Traditionally, the dietary components of behavioral lifestyle interventions have been aimed at those dietary elements associated in the literature with chronic metabolic disease and dysfunction (i.e., dyslipidemia, type 2 diabetes [T2DM], cardiovascular disease [CVD], non-alcoholic fatty liver disease [NAFLD], and some cancers). The body of nutrition-related evidence that makes up the theoretical basis for these interventions supports greater consumption of nutrient dense, high fiber, plant foods (e.g., whole grains, fruits, vegetables, legumes, nuts, and seeds) for prevention and first line treatment of food-related chronic conditions. This same evidence is used by major health organizations in the creation of guidelines that are disseminated to the general public urging adoption of healthy eating patterns—

all of which are plant-predominant with the optional addition of smaller amounts of animal-derived foods.

However, despite the abundance of evidence to support and encouragement to adopt healthy dietary patterns, implementation remains a challenge for many. This is due, in part, to individual variability in social and behavioral factors, such as accessibility of healthy foods, knowledge and skills required to select and prepare healthy foods, and motivation and support to change dietary practices. The interrelationships between these social and behavioral factors presumably play into individual decision-making around food choices (and hence overall diet quality),[5] and may consequently influence engagement with, and response to, specific nutrition-focused healthy living interventions.[5,6] Additionally, there is no consensus on the optimal intake of specific nutrients or which diet is best for whom.[7]

The growing recognition that individual variability—not only in how individuals consume food, but also in how individuals and populations differ in their responses to food—is illustrative of the challenges that clinicians face in providing specific nutrition recommendations to individual patients. There is a growing sentiment among some in the scientific community that there should be a shift in focus away from conventional population-based guidelines toward more personalized nutrition approaches[8] for disease prevention and management, presumably in a healthcare setting. Heralded by advances in human genome sequencing, the field of Precision Nutrition (PN) has emerged as a constituent of Precision Lifestyle Medicine[6] to address the diversity in nutrient metabolism between subgroups (e.g., ethnicity, cultural preferences, life stage, health status, lifestyle, and clinical factors) and the inter-individual variability in responses to dietary interventions.[9]

While PN may sound foreign or futuristic to some, elements of PN have been part of medical practice for many years. For example, in history-taking, patients are asked about family history of lipid disorders, hypertension, and CVD. Positive responses by the patient may prompt the clinician to recommend dietary changes, including DASH,[10] Mediterranean,[11] or low-fat vegan[12] diets prior, or in addition, to medical treatments to reduce risk of a CVD event. For those with established medical or surgical conditions, examples of PN include counseling on a gluten-free diet for patients with celiac disease and optimizing protein and micronutrient intake for patients after gastric bypass, respectively.

Recent advances in high-throughput technologies referred to as "Omics," and the emergence of the nutrigenetic and nutrigenomic disciplines have transformed the focus of PN allowing for the identification interactions between genes and diet with a granularity that had not previously been possible. Greater understanding of the interplay among nutrients, genes, behavior, and environment may inform nutrition recommendations and allow dietary therapies to be customized based on an individual's genetic predisposition to disease, socioeconomic environment, and lifestyle behaviors. The addition of these advanced PN strategies to those already present in clinical practice represents an unprecedented opportunity to refine disease risk stratification[8,13] and better target prevention efforts.

Herein, we review the complex interplay among genes, bioactive nutrients, dietary patterns, and behavioral lifestyle factors, that collectively constitute an individual's nutrition phenotype.[14] Additionally, we address how, in this postgenomic era of research, harnessing the genome and application of new omic technologies have become integrated, vital components of PN approaches to prevent chronic diseases through dietary change.[15] Finally, we provide practical insights into how facets of PN could be adopted into clinical practice to provide tailored dietary therapy and nutrition prescriptions for health promotion.

Leveraging "omics" to create nutrition prescriptions

Nutrigenetics and nutrigenomics: from nutrients to genes and back again

Nutrigenetics and nutrigenomics have emerged as extensions of nutrition and genome wide-association studies (GWAS) in efforts to understand the overall impact of specific dietary compounds on gene expression and the effects that genetic variations have on an individual's response to dietary interventions.[16] The field of nutrigenetics examines the influences of genotypes associated with common chronic diseases on responses to dietary changes. Nutrigenomics is a complementary field which seeks to identify how bioactive dietary compounds affect the expression of genes that regulate critical signaling and metabolic pathways implicated in chronic diseases.[16] Omic technologies have enabled researchers to exploit risk variants in specific genes thus providing a more comprehensive evaluation of specific gene-nutrient or gene-nutriome[1] interactions that could potentially modulate disease susceptibility before any symptoms or signs manifest clinically.[17]

Propelled by the use of molecular genetic tools to map out entire genetic blueprints of disease, nutrigenetic studies have focused on uncovering genetic variations or single nucleotide polymorphisms (SNPs) associated with certain disease traits. As the knowledgebase of nutrigenetics grows, it is likely to find its way into clinical practice. Indeed, aspects of nutrigenetics have already been part of disease management for years. The most well-known example may be phenylketonuria (PKU)—an inherited error in metabolism that develops as a result of mutations in the gene that encodes the hepatic enzyme phenylalanine hydroxylase.[5] Individuals with PKU must follow a lifelong diet devoid of foods high in the amino acid, phenylalanine, which is present in dairy products, meat, fish, chicken, eggs, beans, nuts, and artificial sweeteners. More recently, nutrigenetic studies have identified polymorphisms in genes encoding the enzymes methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MTR). Normally, these enzymes facilitate folate metabolism and aid in regulating DNA synthesis and repair, but missense polymorphisms are associated with increased risk of breast cancer in individuals with low intakes of folate, vitamin B6, and vitamin B12.[15,18]

Nutrigenomic studies have shown that deficiencies in folate and choline disrupt gene expression profiles involved in lipid metabolism, and potentially influence the risk of developing NAFLD.[15] Vitamin B12 deficiency has also been shown to modulate gene expression patterns implicated in the susceptibility to developing dyslipidemia.[15] Selenium, a mineral with well-established anti-angiogenic and anti-metastatic properties, when deficient in the diet may result in both upregulation in the expression of pro-inflammatory cytokines contributing to increased CVD risk, and the upregulation of tumor-suppressor gene expression contributing to increased cancer risk.[19] The most notable example of this is the association of selenium deficiency with clear cell renal cell carcinoma.[19]

Nutrigenetics and nutrigenomics: focusing on dietary pattern

A current aim in nutrigenetics is to better understand the consequences of genetic polymorphisms associated with obesity and obesity-related diseases based on how individuals differentially respond to the same foods or have the same eating pattern. The discovery of SNPs in candidate genes associated with fat mass and obesity—including FTO, PPARγ, MC4R, and MTHFR[17,20]—have been pivotal in elucidating the physiological mechanisms though which SNPs in obesity susceptibility genes might confer obesity and how these mechanisms might be modulated by dietary intake. For example, risk variants located in FTO, a gene recognized for its involvement in appetite control and eating behavior, appears to confer risk of obesity in children[21] and adults[22] through its association with increased food intake frequency and a greater preference toward energy dense high fat foods. Polymorphisms in PPARγ, a regulator of adiposity and glucose homeostasis, have been shown to modulate the associations between total and saturated fat intakes, higher waist circumference, and visceral fat accumulation, and may therefore influence the risk of developing metabolic syndrome

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[1] Nutriome is defined as the full complement of nutrients ingested by an individual over a discrete period of time.

in susceptible individuals.[23] Variants in the MC4R gene, a key regulator of body weight, have been associated with increased risk of both T2DM in individuals reporting low adherence to a Mediterranean style diet[15] and metabolic syndrome in those following a westernized diet high in saturated fats.[24] Congruent with nutrigenetic evaluation of diet and chronic disease risk, nutrigenomic studies have reported associations between Western dietary patterns and upregulation in the expression of genes involved in obesity-related inflammation, glucose intolerance, and hepatic lipid accumulation.[15] Conversely, Mediterranean dietary patterns have been shown to decrease the expression of genes involved in inflammatory and atherogenic pathways and oxidative stress.[25]

Identifying genetic risk in order to identify disease risk

Analytical methods in the nutrigenetic and nutrigenomics are constantly evolving, and newer, more robust application of genetic risk score (GRS) algorithms have been used to capture the integrated effects of genes and nutrients or dietary patterns on disease susceptibility in order to inform on actionable targets for PN intervention. To date, the most compelling GRS algorithms have been created through studies that modeled risk of developing obesity versus number of SNPs associated with body mass index (BMI) or body fat mass. Examples of this modeling approach were demonstrated by Goni and colleagues[26] who identified a greater risk of developing obesity among high-genetic risk individuals (i.e., those carrying ≥7 SNPs) consuming Western-style diets. The team also identified factors, such as fiber and vegetable protein intake, that appeared to have protective effects, particularly in low-risk individuals (i.e., those carrying <7 SNPs). Other applications of GRSs in epidemiological cohort studies have also found interactions between consumption of fried foods, sugar-sweetened beverages,[27,28] saturated fat,[29] and obesity, providing additional mechanistic insight into how poorer dietary quality may modulate obesity risk. Another study found that individuals with greater genetic predisposition to obesity who had the highest consumption of coffee had lower BMIs than those with the lowest coffee consumption, suggesting that habitual coffee consumption may attenuate some of the genetic influence on BMI and obesity risk.[30,31] Investigations have also been forthcoming on the GRS associations with eating behavior and dietary responses to intervention as demonstrated in studies describing the metabolic improvements associated with high protein diets in individuals with a high GRS for T2DM.[32] Collectively, application of GRSs as a genetic tool in PN holds promise in better identifying individuals with a greater risk for obesity-related diseases and informing how changes in eating behaviors may modulate disease risk in individuals with a predisposed genotype.

Metabolomics: understanding the diversity in metabolic signatures

Metabolomics is another rapidly growing area of PN that has emerged as a natural consequence to understanding that certain food-derived biomarkers, or metabolites, mediate the metabolic responses to dietary interventions and physiological aberrations present in disease pathology.[33] In current medical practice, clinicians already capture a small portion of the metabolome through commonly ordered laboratory blood chemistry analyses, such as measuring blood glucose, lipids, and creatinine.[33] However, the field holds opportunities well beyond these typical uses as it provides the metabolic blueprint for the foods and nutrients an individual consumes from an entire meal or through a dietary pattern,[34] and subsequently captures metabolic changes in response to dietary intake that precede the development of metabolic diseases.[13]

Advancements in metabolomic profiling have fostered a new wave of scientific exploration to uncover nutritional biomarkers that may serve as targets for disease prevention and treatment.[33] Among various metabolites, C6-sugars and acylcarnitines have been implicated in impaired glucose metabolism and insulin resistance. Acylcarnitine accumulation

is also a reflection of increased oxidative stress and inflammation and has been consistently positively associated with obesity and inversely associated with whole grain intake.[35]

Cross-sectional data from a subpopulation of the PREDIMED trial revealed that a diet rich in either extra-virgin olive oil or nuts—key components of the Mediterranean diet—reduced the deleterious effects of high plasma concentrations of the branched chain amino acids (BCAAs), leucine and isoleucine, on CVD risk.[36] Elevated levels of metabolites from the BCAAs, tyrosine, phenylalanine, valine, leucine, and isoleucine, have also been associated with metabolic syndrome,[37] prediabetes,[38] and T2DM.[38,39] Together, the findings of these studies suggest potential opportunities to use BCAA metabolites in predicting future risk of developing T2DM.[40] Evidence from other large, population-based, cohort studies has similarly revealed metabolites predictive of changes in blood pressure,[41] incident hypertension,[42] myocardial infarction, and breast cancer[43] in response to dietary changes. Overall, these data highlight the critical role metabolomics has played in providing insight into the inter-individual variability in metabolic responses to intake of the same foods and in identifying new molecular and metabolic targets for disease prevention and treatment. Ongoing advances in metabolomics will further allow investigators to distinguish between individuals or subgroups who may derive benefit from different dietary interventions versus those who may be nonresponders.[44] Accordingly, this could pave the way for more precise, efficient, targeted dietary and medical therapies.

Gut microbiome: understanding gut reactions to chronic diseases

The composition and metabolic activity of the gut microbiome has become a focal point of health research in recent years due to a plethora of studies implicating the gut microbiota with a number of cardiometabolic disorders, such as obesity, T2DM, NAFLD, and atherosclerosis.[45] Thus, a new quest in PN is to optimize the intestinal microflora through diet to reverse disease risk. Overall composition and metabolic activity of the gut microbiome is influenced by a number of factors including age, health status, diet, and geographic location.[46] More interesting, however, is the complex interplay among dietary composition, genes, and the gut microbiome which may act as a stronger modulator of metabolic diseases than genetics alone.[17,47]

Gut microbiota profiling, which characterizes and quantifies the core microbes found in the majority of individuals' gastrointestinal tracts,[46] has become a popular method for examining the relationship between diet and the diversity in the microbial ecology of the gut in current nutrition intervention investigations.[46] Previous reports have noted significant differences among microbial communities across diet types, with smaller microbial populations and lower species diversity observed among those eating Western and other diets enriched in animal fat compared with diets high in fiber, especially those composed primarily of plant foods.[35,48,49] Specific intestinal metabolites produced during digestion of red meat have also been correlated with atherosclerosis and CVD pathogenesis,[47] providing an explanation as to why vegetarian, vegan,[12] and healthy Mediterranean diets,[11] which all emphasize no or low red meat consumption, may be associated with reduced CVD risk.

Greater microbial diversity has been observed among individuals consuming greater quantities of fiber from fruit, legumes, and vegetables following either a Mediterranean or a healthy Western dietary pattern.[48] This provides additional evidence to support findings that the gut microbiome responds to habitually practiced healthy dietary behaviors by eliciting protection against disease, and this benefit is not limited to a specific cultural dietary pattern.[48] There is also preliminary evidence to show that both composition and metabolic activity of the gut microbiota respond to short-term changes in diet, reinforcing the near-immediate benefits and importance of making lifestyle changes.[49]

Although still in its infancy, research focused on the gut microbiome and its interactions with diet has shown tremendous potential to test existing therapeutic nutrition agents, such as foods containing

microbiota-accessible carbohydrates (i.e., prebiotics) or probiotic organisms, as strategies for treating metabolic conditions.[46] Integrating an individual's genetic background with their personal gut microbial composition and function will further our abilities to develop new and unique nutritional therapeutic targets for chronic disease prevention.

Clinical application

While considerable research has been conducted within each of these elements of PN, there has been relatively little utilization of the findings by physicians and other healthcare providers in broad clinical practice. There are a number of potential reasons for this including limited nutrition education in health professional training programs,[50,51] more clinical time and resources spent focusing on medications for treatment rather than on lifestyle changes for prevention of disease,[52] short clinical visit times that make detailed dietary counseling difficult,[53,54] and absence of consensus guidelines on PN topics within fields of clinical practice. Additionally, it could be argued that it is an impossible task for clinicians to add the significant volume of new information needed to personalize recommendations at the omic level to the already large and ever-increasing amount of content[55] that they are expected to know.

A practical place to start paving the way for increased use of PN in clinical practice would be to go back to the basics and improve general nutrition education at all levels (e.g., health professional training programs, continuing education, etc.) that highlights the plant-predominant eating patterns—such as DASH,[56] healthy Mediterranean,[11] and healthy vegetarian diets[7,57]—shown to be associated with better health and lower risk for disease according nutritional epidemiology, randomized controlled intervention trials, and most omic literature.[25,48] These dietary patterns are appropriate for the vast majority of patients and have significant overlap in their components.[58] Building a foundation on practical, broadly applicable content takes relatively little time to learn and could be used with many patients, making it a realistic addition to medical training and practices where it isn't already present.

While the bodies of general and personalized nutrition literature continue to grow, the message about what is healthy at a population level has stayed relatively steady for decades.[59] Given the volume of patients needing healthy dietary counseling paired with the complex interplay among dietary intake, environment, genes, health status, and risk of disease, it is inadvisable and impractical for PN to replace general dietary counseling and nutrition interventions in clinical practice. Instead, a more feasible application of PN that would add to what is already offered clinically would be for PN practitioners to tailor a generally healthy diet in order to incorporate remaining items needing optimization based on PN assessments for a given individual. An example of how this might work in practice would be for a clinician or other healthcare provider to counsel and assist a patient on implementation of the generally healthy diet that is most in-line with their dietary preferences. Then, they could refer them to a dietitian or other specialist trained in PN to assist in the implementation of any remaining adjustments dictated by genetic, metabolomic, microbiome, other assessments, and any current disease considerations (Fig 1). Envisioning the expanded incorporation of PN into clinical practice in this manner could also create opportunities for new specialties within medicine and dietetics as the volume of knowledge needed to stay abreast of in this ever-changing and growing field would be substantial.

Taking a step back and looking once more at present-day applications of PN, it is clear that more research is needed on a variety of aspects of PN including how to best incorporate PN into current medical practice and how to do so in a cost-effective and efficacious manner. Given that we know providing information on a healthy diet is often not enough to get people to make lasting dietary changes, more research is also needed around behavioral lifestyle interventions that increase adoption rates of general and personalized nutrition recommendations. It is possible that by nature of being personalized, patients could be more motivated to change based on PN recommendations compared with those geared toward the general population.[60] As more PN assessments are conducted and treatment plans are implemented, the amount of PN data available will grow. It will be important to continually analyze this expanding repository of data to learn more about PN assessments,
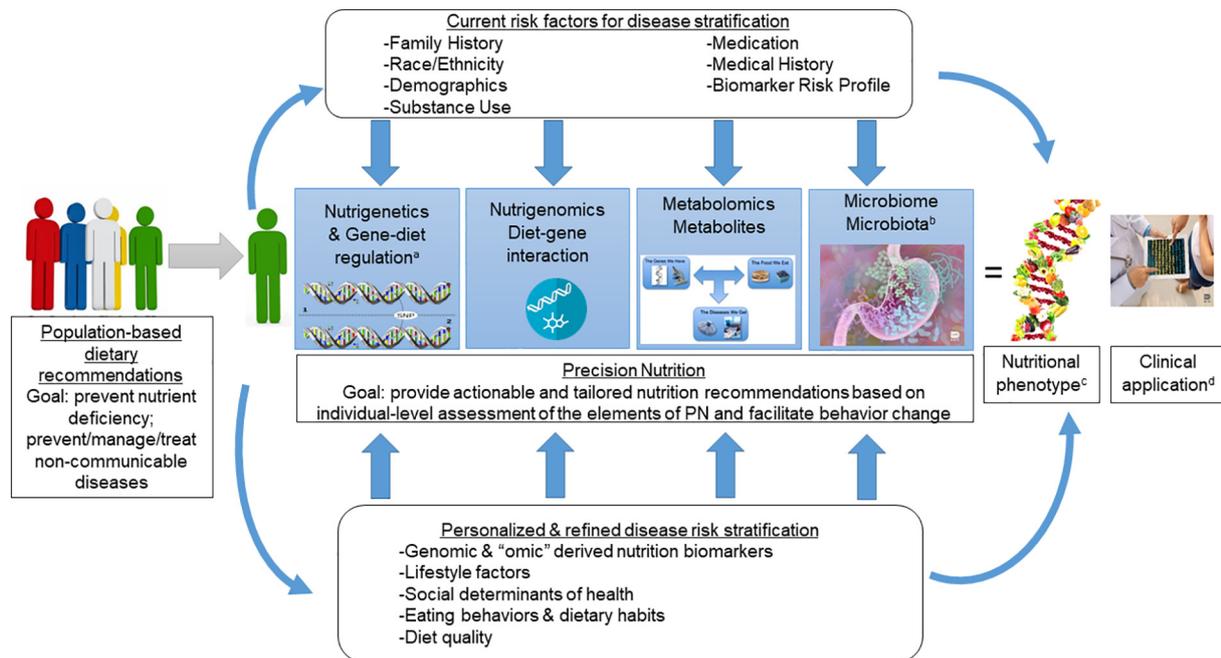

Fig 1. Integrating evidence based recommendations with precision nutrition applications in clinical practice. a Reference: Keller L, CourseSource. Exploring the human genome by investigation of personalized SNPs. 2015; https://doi.org/10.24918/cs.2015.11 Accessed October 29, 2018.2. b Reference: Leja D, National Human Genome Research Institute (NHGRI). Beneficial gut bacteria. https://www.genome.gov/imagegallery/viewimage/?imageID=28442056996. Accessed October 29, 2018. c Reference: Zeisel SH, Freake HC, Bauman DE, et al. The nutritional phenotype in the age of metabolomics. *The Journal of Nutrition.* 2005;135(7):1613–1616. d Reference: Leja D, National Human Genome Research Institute (NHGRI). iPad showing genomic data. https://www.genome.gov/imagegallery/viewimage/?imageID=27493073484. Accessed October 29, 2018.

interventions, short- and long-term health outcomes, cost effectiveness, and societal implications, and to make sure the findings are reflected in clinical practice as is done within other medical specialties.

Conclusion

Harnessing the rapid progress in genome sequencing and the benefits of the "omics" technologies, PN has transformed our understanding of nutritional phenotype[14] by providing clarity in how nutritionally-driven health outcomes are related to the interplay that exists among diet, environment and genes.[44] Advances in PN have helped to identify genetic mutations that may increase risk of certain diseases during nutrient deficient states, and thus inform of specific nutrients that could potentially serve as novel or unconventional biomarkers for disease prediction prior to clinical manifestation, or act as therapeutic targets for disease treatment. Notwithstanding, PN research is still in its infancy and not without controversy as there appear to be more questions than answers regarding its application in public health and clinical settings. For example, while it is clear that an interaction between diet and gene exists, there is limited understanding of the quantity of foods or nutrients that need to be consumed to compensate for a genetic disadvantage and whether bioactive dietary compounds in certain foods are enhanced or diminished when eaten with other foods.[44] Thus far, observational studies that have uncovered associations between SNPs and dietary patterns have been the primary source of data driving genomic-based PN. However, reproducibility of data across these studies and robustness of the findings in larger-scaled trials, and demonstrated efficacy in intervention trials remain limited.[13] This leaves important questions left unanswered, particularly concerning the translatability of research findings to disease diagnosis, and the societal, economic, and ethical implications of using omic technologies to expose an individual's genome to guide health recommendations (e.g. cost effectiveness of application and data analysis of omic technologies, the accessibility of testing, and the impact on genome-guided PN methods on health equity).[44] There is additional skepticism in current medical practice regarding the reliability, sensitivity and specificity of omic technologies, which drive PN recommendations, to prevent and clinically manage clinical disease.[13] Yet, perhaps the greatest uncertainties that remain are whether leveraging PN information to determine disease susceptibility is better than the current standard of care and whether genetically-driven, personalized nutrition plans provide enough incentive to motivate individuals to adhere to life-long dietary behavior changes. To address these questions, more robust data demonstrating the effectiveness of PN interventions compared to traditional dietary counseling is needed.[13] Additionally more research is needed that focuses on how to personalize the approach of incorporating behavioral-lifestyle interventions, such as PN, into one's life as well as strategies to increase adoption rates of PN recommendations in order to effectively reduce disease susceptibility and overall health trajectory. This in turn may allow for the expanded study of PN as much more potential data would be available from patients receiving PN recommendations and interventions.

The "era" of personalized strategies to deliver more "actionable" and realistic nutrition recommendations is approaching, but more work remains in order to solidify the foundation of PN knowledge derived from genetic, omic, and microbiome studies.[44] Until there is more robust and translatable evidence to support PN practice, personalized approaches to nutrition should continue to apply a balance between evidenced-based public health recommendations with PN-informed approaches to diet therapy. Additional focus should be placed on motivating and educating individuals to make healthier, sustainable choices for long-term healthy living practices. When scientifically justified, integration of genetics and omic technologies that help identify a distinct nutrition phenotype can be complementary to refine disease prevention efforts or treatment strategies.[44] Albeit, the ways in which this information is delivered by clinicians and understood by patients will ultimately determine the overall effectiveness of PN approaches to disease prevention and management.

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