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Utilising the precision nutrition toolkit in the path towards precision medicine

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The overall aim of precision nutrition is to replace the 'one size fits all' approach to dietary advice with recommendations that are more specific to the individual in order to improve the prevention or management of chronic disease. Interest in precision nutrition has grown with advancements in technologies such as genomics, proteomics, metabolomics and measurement of the gut microbiome. Precision nutrition initiatives have three major applications in precision medicine. First, they aim to provide more 'precision' dietary assessments through artificial intelligence, wearable devices or by employing omic technologies to characterise diet more precisely. Secondly, precision nutrition allows us to understand the underlying mechanisms of how diet influences disease risk and identify individuals who are more susceptible to disease due to gene–diet or microbiota–diet interactions. Third, precision nutrition can be used for 'personalised nutrition' advice where machine-learning algorithms can integrate data from omic profiles with other personal and clinical measures to improve disease risk. Proteomics and metabolomics especially provide the ability to discover new biomarkers of food or nutrient intake, proteomic or metabolomic signatures of diet and disease, and discover potential mechanisms of diet–disease interactions. Although there are several challenges that must be overcome to improve the reproducibility, cost-effectiveness and efficacy of these approaches, precision nutrition methodologies have great potential for nutrition research and clinical application.

Precision nutrition: Metabolomics: Precision medicine: Personalised nutrition: Multi-omics: Biomarker

Dietary intake is one of the most impactful and modifiable risk factors in human health and disease risk. However, diet is a particularly complex exposure that encompasses a wide degree of variability, both in the known and unknown components of foods, as well as the day-to-day variability in diet and eating patterns. Traditional dietary assessment methods rely on self-reported intakes that are cumbersome and have unavoidable systematic and random error[(1)]. Further, individuals may have varying responses to diet depending on personal characteristics, such as age or stage of life (i.e. pregnant or lactating), sex and health or disease status[(2)]. Further variation can be explained through differences in an individual's genome, epigenome, transcriptome, proteome, lipidome, metabolome and gut microbiome[(3)], which may interact with diet, lifestyle

Abbreviations: DASH, dietary approaches to stop hypertension; PDI, plant-based diet index; SM, sphingomyelins; T2D, type 2 diabetes; TMAO, trimethylamine-N-oxide.

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and environmental factors. The study of genetics, epigenetics, transcriptomics, proteomics, lipidomic, metabolomics and the gut microbiota is collectively referred to as 'omics' research. Recent advances in omic profiling techniques have led to greater focus on *precision nutrition*, an approach that utilises these individual characteristics to develop targeted nutrition recommendations, services or products to prevent and/or manage chronic diseases[4] (Fig. 1). The National Institutes of Health has highlighted precision nutrition as an important strategy in nutrition science in the *2020–2030 strategic plan for NIH nutrition research*[5]. More recently, the National Institutes of Health has funded a new study, *nutrition for precision health powered by all of us research program*, that aims to study and predict individual responses to food and diets through examining interactions between diet, genetics, metabolism, the microbiome and other individual factors[6]. Beyond a clinical application of individual dietary advice or intervention, precision nutrition methodologies have also shown to be useful in biomarker discovery and furthering understanding of diet–disease mechanisms. Here we review some of the tools and uses of precision nutrition research.

Tools of precision nutrition

Advancements in mobile applications, wearable devices and omics technologies have become a major catalyst to precision nutrition efforts. Detailed genome-wide association studies and high-throughput next-generation whole-genome and whole-exome sequencing provide the ability to measure genetic variation and gene function. DNA microarray technology has been developed to assess the expression and transcription of genes. MS and NMR can be used to analyse both known and unknown biological molecules that give a more complete picture of the metabolic status and response to exposures such as foods, diets and dietary patterns. Most recently, advances in high-throughput, high multiplex immune-based assays have paved the way towards protein profiling that covers a broad range of biological processes. The analysis of various omics can each provide a different layer of information – from lifelong traits determined by genetics to more dynamic changes in the epigenetics or short-term variation in metabolism and the microbiome. Integration of multiple omics can help to leverage the strengths and overcome the weaknesses of each individual omic layer, increasing the ability to capture metabolic variation and the chances of identifying robust biomarkers of diet and disease[2].

Genome

The genome is the complete set of genetic information of an individual that determines inherited traits, physical characteristics and any genetic disorders or predispositions to disease risk that are present throughout the lifespan. Genes and gene polymorphisms have been associated with individual metabolic responses to diet[7,8]. One example is genetic diseases that result in defunct or deficient enzymes needed for metabolic pathways. These are referred to as inborn errors of metabolism and can sometimes be treated with nutritional strategies. One such case is phenylketonuria, a condition where individuals are not able to metabolise the amino acid phenylalanine which can lead to serious problems in brain development unless treated with a low-phenylalanine diet[9].

Nutrigenomics is the study of specific nutrient–gene interactions that may explain observed variation in outcome response to nutrients. For example, higher intake of dietary fibre has been thought to help with lowering blood pressure. However, individuals with a common SNP in the gene that encodes angiotensinogen (*AGT*), an important protein involved in regulating blood pressure, do not appear to experience changes in blood pressure in response to a high-fibre diet compared to those without the SNP[10]. Other examples include genetic polymorphisms that are associated with fast *v.* slow metabolism of caffeine[11] or variations in plasma TAG response to fish oil supplements[12].

Epigenome

The epigenome refers to the physical structure and chemical modification of DNA and supporting histone proteins that can alter gene expression without altering the DNA sequence. Types of epigenetic changes include DNA methylation, histone modification and non-coding RNA. Changes in the epigenome can be hereditary but can also be altered by environmental conditions during the lifespan, including lifestyle and diet[13,14]. The epigenome could therefore be an important target for potential diet or lifestyle interventions that may have lasting effects. For example, there is evidence that nutrition during fetal development and early life can impact long-term DNA methylation and, therefore, gene expression[14,15]. Another study demonstrated that habitual diet quality was associated with differences in leucocyte-derived DNA methylation levels[16]. There is also growing evidence that weight loss intervention may be associated with changes in DNA methylation as well[17,18]. In a two-year randomised-controlled trial of energy-reduced diets of varying macronutrient composition, the authors found that higher DNA methylation at *TXNIP* was associated with lower fasting glucose, HbA1c and insulin resistance (measured by homeostatic model assessment of insulin resistance)[18]. Additionally, among those with higher DNA methylation, a moderate protein weight-loss diet was associated with improvement in insulin and homeostatic model assessment of insulin resistance compared to those with a higher protein weight-loss diet.

Transcriptome

The transcriptome encompasses all mRNA transcripts present in the cell, and therefore reflects the genes that are actively being expressed. Besides epigenetic changes that alter gene expression, other factors including vitamins, minerals, macronutrients, phytochemicals and other bioactive components of foods can modify gene

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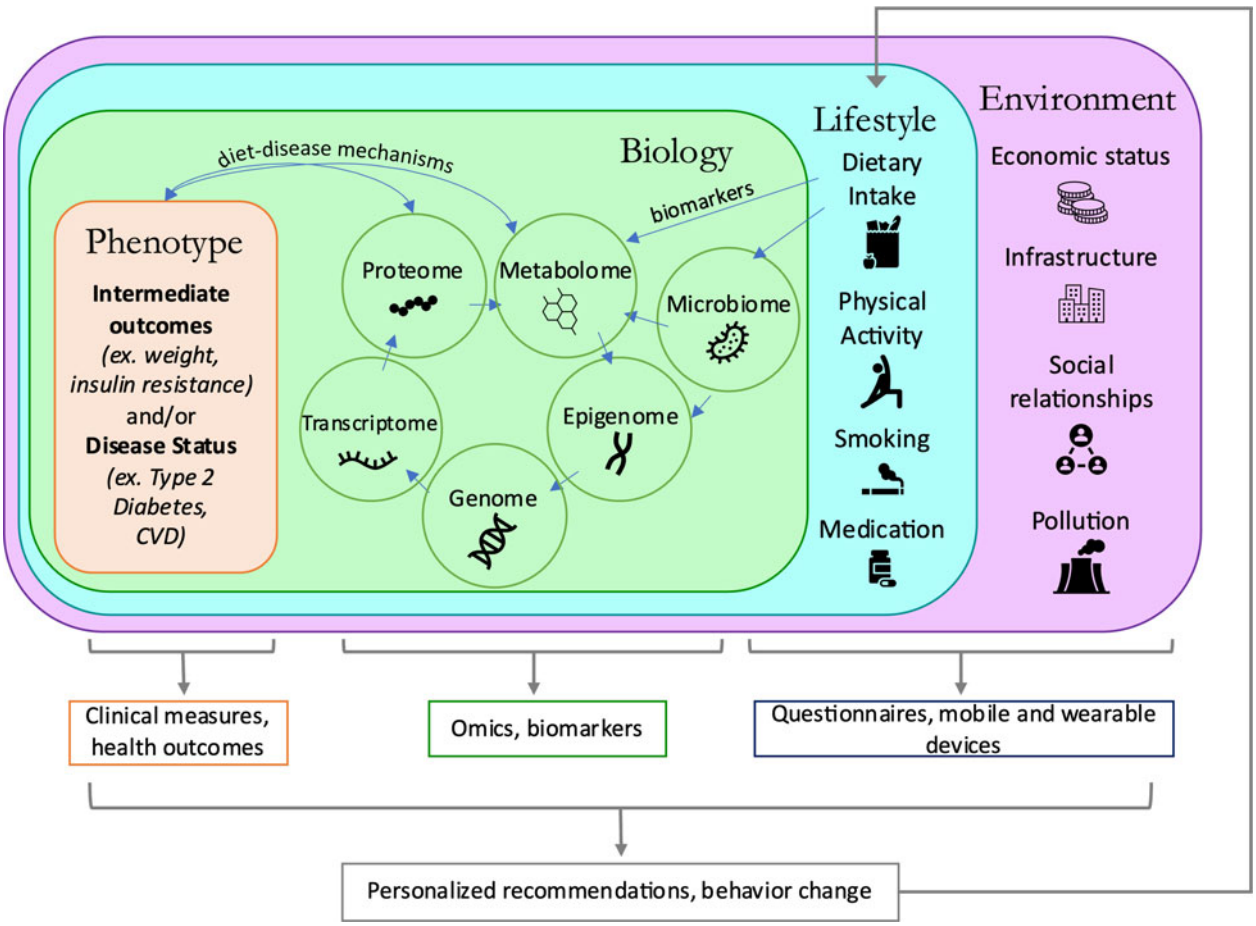

Fig. 1. Precision nutrition in the context of social–ecological model. This figure specifically highlights the complex relationships between dietary intake and the biological systems which are being targeted in omics research. Also indicated are the types of measures that can be made at different levels, which can then be utilised in computer algorithms to predict outcomes or to make personalised dietary recommendations that may improve or prevent disease outcomes.

transcription and translation that impact metabolism and cellular processes[3]. Unlike the genome or epigenome, which can reflect lifetime or longer-term variation in response, the transcriptome measures a single point in time. Therefore, the time, amount and duration of exposure are critical when interpreting these data. For example, numerous animal studies investigating the effects of high-fat and high-sugar diets have demonstrated transcriptomic changes in type 2 diabetes (T2D)-related tissues[19,20].

Proteome

Proteomics measures the end-product of the gene expression cascade, the mature protein, which is more closely related to biological function than mRNA levels[21]. Proteomics data can provide more information regarding functional state, and modern techniques can differentiate between isoforms and post-translational modifications. Investigating perturbations in proteomics profiles may provide detailed insight into cellular responses driven by differences in dietary intakes[22]. Animal studies have already demonstrated the influence of extra virgin olive oils on hepatic antioxidant protein levels in mouse liver[23] and zinc deficiency on lipid metabolism-related protein levels in rat liver[19]. Recently, high-throughput affinity-based proteomics assays have allowed for the examination of proteomic profiles among individuals in large epidemiological studies[24,25]. Differences in proteomic profiles have been observed according to adherence to both theoretical measures of diet quality (alternative healthy eating index, dietary approaches to stop hypertension (DASH) and Mediterranean-style diet score patterns)[26] and empirically derived dietary patterns[27].

Gut microbiome

The gut microbiome consists of the microbial community present in the large intestine that survives largely on dietary fibre that is not digested in the small intestine. The abundance and diversity of microbes present varies between individuals depending on many factors including the diet[28,29]. Evidence suggests that the composition and activity of the gut microbiota may modulate the host response to diet[30]. For example, the ratio of two prominent genera of gut bacterial species, *Prevotella spp.* and

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Bacteroides spp., was reported to predict glucose metabolism in response to a dietary fibre intervention[31]. Microbial metabolism of food components as they pass through the colon can result in the production of small molecules that may be absorbed through the colonic wall. SCFA, for instance, are largely absorbed into the blood stream and have been linked to a variety of physiological effects including energy metabolism[32,33]. The gut microbiota is also a target for precision nutrition interventions given that it can be influenced by diet, although the extent of change may depend on longer-term dietary habits[30].

Metabolome and lipidome

The metabolome refers to the set of metabolites, or small molecules, present in an organism or in a particular biological matrix (i.e. plasma, saliva, etc.). Similarly, the lipidome refers to the complete profile of lipids in a biological matrix. These 'omics' are much more dynamic, responding rapidly to stimuli, including the bioactive components of food. Metabolomic data provide insight into metabolic variation, as well as regulatory or signalling molecules. Evaluating differences in these profiles between individuals and in response to diet is helping to further the understanding of variation in metabolism of individuals and diet disease mechanisms. High-throughput metabolomics profiling has emerged as an important tool in nutritional biomarker discovery for both individual foods and overall dietary patterns[34]. Further refinement of these metabolomic biomarkers and studies integrating these biomarkers into dietary interventions may demonstrate the utility of personalised approaches to dietary advice for prevention of chronic diseases[35].

Precision nutrition applications

In the era of precision medicine, precision nutrition holds great promise to improve human health. First, precision nutrition initiatives allow for more 'precision' dietary assessments. These could be achieved through artificial intelligence, wearables or by employing omic technologies (especially metabolomics) to characterise diet more precisely. Secondly, through the application of omics, precision nutrition allows for us to understand how diet influences disease risk. This by far has been the most promising aspect of precision nutrition research. Finally, precision nutrition can be used for 'personalised nutrition' advice where machine-learning algorithms (based on data from omic technologies) can be integrated with other personal and clinical measures to improve disease risk.

Dietary biomarker discovery

Accurately and objectively assessing diet in free-living individuals remains an ongoing challenge in nutrition research. An individual's diet is a complex pattern of inter-correlated exposures, both of known and unknown constituents, cooking methods and social constructs. This complexity, when coupled with the relatively large within-person day-to-day variability, makes it difficult to accurately quantify a person's diet. Biomarkers, measured in serum, plasma or urine, are an objective method to quantify the intake of nutrients, foods and dietary patterns. Nutrient biomarkers that represent the dietary exposure's true 'bioavailable' or 'internal' dose can serve as the 'gold standard' in the development and validation of many dietary assessment tools, or they can be used to in calibration equations to correct less precise dietary data. However, in nutrition research, there are only a few recovery biomarkers that reflect absolute intake when measured thoroughly over a specified amount of time. These include urinary nitrogen as a biomarker of protein intake, doubly labelled water for total energy intake and urinary potassium and sodium. Unlike recovery biomarkers, concentration or surrogate markers of dietary intake are without a time dimension and can only provide relative intakes. Examples of concentration biomarkers include plasma retinol, plasma vitamin D, plasma ascorbic acid, plasma α-tocopherol, adipose tissue fatty acids, plasma folate and several others. There are few objective dietary biomarkers that can reflect usual/habitual intake of foods or dietary patterns, which are the exposures of interest in many nutritional epidemiologic studies.

The search for dietary biomarkers has most often focused on the plasma metabolome as it most closely represents the phenotype. The metabolome also has the distinct advantage of reflecting the overall metabolic homeostasis resulting from the interaction between the environment, the genome and the microbiome. Metabolites account for variability in intrinsic metabolism by measuring downstream components and therefore, better reflect 'true exposure'. Recent technological advancements in targeted and untargeted metabolomics profiling techniques have allowed for opportunities for discovery of food-based biomarkers. Use of MS-based techniques has allowed researchers to identify novel metabolomic signatures for a wide range of foods and nutrients that can ultimately be leveraged to more precisely characterise diet at the population level. However, for this to happen, there is a tremendous need for well-controlled feeding studies for initial biomarker discovery and external studies for validation at the population level.

Methodological considerations in biomarker discovery

Study design. Several study designs are available for biomarker discovery. Observational studies with information on long-term diet, the nutritionally relevant exposure in epidemiological studies, and stored biospecimens are a valuable resource in identifying biomarkers of foods and dietary patterns. In this approach, participants are ranked according to their dietary intakes measured closest to the timing of the biospecimen collection. Associations between individual metabolites and diet are then assessed using multivariable regression models with statistical corrections for multiple testing. Machine learning tools or other multivariate data reduction strategies can also be applied to derive a multi-metabolite

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'signature' that is reflective of a food or a diet pattern. Given that these are data-driven approaches, it is imperative that the newly developed signatures are replicated in an external independent sample. Because observational studies that utilise food frequency questionnaires can only provide a relative ranking of foods, biomarkers identified in these studies cannot directly quantify food intake or adequately assess dose–response relationships. Moreover, identified metabolites may be reflective of lifestyle rather than the food itself. For example, in some studies, cotinine, a nicotine metabolite, has been part of a metabolomic signature of coffee consumption. Because foods are inter-correlated, biomarkers identified from observational studies are likely to have low specificity.

Randomised-controlled feeding trials are the gold standard to investigate the effects of test foods on the metabolome and for dietary biomarker identification. The dietary intervention often occurs in a rigorously controlled setting such as a metabolic unit with biological samples taken at regular intervals throughout the study period. Sample sizes for these studies tend to be small given the extensive measurements taken and the high cost of metabolomics analyses. These studies can be either acute (lasting a few hours or 1 d) or medium term (lasting several days or sometimes weeks). Acute intervention studies allow researchers to understand the pharmacokinetic behaviour of the metabolites. In this approach, participants refrain from eating the test foods for a few days prior to the start of the intervention. Test foods are provided on the day of the trial and biospecimens, usually urine and plasma, are collected at periodic intervals throughout the day. Metabolomic assays on the biospecimens provide information on the pharmacokinetic behaviour of the putative biomarker. For example, in an orange juice challenge study by Heinzmann *et al*., urinary proline betaine increased dramatically after consumption and peaked at 2 h post intervention[36]. In all participants, proline betaine was excreted rapidly in urine, and urinary excretion was nearly complete after 24 h. This behaviour shows that proline betaine is metabolically inert or minimally metabolised in human subjects. Given that urinary concentrations returned to baseline by the end of 24 h, urinary proline betaine can only be used to reflect recent but not long-term intake of citrus fruit.

To identify biomarkers of longer-term intake or to understand dose–response relationships, intervention studies that span several days to a few weeks or months are typically used. These studies can be parallel arm, or they can be cross-over designs, where each participant crosses over to all other arms in a randomised fashion. The cross-over study design remains the most popular as this design has the distinct advantage of not only lowering the number of study participants needed but also allows for researchers to adequately account for within-person variability as each participant serves as their own control. Although tightly controlled feeding trials remain the gold-standard in nutrition research, they alone cannot identify robust biomarkers of intake. Many of these interventions are either acute or last only a few weeks and, therefore, are not reflective of habitual diet. For these biomarkers to be useful, these foods need to be consumed frequently in adequate amounts. Further, most controlled feeding interventions only include a limited number of participants who are non-smokers, are relatively healthy and not obese. Whether these findings can be extended to free-living individuals remains unknown. In this context, cohort studies with long-term dietary data and stored biospecimens can be employed to validate the biomarkers identified in intervention studies.

Sensitivity and specificity. A key characteristic of a good biomarker is whether it is sensitive to different doses. For example, plasma retinol increases linearly with vitamin A intakes up to 750 μg/d but concentrations plateau with intakes beyond this level. This limits the sensitivity of plasma retinol as a biomarker of vitamin A intake. Controlled feeding trials are an ideal design to understand the dose–response relationship with multiple arms representing multiple doses. In these studies, decisions regarding doses to be tested need to be pegged against national intake data such as NHANES. For foods where national consumption levels are low (e.g. soyabean), it may be prudent to rely on international data.

In addition to sensitivity, it is vital to understand whether a biomarker is specific to a certain food. As before, tightly controlled feeding trials are suitable to testing specificity as participants often consume a standardised background diet with only the test food changing. As a result, any differences in metabolomic profiles can be attributed to the test food. For example, proline betaine is a robust indicator of citrus fruit intake and the quantity of citrus fruit consumed.

Choice of biospecimen. Metabolomic profiles can be measured in different biofluids such as serum/plasma, urine, toenails, stool, hair or saliva. Even tear fluid is being analysed for potential biomarkers of diabetic retinopathy[37]. Comparisons across multiple fluids show that while there are some metabolites that are unique to each fluid, there is also substantial overlap of metabolites present in each fluid[38,39]. Therefore, the choice of biofluid analysed may depend on the specific research question, but also on the convenience of sample collection. Saliva and/or urine collection are less invasive and may reflect similar profiles to plasma metabolites. For food biomarker discovery, however, urine has been the preferred choice as it provides better metabolite coverage and dietary biomarkers are often found in higher concentrations in urine[8]. Compared to spot urine samples, 24 h urine samples will provide a more accurate quantitative prediction of the dietary biomarker[40]. The choice of biofluid will also dictate the biomarkers that are discovered. For example, saliva and urine may provide information on short-term dietary exposures, erythrocytes may provide intermediate dietary exposures, and adipose tissue and toenails are promising biospecimens for capturing long-term exposures. For this reason, measuring multiple biospecimens can often provide us with a broader range of biomarkers in the human body[41].

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Biomarkers identified using omics

Nutritional biomarkers. There have been only a few studies that examined the metabolomic response to single nutrient intakes. A comprehensive scoping review of 24 human studies confirmed that animal and plant protein-rich diets elicit different metabolomic responses[42]. Several metabolites were identified as plausible candidates to explain the differential association of the two diets with cardiometabolic risk. For instance, plant protein-rich diets were positively associated with glycine which is known to be associated with lower cardiometabolic risk. Conversely, animal protein-rich diets were associated with branched chain amino acids, aromatic amino acids, glutamate, short-chain acylcarnitines and trimethylamine-N-oxide (TMAO), which are associated with higher cardiometabolic risk. Like proteins, the quality of carbohydrates can also influence the metabolome, although their utility as biomarkers maybe diminished by individual variation. In a randomised and controlled cross-over feeding trial lasting 4·5 weeks, 3-methylhistidine, phenylethylamine, cysteine, betaine and pipecolic acid were identified as biomarkers in the unrefined carbohydrate diet compared to the refined carbohydrate diet[43]. Still, hierarchical analysis showed that these metabolites at the end of each diet phase were more strongly clustered by the participant than the diet type, thereby limiting their ability to discriminate individuals based on their carbohydrate intake. In a cross-sectional analysis of the PREvencion con Dieta MEDiterranea (PREDIMED) study, glycaemic index, glycaemic load and a carbohydrate quality index were associated with specific metabolomic profiles, and strong correlations (Spearman *r* 0·22–0·37) were observed between the multi-metabolite model and these indices[44]. In the women's health initiative, Zheng *et al.* evaluated potential metabolomic-based biomarkers of protein, carbohydrate and fat intakes using a 2-week controlled feeding study design among 153 postmenopausal women[45]. Their analyses showed that using metabolites alone achieved reasonable prediction of % energy from protein and % energy from carbohydrate (cross-validated *R*2 22·8–37·1 %) with better predictability when combining metabolites from spot urine and 24 h urine. However, for energy intake, prediction improved to about 55 % only after addition of participant characteristics and doubly labelled water. Finally, for fat intake, metabolites did not provide adequate prediction, highlighting the limitation of urine samples for measuring biomarkers of fat intake. It must be appreciated that metabolomic response to a single nutrient intervention may depend on the replacement nutrient and the food source of the nutrient.

Food biomarkers. In one of the earliest studies to identify quantitative food biomarkers, participants were fed different doses of grapes in addition to a standardised meal in a tightly controlled randomised clinical trial. Urinary tartaric acid was identified by 1H NMR spectroscopy as a dose-responsive and quantitative urinary biomarker of grape intake[46]. In another controlled feeding trial, Heinzmann *et al.* identified proline betaine as a quantitative biomarker of citrus fruit intake[36]. Proline betaine was externally validated using data from the International Collaborative Study of Macronutrients, Micronutrients, and Blood Pressure (INTERMAP) where it could distinguish citrus consumers from non-consumers with a specificity of 92·3 % and a sensitivity of 80·6 %. In the NutriTech food intake study, using NMR spectroscopy, urinary guanidoacetate was identified as a quantitative biomarker of chicken intake[47]. Likewise, data from controlled feeding trials identified urinary xylose as a biomarker with a dose–response relationship with apple intake. Importantly, xylose was capable of ranking individuals in a cohort study into categories of apple intake[48]. Plasma alkylresorcinols have been proposed as biomarkers of wholegrain intake in several studies[49–51]. Although plasma alkylresorcinols demonstrate a dose–response relationship with whole grain intake and can distinguish between non-consumers and consumers, they cannot be used to differentiate between participants with whole grain consumption >60 g/d[52]. In a systematic search for biomarkers of sugar-sweetened beverages and low-energy sweetened beverages, Muli *et al.* evaluated specificity and validity of the identified biomarkers following guidelines for biomarker of food intake reviews[53]. They identified13C:12C carbon isotope ratio (δ13C), particularly, the δ13C of alanine, as a robust, sensitive and specific biomarker of sugar-sweetened beverages intake. Although biomarkers for long-term intake of low-energy sweetened beverages were not available, several metabolites including acesulfame-K, saccharin, sucralose, cyclamate and steviol glucuronide showed moderate validity for predicting short-term intake of low-energy sweetened beverages. The food biomarker alliance project performed a literature review to identify biomarkers of tropical fruit intake that fulfilled certain biological and chemical criteria. Even though candidate biomarkers were identified for banana, avocado and watermelon, many of these metabolites, especially banana-derived metabolites had limited data on dose–response relationship. At the same time, for avocado, perseitol and mannoheptulose were reported as candidate biomarkers while citrulline was associated with watermelon intake[54]. Although these biomarkers are promising, validation of these in pharmacokinetic and dose–response studies is essential.

Multi-metabolite biomarker panels may be useful in distinguishing foods and for increasing specificity in prediction of food intake. For example, a three-metabolite biomarker panel (proline betaine, hippurate and xylose) identified from an intervention study had excellent agreement with self-reported fruit intake from a cross-sectional study[55]. Using data from a randomised cross-over dietary intervention trial of meat and the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study, a multi-metabolite marker panel including several glycerophospholipids, 4-hydroxyproline, TMAO, creatine, deoxycarnitine and stearoylcarnitine reflected red meat intake in both the intervention and cohort studies[56]. Because processing itself can influence the metabolomic response, biomarkers of processed meat can vary from those of red meat. For instance, a controlled dietary intervention study of processed meat showed that high urinary and plasma levels of pepper

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alkaloid metabolites were detected after consumption of salami. While this was also replicated in a free-living population, these metabolites performed poorly to predict sausage intake in the EPIC participants (area under the curve (AUC) 0·66–0·69) highlighting their limited value as biomarkers[57].

Biomarkers of dietary patterns. Metabolomics analysis of dietary patterns has been conducted using both observational and controlled feeding trials. In one of the first rigorously conducted randomised, controlled, cross-over feeding trials, Garcia-Perez *et al.* used 1H-NMR spectroscopic profiling of urine to develop a model based on urinary metabolite patterns to classify individuals on the basis of their adherence to the WHO healthy eating guidelines[58]. These metabolite signatures were then externally validated in the INTERMAP study and a Danish cohort. Although there were systematic differences in metabolomic profiles across the least and most adherent diets, there was considerable overlap in metabolite concentrations indicating relatively low sensitivity of this multi-metabolite panel[59]. Several studies aimed to identify metabolomic profiles of meat eaters, vegetarians and vegans. In a cross-sectional study, branched chain amino acids, leucine, isoleucine and valine were higher in meat eaters and non-vegans than in non-meat eaters/vegans[60]. Likewise, in the EPIC cohort, significant differences in metabolomic profiles were seen between meat eaters, fish eaters, vegetarians and vegans. For example, vegans had lower concentrations of some glycerophospholipids, and sphingolipids compared to other groups. At the same time, fish eaters or vegetarians had the highest concentrations of the amino acids and a biogenic amine relative to other diet groups[61]. In the Adventist health study-2, compared with non-vegetarians, vegans had higher plasma carotenoid concentrations and a higher excretion of urinary isoflavones and enterolactone. They also had lower relative abundance of SFA including myristic, pentadecanoic, palmitic and stearic acids but higher linoleic acid (18 : 2*n*-6) and a higher proportion of total *n*-3 fatty acids[62].

Because the anatomy of a healthy diet is universal across various measures of diet quality, it is not surprising that predictive metabolites that represent greater alignment to different diet quality scores were found to be consistent across multiple diet indices. For example, in the Atherosclerosis Risk in Communities (ARIC) study, using an untargeted approach, Kim *et al.* found 17 unique metabolites that were associated with healthy eating index (HEI), alternative healthy eating index (AHEI), alternative Mediterranean diet (aMED), and DASH[63]. Because these diet scores share many components, six of the seventeen metabolites were associated with more than one dietary pattern. Candidate biomarkers of HEI, AHEI and DASH had good predictive capability (*P*-value for difference in *C*-statistics <0·02 for all three diet indices) and could distinguish individuals with highest compared with lowest quintile of diet scores beyond participant characteristics. However, this was not true for candidate biomarkers for aMED indicating that these biomarkers had low prediction ability. In the DASH intervention trial, a serum metabolite panel consisting of ten metabolites (N-methylproline, stachydrine, tryptophan betaine, theobromine, 7-methylurate, chiro-inositol, 3-methylxanthine, methyl glucopyranoside, β-cryptoxanthin and 7-methylxanthine) could distinguish between participants consuming a DASH diet, a fruit and vegetable diet or a control diet with a *C*-statistic of 0·98[64].

Using a unique study design that is applicable to the real-world context, Willis *et al.* considered the whole diet by using menus that delivered a wide range of foods found in conventional UK diets[65]. For this, they recruited free-living participants who prepared and consumed all foods and drinks in their own homes and provided spot-urine samples. The authors identified pyrogallol sulphate, pyrogallol glucuronide and trigonelline as potential biomarkers of beans, peanuts and soy. Trigonelline has been well documented as a coffee metabolite[66], but these data are primarily from populations that have limited legume consumption. Concentrations of urinary eugenol glucuronide and eugenol sulphate were higher after consumption of curry possibly due to the high content of cloves which is rich in eugenol. While there have been limited attempts to examine how cooking alters metabolite profiles, in the current study, 2-furoylglycine discriminated thermally treated foods (pies, grains and toasted wheat products) from non-thermally treated foods (e.g. toasted bread).

Understand diet–disease mechanisms

The use of omics methodologies can not only help identify objective biomarkers of diet but are also useful for elucidating metabolic pathways through which diet can influence disease risk. To this end, researchers have typically employed machine learning methods that can model high-dimensional metabolomics data as scores that reflect dietary adherence. These scores are then examined in relation to disease risk. The intrinsic advantages to using metabolic signatures that reflect dietary adherence as opposed to self-reported diets are several. First, the signature captures cumulative changes in the metabolome due to diet. Secondly, the signature can incorporate individual metabolic variations from other factors that influence dietary metabolism. Finally, metabolomic signatures minimise measurement errors which are inherent to self-reported dietary assessments. A few recent examples of these approaches are discussed here.

Recently, in two studies in China, using a lipidomics panel, Yun *et al.* identified four novel candidate biomarkers of total dairy intake. Given that a third of the phospholipids present in milk are sphingomyelins (SM), it is not surprising that the four candidate biomarkers included SM (OH) C32:2, SM C32:1, SM (2OH) C30:2 and SM (OH) C38:2. The use of these four SM alone or in combination could accurately differentiate individuals with high and low dairy intakes (*C*-statistic ranging from 0·81 to 0·87). Importantly, these SM were inversely associated with changes in systolic and diastolic blood pressure, blood glucose and plasma TAG[67,68]. In our

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prior work, we identified a metabolic profile comprised of 67 metabolites that was robustly associated with adherence to a Mediterranean diet among participants from the Nurses' Health Study (NHS), Health Professionals Follow-up Study (HPFS) and PREDIMED study[69]. In multivariable models, this metabolomic score was inversely associated with incident CVD even after adjusting for known risk factors and self-reported diet. Additional genome-wide association studies analyses showed that this signature was significantly associated with genetic loci involved in fatty acid and amino acid metabolism. Additional diet indices that have been investigated include indices of plant-based diet quality such as the plant-based diet index (PDI), the healthy PDI and unhealthy PDI. In the ARIC study, several metabolites predicted adherence to plant-based diet indices beyond sociodemographic characteristics, health behaviours, clinical factors and total energy intake. Six of these metabolites (glycerate, 1,5-anhydroglucitol, γ-glutamylalanine, γ-glutamylglutamate, γ-glutamylleucine, γ-glutamylvaline) were significantly associated with incident chronic kidney disease[70]. Our previous work in the NHS I and II and HPFS cohorts showed that multi-metabolite profiles of plant-based diet quality were associated with T2D risk. Specifically, metabolite profile scores of PDI were associated with a 19 % (95 % CI 12, 25 %) lower T2D risk while those of healthy PDI were associated with a 23 % (95 % CI 16, 29 %) lower T2D risk even after controlling for self-reported diet. A significant proportion of this risk was accounted for by trigonelline, hippurate, isoleucine and a subset of TAG[71]. In the Malmo diet and cancer study and the Malmo offspring study, a metabolic signature that reflects adherence to a health-conscious food pattern remained inversely associated with T2D after adjustment for self-reported diet intake[72]. These studies are examples of how metabolomic data could further our understanding of the mechanisms by which diet may influence disease development. Other studies have shown that metabolomic or lipidomic profiles can improve the prediction of T2D beyond traditional risk factors alone[73–75].

Proteomic biomarkers of diet quality may help us better understand the specific pathways that are modified by food and nutrient intakes and lead to development of chronic diseases. For example, in a prospective cohort study among Framingham Heart Study participants, 30 out of 71 CVD-related plasma proteins were associated with differences in diet quality (AHEI, DASH and Mediterranean-style diet score)[76]. Four of these proteins were suggested to be mediators of the association between diet quality and incident CVD during a median follow-up of 13 years. New opportunities for protein biomarker discovery have emerged as our ability to estimate a wide range of proteins from small sample volumes improves. Thus, this is a fast-evolving area of research with ample opportunity for discovery of novel biomarkers of foods, nutrients and dietary patterns.

Investigation of the gut microbiome can add an additional layer of understanding how dietary intakes influence metabolism and chronic disease risk. One example is the microbial metabolism of L-carnitine, which is found in red meat, into TMAO[77]. TMAO is known to be proatherogenic, and levels of production depend on diet and microbial species present in the gut[78]. Plasma L-carnitine is also predictive of CVD and CVD-related events[77,79]. These types of studies can inform targeted dietary recommendations, such as reducing red meat intake among individuals with a gut microbiome that is capable of producing higher levels of TMAO. In another study of over 9000 racial/ethnically diverse participants across five different cohorts, a microbial metabolite of tryptophan, indolepropionate, was found to be inversely associated with T2D risk[80]. Interestingly, levels of circulating indolepropionate were associated with fibre-rich foods, but not protein/tryptophan-rich foods, and also with a variant in the *LCT* gene, which encodes lactase. Among individuals with this variant, higher milk consumption was associated with higher levels of indolepropionate and *Bifidobacterium*, a bacterium which was also significantly associated with indolepropionate levels. This study demonstrates the complex interactions between genetics, diet and microbiota that play a role in individual disease risk and suggests that circulating metabolome could be used to identify higher risk individuals that could benefit from dietary intervention or microbiota modulation.

Omics integration for personalised nutrition advice

The development and implementation of personalised nutrition approaches requires integration of novel omics-based recommendations with traditional clinical and dietary measures. Thus, studies testing how personalised nutrition interventions can complement traditional interventions to improve clinical outcomes are necessary before they can be implemented on a large-scale basis. As high-throughput omics-based methods have become faster, cheaper and more comprehensive, the prospect of evaluating personalised nutrition interventions in clinical studies has become a reality. One study integrated gut microbiome data with clinical and dietary data to build predictive models of individual post-prandial glycaemic responses to foods in patients with T2D[81]. Then, results from this machine learning model were utilised to generate personalised dietary recommendations that resulted in significantly lower postprandial glycaemic responses compared to traditional dietary advice for patients with T2D. Other studies have also demonstrated the feasibility of generating personalised dietary advice through integration of clinical biomarkers with omics data[82,83], and one study observed significantly larger improvements in diet quality among intervention arms receiving personalised dietary advice compared to general dietary advice[83]. Thus, as highlighted by others[84,85], early evidence suggests that implementing personalised dietary advice in the clinic has the potential to improve public health, but more research is needed to understand the efficacy, cost-effectiveness and scalability of these types of interventions in large populations.

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Next steps

Rapidly evolving technologies have provided a plethora of opportunities to explore omics data and to integrate them into traditional nutrition epidemiological approaches. Like any new area of research, however, methodological considerations need to be addressed to move forward. Challenges in omics research include variability in protocols, analysis and interpretation. Untargeted metabolomics analysis produces large datasets of metabolites that must be systematically identified. Large-scale, international efforts are needed to implement an infrastructure for data sharing and standard metabolite identification. There is also a need to discover biomarkers, not only of diet but also of diet–gene or diet–microbiota interactions. This will further the ability to link observations to biological pathways and further our understanding of disease mechanisms and how they are influenced by diet.

Most precision nutrition studies have been supported by observational data. In order to translate findings from these studies into personalised nutrition advice, more randomised-controlled trials are needed. These types of studies can evaluate whether implementing personalised nutrition advice can improve clinical outcomes. However, these studies have their own challenges, including the high cost and logistical burden of carrying out long-term interventions. Intermediate clinical markers, such as lipid profiles, blood pressure or HbA1c, could be utilised as disease markers over a shorter time period. Lastly, more research is needed in multi-omics approaches. Integrating data from different omics measures is challenging, but critical to linking mechanistic pathways. This will become increasingly difficult with the addition of new omics areas that are gaining interest, such as the exposome (the measure an individual's environmental exposures) and individual inflammatory responses[86].

Conclusions

Advancements in omics technologies have greatly advanced the field of precision nutrition. Each type of omics data provides a different layer of information from genomics that persist through the lifespan, to highly variable metabolomic profiles that can change in response to diet. These data can be used to identify biomarkers of dietary intake, to elucidate diet–disease mechanisms, and to inform more personalised dietary advice, particularly for higher risk individuals. Precision nutrition and especially omics research is still very new, and while there is great potential, methodological challenges that impact consistency and accessibility must be overcome.

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Conflict of Interest

Dr Bhupathiraju is a scientific consultant for LayerIV for work outside the submitted manuscript.

Authorship

The authors had sole responsibility for all aspects of preparation of this paper.

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