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Guidance and Position of RINN22 regarding Precision Nutrition and Nutriomics

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Keywords

RINN22 · Nutriomics · Precision nutrition · Nutrigenetics · Nutrigenomics · Nutrimetagenomics · Nutriepigenetics · Nutrimetabolomics

Abstract

Background: Precision nutrition is based on the integration of individual's phenotypical and biological characteristics including genetic variants, epigenetic marks, gut microbiota profiles, and metabolite fingerprints as well as medical history, lifestyle practices, and environmental and cultural factors. Thus, nutriomics areas including nutrigenomics, nutrigenetics, nutriepigenetics, nutrimetabolomics, and nutrimetagenomics have emerged to comprehensively understand the complex interactions between nutrients, diet, and the human body's molecular processes through precision nutrition. ***Summary:*** This document from the Ibero-American Network of Nutriomics and Precision Nutrition (RINN22; https://rinn22.com/) provides a comprehensive overview of the concepts of precision nutrition approaches to guide their application in clinical and public health as well as establish the position of RINN22 regarding the current and future state of precision nutrition. ***Key Messages:*** The progress and participation of nutriomics to precision nutrition is an essential pillar for addressing diet-related diseases and developing innovative managing strategies, which will be promoted by advances in bioinformatics, machine learning, and integrative software, as well as the description of specific novel biomarkers. In this context, synthesizing and critically evaluating the latest developments, potential applications, and future needs in the field of nutrition is necessary with a holistic perspective, incorporating progress in omics technologies aimed at

precision nutrition interventions. This approach must address and confront healthy, social, food security, physically active lifestyle, sanitation, and sustainability challenges with preventive, participatory, and predictive strategies of personalized, population, and planetary nutrition for a precision tailored health.

Introduction

A suboptimal diet and nutritional imbalances are considered important contributors to the global prevalence of diet-related diseases including obesity, diabetes, cardiovascular diseases, liver damage, and some types of cancers, with a high global incidence [1]. National nutritional guidelines designed to influence consumer eating behavior and dietary patterns have relatively little health impact, despite the well-established adverse influence of excessive consumption of saturated fats, salt, and simple sugars [2]. Therefore, health objectives, as well as the purposes of sustainability plans, highlight the need for integrated efforts by the population, governments, and social organizations to prioritize nutritional guidelines that promote the intake of *in natura* or minimal processed foods, such as whole grains, fruits, vegetables, nuts, seeds, and legumes [3]. However, the concept of "single or total diet" concerning to national and international dietary guidelines does not take into account physiological, emotional, and sociocultural factors that drive human behavior. Moreover, eating behavior and responses to food are also subject to genetic, phenotypic, and metabolic determinants, the medical history, and lifestyle practices, such as eating habits and physical activity, as well as sociocultural and economic differences among countries related to the food and gastronomic environment, dietetics, and the educational context [4]. This range of potential influences on health has led to the development of personalized and precision nutrition strategies to improve dietary patterns aimed at better nutrition and public health.

In this context, "personalized nutrition" has been defined as a health approach in which individualized data and clinical information are used along with available metabolic traits to design and prescribe specific, unique, and targeted typed nutritional advice and support for human being health [5]. In turn, the general term "precision nutrition" is defined as a methodology to objectively quantify and complementarily integrate genetic, metabolic, and lifestyle information on a global scale often using omics technologies or proxies such as genetics, epigenetics, metabolomics, and metagenomics (Fig. 1). These omics approaches or global methods are focused on the comprehensive analysis and characterization of large sets of biological molecules that holistically make up the structure, function, and dynamics of an organism using high-quality analytical techniques performance and bioinformatics tools [5]. In fact, precision nutrition encompasses "nutriomics," whose term refers to the integration of nutrition with omics technologies, thus emerging the areas of nutrigenomics, nutrigenetics, nutriepigenetics, nutrimetabolomics, and nutrimetagenomics to comprehensively understand the complex interactions between nutrients, diet, and the human body's molecular processes as well as personality and psychological features [6]. A distinction between the two concepts is that personalized nutrition typically considers individualizing characteristics such as gender, age, diet, and habitually available baseline health markers, while precision nutrition adopts a more dynamic and multifactorial approach encompassing nutriomics knowledge together with socioeconomic, psychosocial, and clinical information, and food environments [7]. This document from the Ibero-American Network of Nutriomics and Precision Nutrition (RINN22; https://rinn22.com/) provides a comprehensive overview of the concepts of precision nutrition technologies to guide their application in clinical and public health as well as establish the position of RINN22 regarding the current and future state of precision nutrition.

Nutrigenetic Approaches

Nutritional genetics or nutrigenetics has been conventionally defined as the study of the effect of genetic variation on the dietary response in carriers of mutations, variants or genetic polymorphisms [8]. In fact, genome-wide association studies (identifying relationships between genotypes and phenotypes/diseases) and whole-genome genotyping analysis (providing an overview of the entire genome) have contributed to the identification of a number of genetic variants that influence individual outcomes upon dietary advice, which are located in genes related to energy intake, appetite, adipogenesis/lipid metabolism, inflammation, and insulin resistance [4].

In the last decades, the increasing prevalence of obesity has led to the investigation of genes responsible for energy homeostasis, such as *FTO* gene, whose polymorphisms have shown to influence body composition with a variation in weight of around 1–2 kg under equal personal conditions for each risk allele [9]. Several studies of the polymorphisms in the *FTO* gene appear to interact with dietary factors in relation to adiposity phenotypes and

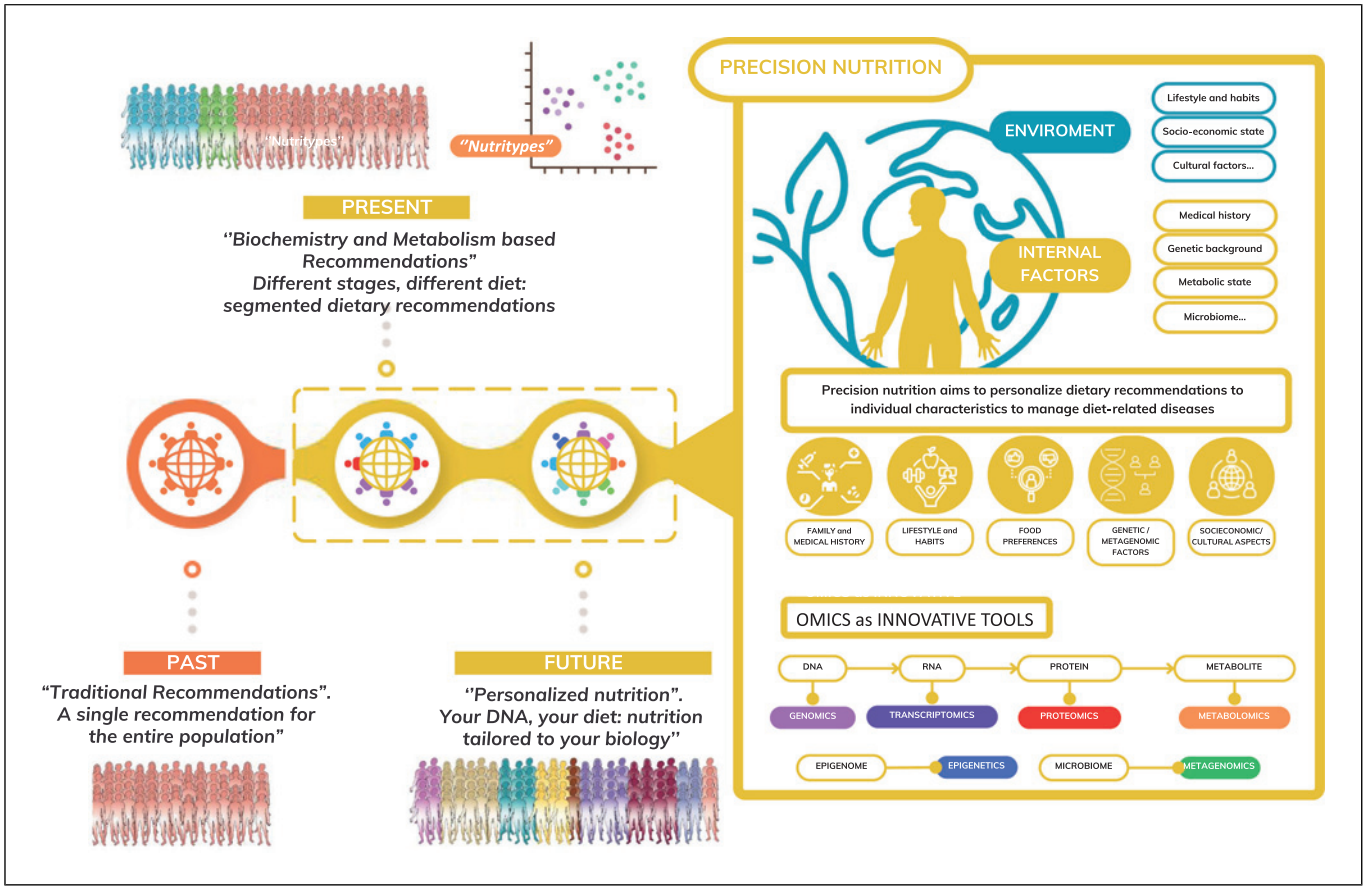

Fig. 1. Overview of the past, present, and future of nutritional recommendations and internal and environmental factors and omics tools of an integrative precision nutrition approach.

nutritional responsiveness, as well as appetite [10]. In patients with type 2 diabetes, the high-fat and low-fiber intakes were associated with risk allele (A) of the *FTO* gene rs9939609 polymorphism [11]. Also, a cross-sectional study of Chilean children was conducted in order to assess the association between the rs9930609 variant of the *FTO* gene and eating behavior. Overweight carriers of the A allele showed higher scores on food responsiveness, emotional overeating, enjoyment of food, and food choice subscales. Contrary to this, they scored lower on both satiety responsiveness and slowness in eating [12]. Additionally, a study in Brazilian individuals with type 2 diabetes demonstrated that the C allele of the rs7204609 polymorphism in the *FTO* gene increased the chance for the presence of metabolic syndrome, especially central obesity, and microalbuminuria, regardless of energy and nutrient intake [13].

A higher prevalence of obesity and other cardiometabolic diseases has also been linked to variants in circadian-related genes, affecting transcriptional/translational feedback loops that govern circadian rhythms. Indeed, nutrigenetic research has focused on the study of the interactions between circadian-related genes and nutrients, aiming to modulate disease risk and account for individual differences in responses to nutritional programs [14]. Thus, *CRY*, *PER*, *BMAL*, and *REV-ERB* variants have been associated with changes in body weight, food intake, or type 2 diabetes [14]. Specifically, the *CLOCK* variants rs3749474 and rs1801260 have been linked to higher body weight in a Spanish population of overweight/obese subjects recruited into a weight loss program [15]. In line with these findings, a study carried out in the USA with overweight participants found an association of these SNPs and also for the *CLOCK* rs4580704 SNP with total energy intake [16].

Another example of nutrigenetics is related to the close association between the *MTHFR* C677T polymorphism and the risk of cardiovascular disease. This variant reduces the activity of the MTHFR enzyme and contributes to hyperhomocysteinemia, reduced folate levels, and

several cardiovascular diseases [17]. This association has been recently replicated in a meta-analysis and has confirmed the effect of this variant on coronary artery disease showing a higher and significant risk for the dominant model TT + TC versus CC in the Chinese population [18].

Potential applications of nutrigenetic approaches are also focused on the treatment of hepatic steatosis. In this sense, a systematic review concluded that individuals homozygous for *PNPLA3* 148M might benefit with the adoption of lifestyle changes, including calorie restriction and physical exercise, while benefit less or not at all from omega 3 fatty acids to reduce hepatic steatosis [19]. In addition, a study that prescribed a dietary treatment with an energy restriction of 30% of the individual's requirements for 6 months found that subjects carrying the T allele (CT/TT genotypes) of the *SH2B1* rs7359397 polymorphism displayed a greater decrease in liver fat content compared to CC genotype carriers [20].

In addition, several precision nutrition studies have used nutrigenetic approaches to design and deliver individually tailored dietary advice. Thus, the Food4Me project was the first controlled proof-of-concept study on personalized nutrition [21]. In this study, participants from seven European countries were genotyped for five polymorphisms known to substantively impact nutrient metabolism: *FTO*, *FADS1*, *TCF7L2*, *APOE*, and *MTHFR* [21]. After 6 months of the intervention, these researchers found an improvement in diet quality (Healthy Eating Index), changes in energy intake and reductions in red meat consumption, salt, and saturated fat in participants who received personalized advice compared to the control [22]. Moreover, subsequent analyzes of the Food4Me project revealed a benefit from genotype-based counseling (including *ADRB2*, *AGT*, *APOE*, *FTO*, *GC*, and *CETP* genes) to reduce the intake of foods rich in salt, sugars, and saturated fats and to improve adherence to the Mediterranean diet [23]. This nutrigenetic study focused on genotypes with potential scientific evidence to benefit from changes in diet and physical activity [23].

In this same field, a 4-month nutritional intervention that incorporated genetic, phenotypic, and lifestyle information in a decision algorithm found evidence of genotype interactions with dietary intervention [24]. This design included a calculation of genetic risk scores based on 95 SNPs related to obesity, appetite, and weight loss induced by low-calorie diets, allowing the personalized prescription of diets with different distribution of macronutrients (moderately high in protein and low-fat, respectively) to Spanish participants with overweight/obesity [24]. Furthermore, this trial showed an influence of genotype on the regulation of blood cholesterol, finding that an energy-restricted and moderately high-protein diet could be more beneficial than a low-fat diet in reducing serum cholesterol among subjects with obesity who were carriers of the *PPARGC1A* Gly482Gly genotype [25].

Furthermore, a nutrigenetic study verified whether a genetic risk score of the plasma triglyceride response to an n-3 fatty acids supplementation (2.7 g/d of docosahexaenoic and eicosapentaenoic acids) developed within a French Canadian sample can explain the plasma triglyceride response to n-3 fatty acids in Mexicans [26]. Findings of the study showed that the predictive capacity slightly differs between ethnic groups, suggesting that nutrigenetic studies need to be expanded by examining a broader range of multiracial populations to ensure that precision nutrition approaches avoid racial or ethnic bias with the potential to be effective for each individual [26].

Nutrigenomic Approaches

Nutritional genomics, or nutrigenomics, refers to the study of the effect of foods, nutrients, dietary products, bioactive compounds, or dietary patterns on gene expression and function [27]. The knowledge of the precise effect of a certain type of diet on gene expression leads to the preparation of new nutrigenomic tools (e.g., functional foods) for preventive and therapeutic purposes. Thus, advances in nutrigenomics have provided greater understanding of the role of different foods and bioactive nutrients in cellular physiology and homeostatic control. Notable examples of such diet-induced metabolic regulatory pathways include the increased expressions of the insulin gene upon glucose consumption or the *ChREBP* gene on glycolysis as well as the positive impact of ingestion of fat in the expression of the *PPAR* gene in the metabolism of lipids or energy intake that downregulates the gene expression of ghrelin. Dysfunctions or alterations in these pathways are often responsible for the appearance of metabolic disorders such as obesity, insulin resistance, type 2 diabetes, cardiovascular events, and cancer [27].

Important evidences have shown the positive effect of weight loss through different strategies on gene expression profile and metabolic disorders. For example, in individuals with obesity, survivin gene expression levels were reduced following weight loss due a very low-calorie ketogenic diet or bariatric surgery, achieving values similar to those of the normal weight individuals [28]. Also, bariatric surgery was capable to modify the

expression of 1,366 genes related to lipid metabolism, insulin resistance, inflammation, and immune response. These transcriptomic changes were related to the weight loss after surgical procedure [29].

Several precision nutrition studies have used nutrigenomic approaches to design and offer personalized dietary advice. A paradigmatic example links the intake of a "cafeteria" diet in an animal model with the expression of *UCP1* and *PPAR* genes depending on the time of intake [30]. Also, in the randomized NOW study, it was demonstrated that participants assigned to receive the nutrigenomic-oriented group lifestyle program significantly reduced their total fat intake [31]. Other trials based on nutrigenomic approaches support the potential of prescribed interventions in these individuals to motivate long-term changes in specific nutrients, such as total fat intake [32]. However, recent reviews highlight important gaps in the evidence for the effective integration of nutrigenomics approaches into the behavioral sciences [33]. In particular, motivations for behavior change are likely to be specific to the nature of the intervention and the target population. Thus, interventions targeting weight control in middle-aged adults may be more sensitive to nutrigenomic messages compared to interventions aimed at young adults, who may be less motivated to improve their health [33]. Besides, the use of motivational particular optimist strategies to increase adherence to nutritional interventions shows improvements in weight loss responses in subjects with obesity [34].

Human intervention studies have also been conducted to examine the impact of meals and snacks on gene expression pathways. In a recent randomized postprandial crossover study, transcriptomic regulation of adipose tissue after a high-lipid meal was investigated in men with and without metabolic syndrome [35]. The results demonstrated increases in gene expression related to cellular nutrient responses in control participants after a high-fat meal, while the response was lower in men with metabolic syndrome [35]. Specifically, in healthy men, genes related to the activation of cellular metabolism and nutrient response pathways were upregulated, such as mTOR pathways through the activation of *MAPK1*, *STAT3*, and *TGFB3* genes [35]. Whereas, a trial conducted in healthy adults analyzed the effects of a single dose of high-polyphenols cocoa powder on gene expression in circulating white cells. The polyphenols intake modified the expression of genes in anti-inflammatory and antioxidant pathways. The clustering of the transcriptional profile of the analyzed samples suggested that differences were mainly dependent on the baseline expression profile of each individual [36]. Another study carried out in Latin America evaluated the effect of a diet based on fruits, avocado, whole grains, and trout on the expression of genes related to obesity. After 8 weeks of intervention, the expression of inflammatory genes (*NFKB1*, *IL6*, *IL1b*) and oxidative stress genes (*NFE2L2*) decreased with the intervention diet [37]. Furthermore, the European NUGENOB study showed that changes in the expression of genes involved in the functions of hormone-sensitive lipase or leptin were more attributable to the reduction in caloric intake than to the proportion of fat consumed in diets of weight loss [38].

To gain insight into mechanistic studies and the molecular effects of foods, the exploration of multiple-omic experiments available in public databases (which have generated gene expression data following the treatment of different systems with different food nutrients and bioactive compounds) will offers excellent possibilities for future personalized nutrition based on nutrigenomics. Indeed, there are several such databases, including NutriGenomeDB [39] and others.

Nutriepigenetic Approaches

Nutrition is one of the most studied and best understood lifestyle factor associated with epigenetics, which refers to heritable changes in gene expression that are not attributable to alterations in the DNA sequence [40]. Thus, epigenetic signatures, especially DNA methylation patterns and non-covalent histone modifications, are modifiable and susceptible to environmental factors such as diet [41]. In particular, methyl donor nutrients, such as folate, methionine, choline, and some B vitamins, play a relevant role in DNA methylation by participating as methyl donors or coenzymes in one-carbon metabolism, modifying the DNA methylation and expression of miRNAs with modulating capacity on the genes involved. In this context, nutriepigenetic research encompasses the study of the effect of foods and nutrients that can impact epigenetic marks and cellular phenotypes with interest for precision nutrition [42]. In this context, a systematic review described different interactions between fatty acids and epigenetic features [43]. Particularly, omega 3 (docosahexaenoic and eicosapentaenoic acids) have been related to the prevention of metabolic alterations such as lipid metabolism disturbances, inflammation, and insulin resistance), whereas omega 6 (arachidonic acid) have been associated with an increased risk for these metabolic alterations through epigenetic mechanisms. These include DNA methylation

(hyper or hypomethylation), acetylation or deacetylation of histones, and miRNAs related to repression, or activation of genes.

Knowledge of the range of foods, bioactive compounds, and dietary patterns that exert epigenetic effects is growing. In this regard, low folate intake in patients with metabolic syndrome has been associated with hypomethylation of the *CAMKK2* gene at specific CpGs sites related to insulin resistance [44]. Meanwhile, higher fruit intake was related to better glucose tolerance in healthy subjects, partially mediated by lower *TNFα* methylation in Brazilian young adults [45]. Still in young Spanish people, DNA methylation levels of *TNFα* gene were associated with n-6 PUFA intake, while those young women with higher truncal fat showed lower methylation levels of *TNFα* promoter in white blood cells and higher plasma TNFα concentrations, reinforcing a complex nutriepigenomic network [46]. Interestingly, changes in DNA methylation levels of the circadian gene *BMAL1* were associated with the effects of a weight loss intervention on blood lipid levels in women [47]. Similarly, adherence to the Mediterranean diet was associated with changes in methylation of inflammation-related genes in volunteers at high cardiovascular risk [48]. Furthermore, a higher regional level of methylation in the *TXNIP* gene was significantly associated with improvements in insulin resistance when following a weight loss diet [49]. Also, array analysis performed in blood showed DNA methylation changes in individuals with obesity after short-term hypocaloric intervention [50]. Moreover, the beneficial effects of a very low-calorie ketogenic diet therapy in patients with obesity involve changes in the methylation levels of genes involved in the insulin signaling pathway, such as *HRAS*, *RPTOR*, *INSR*, *ACACB*, *MKNK2*, *PRKCZ*, *TSC2*, and *PRKAG2*, as well as genes involved in adipocyte signaling such as *CHUK*, *TRAF2*, *CAMKK1*, *ACACB*, *RELA*, and *PRKAG2* [51].

Regarding the effect of maternal diet during pregnancy on the methylome and health of newborns, epigenomic-scale analysis revealed that prenatal exposure to famine was related to epigenetic signatures (intermediate levels of DNA methylation) in pathways associated with growth and metabolism neonatal [52]. Findings from the MANOE study showed that maternal dietary intake supplemented with methyl group donors (folate, betaine, and choline) can influence infant DNA methylation rates (hypomethylation) in genes related to appetite regulation, growth, and development [53].

In addition to the effects on DNA methylation, several miRNAs have been identified as potential biomarkers in response to different diets and foods. Thus, miRNAs are modified by the dietary polyphenols found in fruits, vegetables, tea, coffee and wine, with implications in brown adipocyte regulation [54]. Also, a systematic review presented how the consumption of pistachio, a nut with high content of MUFA, polyphenols, and carotenoids, can affect glucose metabolism by modulation of specific miRNA involved in the PI3K-AKT signaling pathway [55]. Regarding fat intake, seven circulating miRNAs related to adiposity (miR-130a-3p, miR-142-5p, miR-144-5p, miR-15a -5p, miR-22-3p, miR-221-3p, and miR-29c-3p) were associated with response to a low-fat dietary intervention prescribed for weight loss [56], while let-7b, a miRNA related to pro-inflammatory pathway appeared to be modulated by oleic acid [57]. As a proof of concept of personalized dietary intervention to specifically modulate circulating miRNAs, 1-year intervention in Huntington disease patients specifically modulated deregulated miRNAs [58]. Similarly, plasma levels of miR-23a-3p expression were positively correlated with sodium intake and negatively correlated with dietary vitamin E, while vitamin D intake was inversely associated with miR-1277-5p and miR-144-3p expressions in healthy European volunteers [59]. In subjects with metabolic syndrome, treatment with a grape pomace supplement led to improvements in glycemic control related to changes in expression of miR-30c and miR-222, two microRNAs associated with insulin resistance and diabetes [60]. Several miRNAs has been also associated to postprandial response to fats, including miR-206-3p, miR-27-5p or miR-409-3p [61]. Circulating miRNAs transported in exosomes are being incorporated into nutritional studies [62]. Postprandial analysis of circulating miRNAs is being actively incorporated into nutritional studies and will help to shape precision nutrition approaches.

The health benefits of consuming dietary bioactive compounds (such as genistein, sulforaphane, curcumin, resveratrol, and epigallocatechin) appear to be mediated, at least in part, by epigenetic mechanisms that include the regulation of histone acetyltransferase and deacetylase activities [63]. Specifically, it was shown that consumption of 68 g of broccoli (equivalent to a daily dietary intake of 105 mg of sulforaphane) showed hyperacetylation of histones H3 and H4 in circulating blood cells in healthy human volunteers [64]. Furthermore, in vitro experiments revealed that quercetin (a dietary polyphenol found in many fruits, vegetables, nuts, and red wine) exerted anti-inflammatory and antitumor effects through inhibition of histone acetylation activity [65]. Other bioactive compounds with potential histone inhibitory activities (a promising therapeutic approach in the

clinical setting) include short-chain fatty acids, isoflavones, indoles, organosulfur/organ selenium agents, and sesquiterpene lactones [66].

Nutrimetabolomic Approaches

Nutrimetabolomic research focuses on analyzing the profile of metabolites in biofluids, cells and tissues, providing an invaluable tool for the description of biomarkers of intake and response to food, as well as the characterization of nutrient metabolic pathways [67]. Advances in analytical and informatics technologies have led to the rapid adoption of metabolomics investigations to pinpoint and individualize various pathophysiological conditions and chronic diseases [68]. In particular, the application of metabolomic approaches has shown potential to improve the accuracy of dietary assessment through the identification of biomarkers of food intake and the typing of metabolites and metabolic signatures that can serve as targets for precision nutrition interventions [69]. There are currently two preferred metabolomics strategies: untargeted metabolomics, which involves an exhaustive analysis of all measurable metabolites in a sample, being especially useful when there is no a priori metabolic hypothesis; and targeted metabolomics, based on the measurement of previously defined metabolites, yielding high sensitivity and selectivity of targets of interest [70]. In untargeted metabolomics, the compound identifications and quantifications remain challenging for all detected metabolites or metabolic features; while for targeted metabolomics the coverage of detected metabolites is generally limited because it is difficult to obtain all the required chemical standards for the metabolites of interest [71].

Future perspectives in "nutriomics" research identify three metabolomic opportunities to improve the accuracy of dietary assessment and adherence to nutritional patterns in the field of nutritional epidemiology: (1) determination of food intake based on biomarker levels supported by dietary surveys and feeding studies, (2) classification of individuals in dietary patterns based on plasma and urinary metabolic profiles, and (3) application in association studies of the metabolome with pathophysiological profiles related to nutrition for its application in dietary interventions in the health and illness [72]. Many of these endeavors require rapid and effective data integration with powerful bioinformatics tools.

Research in dietary metabolomics has traditionally focused on describing specific metabolites, such as 2-hydroxy-3-methylbutyric acid as a biomarker to characterize the habitual ethanol consumer [73]. Many other analyzes have identified combinations of metabolites, known as metabolic signatures, that are associated with dietary exposures, consumption of specific foods, or specific diseases [74]. In fact, metabolic signatures can be used to identify population groups at risk of a certain chronic disease since with a blood or urine sample the risk of disease can be estimated, as well as to simultaneously estimate the associated dietary intake in a way precision personalized [75].

In this context, some pioneering studies have found relationships between cocoa consumption and intake markers, based on metabolomic analysis, which in turn were associated with metabolites related to mood [76]. Indeed, the intake of cocoa extract within an energy-restricted diet contributed to an increase in plasma concentrations of hydroxy-vanillic acid, whose concentration was associated with a reduction in depressive symptoms and with subtle changes in monoamines [77]. In addition, a metabolomic assay investigated the possible role of the administration of α-lipoic acid (naturally occurring in beets, carrots, potatoes, spinach, and broccoli) in the reduction of body weight healthy overweight/obese women [78]. The results evidenced anti-obesity effects of α-lipoic acid, which were mediated by metabolites such as isomers of trihydroxy-dioxohexanoate or dihydroxy-oxohexanedionate [78]. Moreover, a nutritional intervention study identified 22 urinary compounds specific to golden berry, demonstrating its bioavailability and detoxifying effects [79]. Besides, the application of metabolomics allowed the monitoring of lycopene after a nutritional intervention with tomato sauces [80]. Furthermore, chromatography/mass spectrometry metabolomics was also a useful tool to analyze and predict the response to a weight loss dietary intervention, where baseline palmitoleic acid (C16:1) was found to predict weight loss and that isoleucine decreased significantly in serum samples after a weight reduction intervention [81].

Certainly, a number of cutting-edge studies have used metabolomic approaches to understand individualized responses to dietary intake and metabolic outcomes [82]. Therefore, integrative precision nutrition approaches have potential to combine physiological, behavioral, and nutritional factors in targeted dietary counseling and support, as well as to recognize metabolic pathways to precisely implement personalized nutrition through integrated metabolomic strategies.

Nutrimetagenomic Approaches

Metagenomics is defined as the exhaustive study of microbial and host genetic material (DNA and RNA) in patient samples without prior need for culture [83]. The gut microbiome has a vast potential for genetic information influencing host physiology including enterocyte structure, immunity, and energy homeostasis, with a potential for explain human variability in dietary response "nutrimetagenomics" [84]. As a result, analysis of fecal microorganisms has allowed to find associations between bacterial species and metabolic alterations such as obesity, diabetes, or hepatic steatosis [85]. Lately, the determination of intestinal microbial profiles has been associated with dietary patterns or the intake of different foods or nutrients, providing a new instrumental possibility to measure dietary intake without resorting to tedious traditional questionnaires [86].

Initial studies have demonstrated the potential for metagenomic approaches to be used at the population level, such as the Belgian Flemish Gut Flora Project, which has generated one of the best characterized fecal microbiota databases currently available [87]. As part of the project, fiber consumption was identified as one of the most influential dietary determinants in the intestinal microbiome, along with fatty acids, polyphenols, and various glycans, which would not be possible without technical advances in metagenomic equipment with high analytical performance [87]. Since then, subsequent studies have used similar metagenomic approaches in longitudinal trials, including a study of Chinese adults, where a healthy dietary pattern was associated with increased diversity of microbial gene families associated with metabolic pathways, as well as modifications in symbiotic functions [88].

Some trials have applied metagenomic approaches to understand individualized responses to dietary intake. Thus, in an 8-week trial of Danish adults at risk of metabolic syndrome, metagenomics analyses revealed that a diet rich in whole grains induced a reduction in *E. ramosum* (a bacteria associated with obesity), which could help explain the observed reduction in body weight and low-grade inflammation [89]. Recently, it was evidenced that 8-week consumption of Brazilian nuts increased fecal propionic acid and potentially beneficial bacteria such as *Ruminococcus*, *Roseburia*, *Bacteroides*, and *Lachnoclostridium* in overweight women [90]. Also, in a substudy of the DIETFITS project, it was revealed that dietary intervention (lower carbohydrate or lower fat diets) resulted in substantive changes in the microbiota 3 months after the start of the intervention, primarily due to specific changes typical of the low-carbohydrate diet, although this exchange was not maintained at 12 months [91]. These authors speculate that this finding could be the result of a microbiome-based "memory" of obesity, in which there is a resistance of the microbiota to dietary change by the host and the presence of a homeostatic force in the microbial community to return to a previous state in patients with metabolic syndrome [91]. This microbial resistance could have important implications for precision nutrition approaches, which aim to achieve sustained changes in diet, gut microbiota and health in individuals with obesity, and warrants further research focused on accuracy of personalized nutrition [91]. In fact, an Israeli study demonstrated a great ability to predict postprandial glycemia with a metagenomic approach accompanied by dietary information and body composition data [92].

Continuous Monitoring of Biological, Physiological, Diet, and Lifestyle Parameters: The Era of Biosensors and Deep Phenotyping

With the rapid development of information technology and artificial intelligence, people have acquired the abilities to capture data about when, what, and how much people eat and drink, which begins to shed light on intelligent and precise food nutrition. Traditional dietary assessment methods and lifestyle determinations, including food frequency questionnaires, diet records, diet recalls, exercise activity, sleep, or quality of life questionnaires, have limited resolution and suffer from a number of important limitations [93]. Diaries are burdensome to complete, food frequency questionnaires only capture average food intake, and both suffer from difficulties in self estimation of portion size and biases resulting from misreporting. Online and app versions of these methods have been developed, but issues with misreporting and portion size estimations remain. Hence, intelligence software has been developed because they are more effective than traditional systems in terms of dietary assessment, nutrient recommendations, and health monitoring. In this regard, "AI nutritionist" is an intelligent software that includes wearable devices and sensors, mobile applications, and web-based tools to provide detailed dietary analyses through users' self-monitoring, thereby providing tailored professional advice [94]. This tool has been gradually advancing the efficiency of dietary recording, nutritional assessment, and nutrient recommendations.

Continuous monitoring of vital/physiological signals over extended temporal windows plays a substantial role in a comprehensive perspective on the overall health status of an individual, enabling early disease prediction, self-directed diagnostics, personalized therapeutics, and improved management of chronic health conditions. Recent advances in wearable electronics, particularly those incorporated within skin-integrated or textile-based devices, have facilitated the continuous on-body biosignal monitoring during daily activities [95]. In this context, continuous ketone monitoring in response to diet is being incorporated into precise nutrition approaches. Other continuous monitoring biosensors are being developed including those to evaluate triglyceride levels or cholesterol levels using smart contact lens or many other intelligent wrist-based monitoring that evaluate physical activity, stress, and sleep, among many other parameters. In addition, precise nutrition services are being commercialized using at-home sampling and testing using DNA collection kits, fecal collection kits, dried blood spot cards, and continuous glucose monitors, which are now commercially available. More comprehensive devices under development may replace some of the current options and enable higher resolution and real-time nutrient, behavior, and health tracking [96].

Although next-generation wearables are being developing, the next frontier in this topic is the brain-computer interface, and how and when this will be incorporated into nutritional intervention studies remains unknown. But the new era of precise nutrition (Fig. 2) will provide a better understanding of disease prevention and health maintenance.

Precision Nutrition: "Big Data" and "Machine Learning"

The evolution of "omics" technologies and emerging bioinformatics analyzes of "Big Data" have deepened the understanding and characterization of chronic diseases related to nutrition through the application of artificial intelligence or machine learning (ML) methods. These refer to the ability to design algorithms and other information categorization/grouping strategies to produce inferences or find patterns from the statistical analysis of very large datasets [97]. These approaches are capable of managing huge and complex matrices of data, incorporating potential interactions and mediations, or identifying linear and nonlinear associations as well as classify subjects or categorize groups [98].

Extracting valuable insights from "omics" data remains a challenge in bioinformatics, which often needs increasingly innovative methods for efficient handling and to reach effective conclusions and results. In this sense, ML plays an important role in the integration and interpretation of "multi-omics" techniques aimed at nutritional research, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and metagenomics. This information can be used for computational modeling, mining of data, grouping of samples, and categorization of nutritypes based on the response to dietary intake, as well as the implementation of nutritional "scores" or quantitative nutriindexes [99]. The combination of these tools can be translated into practical applications of clinical and population human nutrition, such as supporting decision-making and development of diet optimization schemes, providing a general and integrative vision for precision nutrition [100]. However, there are some factors that limit the current use of ML in research and practice including the need to create large datasets with diverse participants and health conditions to compute accurate ML models as well as externally validate them on large and heterogeneous samples to ensure generalization to different populations. To overcome these limitations, it may require researchers to collaborate and combine huge emerging international databases, developing standards for data sharing given the clinical diverse data ecosystems [101]. Also, the creation of customized, scalable, computational, and analytical tools to increase speed and capable of dealing with data heterogeneity, in addition to the ability to process and group them in a coherent way, has been a strategy to mitigate these issues, while the application of multitask learning may enhance the model's predictive performance. Furthermore, training health professionals to interpret and properly use the information generated by ML and other artificial intelligence methods are essential together with appropriate bioinformatics programs. In any case, artificial intelligence instruments still need supervision for skilled professionals.

In fact, a common application of precision nutrition is the creation of computational decision algorithms. In this context, an integrative approach with ML algorithms was performed to predict obesity using genetic, epigenetic, and environmental data and exploring gene-gene and gene-diet interactions [102]. Furthermore, an ML model based on routine, quantitative, and easy-to-measure variables (such as age, systolic blood pressure, conventional blood/urine tests, and dietary intake values) was able to detect the presence and extent of the subclinical atherosclerosis in young and asymptomatic individuals

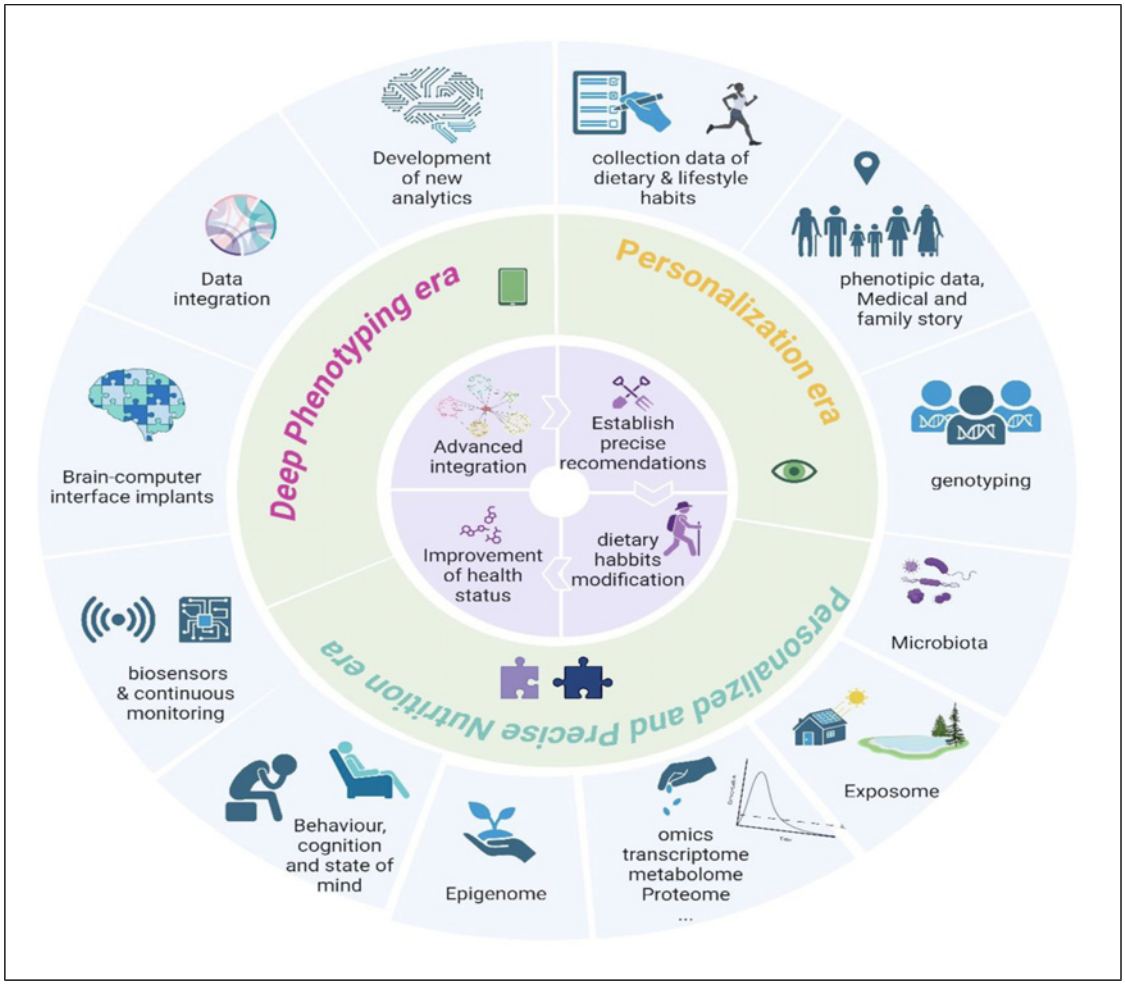

Fig. 2. The landscape of the eras of personalized nutrition. Levels of advice in the development of a personalized nutrition approach.

[103]. Another example of ML applications includes findings from the PREDICT 1 clinical trial, which identified individual variations in postprandial triglyceride and glucose responses to standardized meals using genetic, metabolic, microbiome, and meal context data [104]. Similarly, a ML algorithm integrating blood markers, dietary habits, anthropometry, physical activity, and gut microbiota composition was fine-tuned to accurately predict individual glycemic responses to real-life meals [105]. Indeed, algorithmic prototypes have been published to prescribe hypocaloric weight loss diets that are moderately high in protein or low in lipid based on phenotypic and genotypic markers and information on lifestyle and dietary preferences [106].

The application of "Big Data" and ML has significant potential to advance nutrition and nutritional epidemiology. Specifically, ML can be used to improve the accuracy and validity of dietary determinations and provide more potential tools for modeling dietary complexity and its relationship to disease. Interestingly, findings from the ATTICA study revealed that ML techniques led to a more accurate assessment of the association between dietary patterns and 10-year cardiometabolic risk [107]. Such advances in the application of ML and other artificial intelligence approaches to food and nutritional epidemiology have been encouraged by concurrent developments of dietary intake monitoring based on omics technologies [108]. Another important tool in ML and "Big Data" analysis is the design and use of biomarkers. Potential nutritional applications of biomarkers include quantifying dietary intake, analyze metabolic and pathophysiological responses to food or diet components, characterize therapeutic targets, identify individuals with specific nutritional deficiencies, provide information on

interindividual variations in response to diets, and help design personalized nutritional recommendations for particular metabolic phenotypes to achieve optimized health [109].

Challenges for the Development of Precision Nutrition

The opportunities for precision nutrition are enormous, but the challenges to developing and implementing such approaches require specific consideration. The ethical, legal, and social issues of the use of genetic information and other highly sensitive personal information have been reviewed within the content of human rights requirements and specifically in the context of personalized nutrition [110]. Although the legal framework surrounding genetic testing remains complex and country-specific, there is growing concern about the importance of ethical and social issues. Primarily, responsible handling of genetic information is critical, as the results can have far-reaching implications for the health and legal status of the consumer and their family. As a result, individuals undergoing genetic testing must give informed consent, where they become aware of the benefits and risks associated with such testing. However, consumer protection goes beyond personal approval, as the responsible handling of genetic information must also consider epidemiologically the attributes of these tests. Quality control includes ensuring that the databases used and the personalized advice provided by laboratories, companies, and healthcare professionals are appropriate [111]. The improvement of the skills and knowledge of nongenetic health professionals is considered an unmet need in recent years, which is why there is a growing number of training and updating resources, which is essential to satisfy the commercialization of genetics tests. An example of these conditions are the ethical requirements in precision public health that aim to ensure that the benefit of precision nutrition approaches, based on advances in genomic research, outweigh any possible epidemiological risk for people, families, and vulnerable members of the population [112].

The advances in precision nutrition lead to transcendental considerations about who decides the limits of the use of genomic biotechnology? Thus, the bioethical dilemma can be analyzed from the possible risks and benefits focused on the care of people's health and life. Therefore, the integration of precision nutrition into clinical care requires a bioethical analysis focused on the unity of the person, which considers the principles of therapeutic totality, freedom, and integrity [113]. Future research should continue to strengthen ethical, legal, and social procedures for integrating genetic information and all other sensitive biological, cultural, or behavioral information into precision nutrition approaches for personalized care.

The general view of current trends in "omics" technologies is that they will support the future success of holistic and global approaches to precision nutrition since interindividual genetic variations only partially explain heterogeneity in response to a given diet. Over the past two decades, nutritional studies and publications on the gut microbiota and metabolomics have increased exponentially, improving the understanding of the metabolic pathways through which dietary intake can affect health and disease [114]. These emerging fields of research require the use of high-throughput and deep phenotyping technologies, which provide physiological and genetic information on the metabolic pathways of foods and bioactive nutrients. In turn, such concepts will help inform the optimal design of precision dietary interventions to improve and maintain health in people. New frontiers in "Big Data" and ML will undoubtedly pave the way to deliver integrated precision nutrition, where multi-omics approaches can be combined with lifestyle and behavioral determinants of diet and health to improve diets of the population on an epidemiological scale. In fact, it is necessary to have genotypic and phenotypic data, as well as perinatal, clinical, and demographic/socioeconomic and, notably, lifestyle determinants, for a holistic and harmonized interpretation [115]. However, for assuring an effective implementation of omics research in clinical care need to take in account the benefits, the risks, associated ethical and social aspects, and room for innovation. The integration of these components requires a strong communication between all stakeholders, where patients should be placed at the center, be involved, and participate in the research (taking control as much as possible of their treatment), thus empowering working with researchers, clinicians, industry, and regulators, which hopefully will be achieved in the next years [116].

Precision nutrition results will help understand trends in the design and application of precision nutrition approaches for use in research, healthcare, and industry [117]. The global application of precision nutrition requires an understanding of population health, political issues, and the technological and digital landscape of the region and country in question, prior to the implementation of such approaches. Furthermore, multidisciplinary collaborations between researchers, health professionals, and the food industry are certain to become

even more important to aid the generation, interpretation, and implementation of integrative precision nutritional data. Other challenges derive from the lack of studies across different populations, since most of the information was obtained in Caucasian populations, and the need for harmonized protocols for data collection and analysis that will allow the comparison and integration of data from different studies.

Sustainability, Planetary Diets, and Precision Nutrition

One of the factors that have been poorly considered when developing precision nutrition approaches is the sustainability of diets. The modern global food system seems to be a major contributor to the climate change crisis, accounting for an estimated 26% of all anthropogenic greenhouse gas emissions, approximately 40% of land use, and 70% of global freshwater use [118]. Moreover, while global yields of major crops are not increasing anymore, temperature increase seems to reduce global yields of major crops [119]. This raises the question of how to provide health diets for nearly 10 billion people by 2050. In this context, some initiatives have been arising including EAT-Lancet Commission on healthy diets from sustainable food systems aiming to achieve "planetary health" diet [120] that seeks to optimize both chronic disease prevention as well as global environmental health through diet. A person following the EAT-Lancet reference diet would be "flexitarian," eating plants on most days and occasionally a small amount of meat or fish [121]. Although there still exists a large pathway from the different regions of the world to resemble the planetary health diet, in many regions, following the proposed diet would be prohibitively expensive. Moreover, there are cultural barriers to such a planetary diet. Thus, there is a need to search for alternatives that may be more acceptable and realistic for a sustainable diet across different groups in the population or in different regions. Very few studies have been performed regarding the adherence to the EAT-Lancet sustainable reference diet in Latin America, but estimates suggest a very low adherence [122].

Despite these inconveniences, adherence to planetary health diet was associated with a lower risk of cardiovascular disease in certain regions including North America [123] or other Latin American countries like Brazil [124]. These observations support the planetary health diet as a promising strategy to promote both human and planetary health. But how to personalize when a planetary health diet is proposed? Indeed, diet is not a one-fits-all recommendation. Moreover, the widespread use of biosensors and the continuous deep phenotyping for precision nutrition approach would also produce a large amount of planetary electronics contaminants and energy-consuming on data saving and analysis that goes against our environment. All these factors need to be incorporated in future studies of personalized and precise nutrition approaches in order to determine whether the benefits of precise nutrition outweigh the environmental aspects of their implementation.

Conclusions and Future Perspectives

The progress and participation of nutrigenetics, nutrigenomics, nutriepigenetics, nutrimetabolomics, and nutrimetagenomics to precision nutrition is an essential pillar for addressing diet-related diseases and developing innovative managing strategies, which will be promoted by advances in bioinformatics, ML, and integrative software as well as the description of specific novel biomarkers. In this sense, the omics technologies, Big Data creation, and artificial intelligence methods must be incorporated in the academic curriculum to qualification of health professionals, while new research related to data analysis and interpretation and validation studies in different populations and stages of life should be a priority for the development of precision nutrition. Moreover, the nutrition of the future must comprehensively address and confront healthy, social, food security, physically active lifestyle, sanitation, and sustainability challenges with preventive, participatory, and predictive strategies of personalized, population, and planetary nutrition for a precision single health. At the polity policies level, government and industry must provide substantial financial support for induce the research in this area, which still has a little number of studies with high level of scientific evidence (e.g., randomized controlled trials). Government, scientific community, and society also should discuss potential regulatory rules for application of nutrition precision with ethical/legal practice. This agenda is fundamental to nutrition precision achieve the optimal clinical practice and effectively benefit the society, applying personalized nutrition recommendation to health promotion and management of diseases.

One of the challenges in the next years is to integrate precision nutrition into public health initiatives. A problem here is the cost: with the current technology,

genetic, epigenetic, metagenomic, and metabolomic analyses being expensive to be included in the public health system. Probably, genetic tests focused on clinically useful gene-diet interactions can be the first step, for example, the monogenic disorders lactose intolerance (lactase gene), celiac disease (*HLA* variants), phenylketonuria (*PAH* gene), or bitter tasting (*TAS2R38* gene). Polygenic diseases are more complex, and the implementation of nutrigenetic analyses in clinical practice is more expensive, but some targets can be routinely analyzed. For example, targeting the *APOE* gene can help reduce saturated fat intake and the concomitant cardiovascular risk. Targeting the *FTO* gene can help implement more effective nutritional and lifestyle approaches to combat obesity. And the analysis of polymorphisms in the *ACE* gene can help personalize the treatment of hypertension and cardiovascular disease. Probably epigenetics, miRNAomics, and transcriptomics are far to be implemented in the nutritional practice since the scientific community needs more information based on large cohorts and dietary interventions. Microbiota analyses are not cheap, but they could be applied to people with suspicion of dysbiosis and bacterial overgrowth. To increase the knowledge of the health status, they can be accompanied by tests of endotoxemia and intestinal permeability. Additionally, there are other analyses that can be very informative of the nutritional status of the population that can be more easily implemented, for example, some vitamins (folic acid, vitamins D, and B12) and minerals (iron, iodine, maybe magnesium, selenium, and zinc) in blood, or even the levels of some fatty acids, such as omega 3 and 6. This sort of nutritional phenotyping can help detect deficiencies that can be easily overcome by selective supplementation or dietary advice. In a similar way, metabolomics can be applied to categorize individuals into bad/good responders or slow/fast metabolizers for specific foods or nutrients, including polyphenols and other phytochemicals.

Understanding the variability of biological responses to food is crucial for effectively preventing and managing diet-related diseases. For this reason, it is imperative to perform new larger, intervention studies monitoring the individual's genetics, microbiota and metabolic parameters, including also reliable analyses of the exposome (set of human environmental exposures in a lifetime) as well as dietary intake. These intervention studies contribute to gaining insight into an individual's response to dietary intake and for identification of the specific metabotypes (classifying individuals into similar metabolic groups) to advise diet plans. This is a promising way to categorize individuals based on their unique metabolic profiles and responses, in order to further deliver tailored advice. Of course, these intervention studies must include individuals of different genetic backgrounds, dietary habits, and geographic origins since it is known that gut microbiota and genetic polymorphisms are greatly dependent on these factors. For these reasons, it is mandatory that these studies are multicentric, transnational, and conducted at multinational level. It is especially important to include population from the developing and least developed countries since most of the published studies have been conducted in Europe, North America, and East Asia.

Moreover, there are some areas in which more clinical and intervention trials are expected including those related to diseases that are considered the pandemics of the XXI century because of their increasing rates and the difficulty of treatment: obesity, type 2 diabetes, liver dysfunction, neurodegenerative disorders, and some types of cancer (i.e., breast, liver, colorectal, and other tumors related to the gastrointestinal tract). Many of these diseases are related to aging, which is a problem that will be common to almost all the countries in the next decades because of its significant impact on health status, functional capacity, and quality of life. Of course, the focus on these diseases must not only be limited to the older populations, but the studies must start earlier in life in order to know the exposome, microbiota, and epigenetic drivers that can affect the future development of the diseases. With this approach, it will be easier in the future to establish preventive measures, including lifestyle recommendations.

Regarding the guide and position of RINN22 on precise nutrition and considering the currently (limited) available studies performed within Ibero-American countries, we consider the need of focusing on: (i) the promotion of precision nutrition studies, both clinical and community-based, in order to get compelling data for future generalization of recommendations at regional level; (ii) incorporate and standardize – whenever possible in terms of budget and capabilities – omics technologies to precision nutrition studies; (iii) increase the number of studied subjects – Ibero-American studies in general have personalized nutrition studies with a limited number of volunteers – in order to benefit from the incorporation of big data and ML analyses; (iv) incorporate indigenous nutrition knowledge and foods for future

personalization and planetary diet. Ibero-American have many indigenous populations along the whole continent, with specific traditional foods that has not been appropriately characterized in appropriate clinical trials; (v) try to personalize the diet with available foods present in each community or region; (vi) try to practice nutrition with an acute awareness of sustainable resource utilization, aiming to mitigate lasting detrimental effects on the environment and climate.

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The authors have no conflicts of interest to declare.

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References

1 Bruins MJ, Van Dael P, Eggersdorfer M. The role of nutrients in reducing the risk for noncommunicable diseases during aging. Nutrients. 2019;11(1):85. https://doi.org/10.3390/nu11010085

2 Ares G, Aschemann-Witzel J, Vidal L, Machín L, Moratorio X, Bandeira E, et al. Consumer accounts of favourable dietary behaviour change and comparison with official dietary guidelines. Public Health Nutr. 2018;21(10):1952–60. https://doi.org/10.1017/S1368980018000241

3 Martínez-González MA, Kim HS, Prakash V, Ramos-Lopez O, Zotor F, Martinez JA. Personalised, population and planetary nutrition for precision health. BMJ Nutr Prev Health. 2021;4(1):355–8. https://doi.org/10.1136/bmjnph-2021-000235

4 Ramos-Lopez O, Milagro FI, Allayee H, Chmurzynska A, Choi MS, Curi R, et al. Guide for current nutrigenetic, nutrigenomic, and nutriepigenetic approaches for precision nutrition involving the prevention and management of chronic diseases associated with obesity. J Nutrigenet Nutrigenomics. 2017;10(1–2):43–62. https://doi.org/10.1159/000477729

5 Bush CL, Blumberg JB, El-Sohemy A, Minich DM, Ordovás JM, Reed DG, et al. Toward the definition of personalized nutrition: a proposal by the American nutrition Association. J Am Coll Nutr. 2020;39(1):5–15. https://doi.org/10.1080/07315724.2019.1685332

6 Ramos-Lopez O, Martinez JA, Milagro FI. Holistic integration of omics tools for precision nutrition in health and disease. Nutrients. 2022;14(19):4074. https://doi.org/10.3390/nu14194074

7 Livingstone KM, Ramos-Lopez O, Pérusse L, Kato H, Ordovas JM, Martínez JA. Precision nutrition: a review of current approaches and future endeavors. Trends Food Sci Technology. 2022;128:253–64. https://doi.org/10.1016/j.tifs.2022.08.017

8 Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French TA, Tai ES, et al. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. J Nutrigenet Nutrigenomics. 2011;4(2):69–89. https://doi.org/10.1159/000327772

9 Cheung MK, Yeo GS. FTO biology and obesity: why do a billion of us weigh 3 kg more? Front Endocrinol. 2011;2:4. https://doi.org/10.3389/fendo.2011.00004

10 Hosseini-Esfahani F, Koochakpoor G, Daneshpour MS, Mirmiran P, Sedaghati-Khayat B, et al. The interaction of fat mass and obesity associated gene polymorphisms and dietary fiber intake in relation to obesity phenotypes. Sci Rep. 2017;7(1):18057. https://doi.org/10.1038/s41598-017-18386-8

11 Steemburgo T, Azevedo MJ, Gross JL, Milagro FI, Campión J, Martínez JA. The rs9939609 polymorphism in the FTO gene is associated with fat and fiber intakes in patients with type 2 diabetes. J Nutrigenet Nutrigenomics. 2013;6(2):97–106. https://doi.org/10.1159/000350741

12 Obregón Rivas AM, Santos JL, Valladares MA, Cameron J, Goldfield G. Association of the FTO fat mass and obesity-associated gene rs9939609 polymorphism with rewarding value of food and eating behavior in Chilean children. Nutrition. 2018;54:105–10. https://doi.org/10.1016/j.nut.2018.03.001

13 Steemburgo T, de Azevedo MJ, Gross JL, Milagro F, Campión J, Martínez JA. The rs7204609 polymorphism in the fat mass and obesity-associated gene is positively associated with central obesity and microalbuminuria in patients with type 2 diabetes from Southern Brazil. J Ren Nutr. 2012;22(2):228–36. https://doi.org/10.1053/j.jrn.2011.03.004

14 Micó V, Díez-Ricote L, Daimiel L. Nutrigenetics and nutrimiromics of the circadian system: the time for human health. Int J Mol Sci. 2016;17(3):299. https://doi.org/10.3390/ijms17030299

15 Garaulet M, Corbalán MD, Madrid JA, Morales E, Baraza JC, Lee YC, et al. CLOCK gene is implicated in weight reduction in obese patients participating in a dietary programme based on the Mediterranean diet. Int J Obes. 2010;34(3):516–23. https://doi.org/10.1038/ijo.2009.255

16 Garaulet M, Lee YC, Shen J, Parnell LD, Arnett DK, Tsai MY, et al. Genetic variants in human CLOCK associate with total energy intake and cytokine sleep factors in overweight subjects (GOLDN population). Eur J Hum Genet. 2010;18(3):364–9. https://doi.org/10.1038/ejhg.2009.176

17 Liew SC, Gupta ED. Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases. Eur J Med Genet. 2015;58(1):1–10. https://doi.org/10.1016/j.ejmg.2014.10.004

18 Li L, Yu H, Zhang H, Wang J, Hu W. Association between MTHFR C677T polymorphism and risk of coronary artery disease in the Chinese population: meta-analysis. Herz. 2022;47(6):553–63. https://doi.org/10.1007/s00059-021-05087-2

19 Boeckmans J, Gatzios A, Schattenberg JM, Koek GH, Rodrigues RM, Vanhaecke T. PNPLA3 I148M and response to treatment for hepatic steatosis: a systematic review. Liver Int. 2023;43(5):975–88. https://doi.org/10.1111/liv.15533

20 Perez-Diaz-Del-Campo N, Marin-Alejandre BA, Cantero I, Monreal JI, Elorz M, Herrero JI, et al. Differential response to a 6-month energy-restricted treatment depending on SH2B1 rs7359397 variant in NAFLD subjects: fatty Liver in Obesity (FLiO) Study. Eur J Nutr. 2021;60(6):3043–57. https://doi.org/10.1007/s00394-020-02476-x

21 Celis-Morales C, Livingstone KM, Marsaux CF, Forster H, O'Donovan CB, Woolhead C, et al. Design and baseline characteristics of the Food4Me study: a web-based randomised controlled trial of personalised nutrition in seven European countries. Genes Nutr. 2015;10(1):450. https://doi.org/10.1007/s12263-014-0450-2
22 Celis-Morales C, Livingstone KM, Marsaux CF, Macready AL, Fallaize R, O'Donovan CB, et al. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial. Int J Epidemiol. 2017;46(2):578–88. https://doi.org/10.1093/ije/dyw186
23 San-Cristobal R, Navas-Carretero S, Livingstone KM, Celis-Morales C, Macready AL, Fallaize R, et al. Mediterranean diet adherence and genetic background roles within a web-based nutritional intervention: the Food4Me study. Nutrients. 2017;9(10):1107. https://doi.org/10.3390/nu9101107
24 Ramos-Lopez O, Riezu-Boj JI, Milagro FI, Cuervo M, Goni L, Martinez JA. Models integrating genetic and lifestyle interactions on two adiposity phenotypes for personalized prescription of energy-restricted diets with different macronutrient distribution. Front Genet. 2019;10:686. https://doi.org/10.3389/fgene.2019.00686
25 Ramos-Lopez O, Riezu-Boj JI, Milagro FI, Goni L, Cuervo M, Martinez JA. Association of the Gly482Ser PPARGC1A gene variant with different cholesterol outcomes in response to two energy-restricted diets in subjects with excessive weight. Nutrition. 2018;47:83–9. https://doi.org/10.1016/j.nut.2017.10.008
26 Vallée Marcotte B, Guénard F, Marquis J, Charpagne A, Vadillo-Ortega F, Tejero ME, et al. Genetic risk score predictive of the plasma triglyceride response to an omega-3 fatty acid supplementation in a Mexican population. Nutrients. 2019;11(4):737. https://doi.org/10.3390/nu11040737
27 Ferguson LR, De Caterina R, Görman U, Allayee H, Kohlmeier M, Prasad C, et al. Guide and position of the International Society of nutrigenetics/nutrigenomics on personalised nutrition: Part 1 – fields of precision nutrition. J Nutrigenet Nutrigenomics. 2016;9(1):12–27. https://doi.org/10.1159/000445350
28 Izquierdo AG, Carreira MC, Rodriguez-Carnero G, Fernandez-Quintela A, Sueiro AM, Martinez-Olmos MA, et al. Weight loss normalizes enhanced expression of the oncogene survivin in visceral adipose tissue and blood leukocytes from individuals with obesity. Int J Obes. 2021;45(1):206–16. https://doi.org/10.1038/s41366-020-0630-7
29 Pinhel MAS, Noronha NY, Nicoletti CF, de Oliveira BAP, Cortes-Oliveira C, Pinhanelli VC, et al. Changes in global transcriptional profiling of women following obesity surgery bypass. Obes Surg. 2018;28(1):176–86. https://doi.org/10.1007/s11695-017-2828-x
30 Rodríguez E, Ribot J, Rodríguez AM, Palou A. PPAR-gamma2 expression in response to cafeteria diet: gender- and depot-specific effects. Obes Res. 2004;12(9):1455–63. https://doi.org/10.1038/oby.2004.182
31 Horne J, Gilliland J, O'Connor C, Seabrook J, Madill J. Enhanced long-term dietary change and adherence in a nutrigenomics-guided lifestyle intervention compared to a population-based (GLB/DPP) lifestyle intervention for weight management: results from the NOW randomised controlled trial. BMJ Nutr Prev Health. 2020;3(1):49–59. https://doi.org/10.1136/bmjnph-2020-000073
32 Bordoni L, Petracci I, Zhao F, Min W, Pierella E, Assmann TS, et al. Nutrigenomics of dietary lipids. Antioxidants. 2021;10(7):994. https://doi.org/10.3390/antiox10070994
33 Lee BY, Ordovás JM, Parks EJ, Anderson CAM, Barabási AL, Clinton SK, et al. Research gaps and opportunities in precision nutrition: an NIH workshop report. Am J Clin Nutr. 2022;116(6):1877–900. https://doi.org/10.1093/ajcn/nqac237
34 González-Becerra K, González-Cantero JO, Martín-Moreno AM, Barrón-Cabrera E, Mora-Jiménez A, Martínez-López E. Brief intervention as strategy treatment that improves nutritional adherence in obesity: a pilot study. Rev Mex Endocrinol Metab Nutr. 2023;10(2):68–75. https://doi.org/10.24875/RME.22000052
35 Dordevic AL, Coort SL, Evelo CT, Murgia C, Sinclair AJ, Bonham MP, et al. Blunted nutrient-response pathways in adipose tissue following high fat meals in men with metabolic syndrome: a randomized postprandial transcriptomic study. Clin Nutr. 2021;40(3):1355–66. https://doi.org/10.1016/j.clnu.2020.08.024
36 Barrera-Reyes PK, Hernández-Ramírez N, Cortés J, Poquet L, Redeuil K, Rangel-Escareño C, et al. Gene expression changes by high-polyphenols cocoa powder intake: a randomized crossover clinical study. Eur J Nutr. 2019;58(5):1887–98. https://doi.org/10.1007/s00394-018-1736-8
37 Muñoz-Pérez DM, González-Correa CH, Astudillo Muñoz EY, Sánchez-Giraldo M, Carmona-Hernández JC, López-Miranda J, et al. Effect of 8-week consumption of a dietary pattern based on fruit, avocado, whole grains, and trout on postprandial inflammatory and oxidative stress gene expression in obese people. Nutrients. 2023;15(2):306. https://doi.org/10.3390/nu15020306
38 Jocken JW, Langin D, Smit E, Saris WH, Valle C, Hul GB, et al. Adipose triglyceride lipase and hormone-sensitive lipase protein expression is decreased in the obese insulin-resistant state. J Clin Endocrinol Metab. 2007;92(6):2292–9. https://doi.org/10.1210/jc.2006-1318
39 Martín-Hernández R, Reglero G, Ordovás JM, Dávalos A. NutriGenomeDB: a nutrigenomics exploratory and analytical platform. Database. 2019;2019:2019:baz097. https://doi.org/10.1093/database/baz097
40 Hamilton JP. Epigenetics: principles and practice. Dig Dis. 2011;29(2):130–5. https://doi.org/10.1159/000323874
41 Pesqueda-Cendejas K, Campos-López B, Mora-García PE, Moreno-Ortiz JM, De la Cruz-Mosso U. Methyl donor micronutrients: a potential dietary epigenetic target in systemic lupus erythematosus patients. Int J Mol Sci. 2023;24(4):3171. https://doi.org/10.3390/ijms24043171
42 Li X, Qi L. Epigenetics in precision nutrition. J Pers Med. 2022;12(4):533. https://doi.org/10.3390/jpm12040533
43 González-Becerra K, Ramos-Lopez O, Barrón-Cabrera E, Riezu-Boj JI, Milagro FI, Martínez-López E, et al. Fatty acids, epigenetic mechanisms and chronic diseases: a systematic review. Lipids Health Dis. 2019;18(1):178. https://doi.org/10.1186/s12944-019-1120-6
44 Ramos-Lopez O, Samblas M, Milagro FI, Zulet MA, Mansego ML, Riezu-Boj JI, et al. Association of low dietary folate intake with lower CAMKK2 gene methylation, adiposity, and insulin resistance in obese subjects. Nutr Res. 2018;50:53–62. https://doi.org/10.1016/j.nutres.2017.11.007
45 Carraro JC, Hermsdorff HH, Mansego ML, Zulet MÁ, Milagro FI, Bressan J, et al. Higher fruit intake is related to TNF-α hypomethylation and better glucose tolerance in healthy subjects. J Nutrigenet Nutrigenomics. 2016;9(2–4):95–105. https://doi.org/10.1159/000448101
46 Hermsdorff HH, Mansego ML, Campión J, Milagro FI, Zulet MA, Martínez JA. TNF-alpha promoter methylation in peripheral white blood cells: relationship with circulating TNFα, truncal fat and n-6 PUFA intake in young women. Cytokine. 2013;64(1):265–71. https://doi.org/10.1016/j.cyto.2013.05.028
47 Samblas M, Milagro FI, Gómez-Abellán P, Martínez JA, Garaulet M. Methylation on the circadian gene BMAL1 is associated with the effects of a weight loss intervention on serum lipid levels. J Biol Rhythms. 2016;31(3):308–17. https://doi.org/10.1177/0748730416629247
48 Arpón A, Riezu-Boj JI, Milagro FI, Marti A, Razquin C, Martínez-González MA, et al. Adherence to Mediterranean diet is associated with methylation changes in inflammation-related genes in peripheral blood cells. J Physiol Biochem. 2016;73(3):445–55. https://doi.org/10.1007/s13105-017-0552-6
49 Li X, Shao X, Bazzano LA, Xue Q, Koseva BS, Grundberg E, et al. Blood DNA methylation at TXNIP and glycemic changes in response to weight-loss diet interventions: the POUNDS lost trial. Int J Obes. 2022;46(6):1122–7. https://doi.org/10.1038/s41366-022-01084-5

50 Nicoletti CF, Cortes-Oliveira C, Noronha NY, Pinhel MAS, Dantas WS, Jácome A, et al. DNA methylation pattern changes following a short-term hypocaloric diet in women with obesity. Eur J Clin Nutr. 2020;74(9):1345–53. https://doi.org/10.1038/s41430-020-0660-1
51 Crujeiras AB, Izquierdo AG, Primo D, Milagro FI, Sajoux I, Jácome A, et al. Epigenetic landscape in blood leukocytes following ketosis and weight loss induced by a very low calorie ketogenic diet (VLCKD) in patients with obesity. Clin Nutr. 2021;40(6):3959–72. https://doi.org/10.1016/j.clnu.2021.05.010
52 Tobi EW, Goeman JJ, Monajemi R, Gu H, Putter H, Zhang Y, et al. DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nat Commun. 2014;5:5592. https://doi.org/10.1038/ncomms6592
53 Pauwels S, Ghosh M, Duca RC, Bekaert B, Freson K, Huybrechts I, et al. Maternal intake of methyl-group donors affects DNA methylation of metabolic genes in infants. Clin Epigenetics. 2017;9:16. https://doi.org/10.1186/s13148-017-0321-y
54 Lorente-Cebrián S, Herrera K, I Milagro F, Sánchez J, de la Garza AL, Castro H. miRNAs and novel food compounds related to the browning process. Int J Mol Sci. 2019;20(23):5998. https://doi.org/10.3390/ijms20235998
55 Ribeiro PVM, Silva A, Almeida AP, Hermsdorff HH, Alfenas RC. Effect of chronic consumption of pistachios (Pistacia vera L.) on glucose metabolism in prediabetics and type 2 diabetics: a systematic review. Crit Rev Food Sci Nutr. 2019;59(7):1115–23. https://doi.org/10.1080/10408398.2017.1392290
56 Assmann TS, Riezu-Boj JI, Milagro FI, Martínez JA. Circulating adiposity-related microRNAs as predictors of the response to a low-fat diet in subjects with obesity. J Cell Mol Med. 2020;24(5):2956–67. https://doi.org/10.1111/jcmm.14920
57 Marques-Rocha JL, Garcia-Lacarte M, Samblas M, Bressan J, Martínez JA, Milagro FI. Regulatory roles of miR-155 and let-7b on the expression of inflammation-related genes in THP-1 cells: effects of fatty acids. J Physiol Biochem. 2018;74(4):579–89. https://doi.org/10.1007/s13105-018-0629-x
58 Aganzo M, Montojo MT, López de Las Hazas MC, Martínez-Descals A, Ricote-Vila M, Sanz R, et al. Customized dietary intervention avoids unintentional weight loss and modulates circulating miRNAs footprint in Huntington's disease. Mol Nutr Food Res. 2018;62(23):e1800619. https://doi.org/10.1002/mnfr.201800619
59 Ferrero G, Carpi S, Polini B, Pardini B, Nieri P, Impeduglia A, et al. Intake of natural compounds and circulating microRNA expression levels: their relationship investigated in healthy subjects with different dietary habits. Front Pharmacol. 2020;11:619200. https://doi.org/10.3389/fphar.2020.619200
60 Léniz A, Martínez-Maqueda D, Fernández-Quintela A, Pérez-Jiménez J, Portillo MP. Potential relationship between the changes in circulating microRNAs and the improvement in glycaemic control induced by grape pomace supplementation. Foods. 2021;10(9):2059. https://doi.org/10.3390/foods10092059
61 Mantilla-Escalante DC, López de Las Hazas MC, Gil-Zamorano J, Del Pozo-Acebo L, Crespo MC, Martín-Hernández R, et al. Postprandial circulating miRNAs in response to a dietary fat challenge. Nutrients. 2019;11(6):1326. https://doi.org/10.3390/nu11061326
62 Mantilla-Escalante DC, López de Las Hazas MC, Crespo MC, Martín-Hernández R, Tomé-Carneiro J, Del Pozo-Acebo L, et al. Mediterranean diet enriched in extra-virgin olive oil or nuts modulates circulating exosomal non-coding RNAs. Eur J Nutr. 2021;60(8):4279–93. https://doi.org/10.1007/s00394-021-02594-0
63 Vahid F, Zand H, Nosrat-Mirshekarlou E, Najafi R, Hekmatdoost A. The role dietary of bioactive compounds on the regulation of histone acetylases and deacetylases: a review. Gene. 2015;562(1):8–15. https://doi.org/10.1016/j.gene.2015.02.045
64 Dashwood RH, Ho E. Dietary histone deacetylase inhibitors: from cells to mice to man. Semin Cancer Biol. 2007;17(5):363–9. https://doi.org/10.1016/j.semcancer.2007.04.001
65 Xiao X, Shi D, Liu L, Wang J, Xie X, Kang T, et al. Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. PLoS One. 2011;6(8):e22934. https://doi.org/10.1371/journal.pone.0022934
66 Kim E, Bisson WH, Löhr CV, Williams DE, Ho E, Dashwood RH, et al. Histone and non-histone targets of dietary deacetylase inhibitors. Curr Top Med Chem. 2016;16(7):714–31. https://doi.org/10.2174/1568026615666150825125857
67 McNamara AE, Brennan L. Potential of food intake biomarkers in nutrition research. Proc Nutr Soc. 2020;79(4):487–97. https://doi.org/10.1017/S0029665120007053
68 Aderemi AV, Ayeleso AO, Oyedapo OO, Mukwevho E. Metabolomics: a scoping review of its role as a tool for disease biomarker discovery in selected noncommunicable diseases. Metabolites. 2021;11(7):418. https://doi.org/10.3390/metabo11070418
69 Clarke ED, Ferguson JJ, Stanford J, Collins CE. Dietary assessment and metabolomic methodologies in human feeding studies: a scoping review. Adv Nutr. 2023;14(6):1453–65. https://doi.org/10.1016/j.advnut.2023.08.010
70 Tebani A, Bekri S. Paving the way to precision nutrition through metabolomics. Front Nutr. 2019;6:41. https://doi.org/10.3389/fnut.2019.00041
71 Chen L, Zhong F, Zhu J. Bridging targeted and untargeted mass spectrometry-based metabolomics via hybrid approaches. Metabolites. 2020;10(9):348. https://doi.org/10.3390/metabo10090348
72 Valdés A, Álvarez-Rivera G, Socas-Rodríguez B, Herrero M, Ibáñez E, Cifuentes A. Foodomics: analytical opportunities and challenges. Anal Chem. 2022;94(1):366–81. https://doi.org/10.1021/acs.analchem.1c04678
73 Loftfield E, Stepien M, Viallon V, Trijsburg L, Rothwell JA, Robinot N, et al. Novel biomarkers of habitual alcohol intake and associations with risk of pancreatic and liver cancers and liver disease mortality. J Natl Cancer Inst. 2021;113(11):1542–50. https://doi.org/10.1093/jnci/djab078
74 Shah RV, Steffen LM, Nayor M, Reis JP, Jacobs DR, Allen NB, et al. Dietary metabolic signatures and cardiometabolic risk. Eur Heart J. 2023;44(7):557–69. https://doi.org/10.1093/eurheartj/ehac446
75 Qiu S, Cai Y, Yao H, Lin C, Xie Y, Tang S, et al. Small molecule metabolites: discovery of biomarkers and therapeutic targets. Signal Transduct Target Ther. 2023;8(1):132. https://doi.org/10.1038/s41392-023-01399-3
76 Ibero-Baraibar I, Romo-Hualde A, Gonzalez-Navarro CJ, Zulet MA, Martinez JA. The urinary metabolomic profile following the intake of meals supplemented with a cocoa extract in middle-aged obese subjects. Food Funct. 2016;7(4):1924–31. https://doi.org/10.1039/c5fo01191d
77 Ibero-Baraibar I, Perez-Cornago A, Ramirez MJ, Martínez JA, Zulet MA. An increase in plasma homovanillic acid with cocoa extract consumption is associated with the alleviation of depressive symptoms in overweight or obese adults on an energy restricted diet in a randomized controlled trial. J Nutr. 2015;146(4):897S–904S. https://doi.org/10.3945/jn.115.222828
78 Romo-Hualde A, Huerta AE, González-Navarro CJ, Ramos-López O, Moreno-Aliaga MJ, Martínez JA. Untargeted metabolomic on urine samples after α-lipoic acid and/or eicosapentaenoic acid supplementation in healthy overweight/obese women. Lipids Health Dis. 2018;17(1):103. https://doi.org/10.1186/s12944-018-0750-4
79 Vaillant F, Llano S, Ángel Martín A, Moreno-Castellanos N. Main urinary biomarkers of golden berries (Physalis peruviana) following acute and short-term nutritional intervention in healthy human volunteers. Food Res Int. 2023;173(Pt 2):113443. https://doi.org/10.1016/j.foodres.2023.113443

80 Bondia-Pons I, Cañellas N, Abete I, Rodríguez MÁ, Perez-Cornago A, Navas-Carretero S, et al. Nutri-metabolomics: subtle serum metabolic differences in healthy subjects by NMR-based metabolomics after a short-term nutritional intervention with two tomato sauces. OMICS. 2013;17(12):611–8. https://doi.org/10.1089/omi.2013.0027
81 Perez-Cornago A, Brennan L, Ibero-Baraibar I, Hermsdorff HH, O'Gorman A, Zulet MA, et al. Metabolomics identifies changes in fatty acid and amino acid profiles in serum of overweight older adults following a weight loss intervention. J Physiol Biochem. 2014;70(2):593–602. https://doi.org/10.1007/s13105-013-0311-2
82 Guasch-Ferré M, Bhupathiraju SN, Hu FB. Use of metabolomics in improving assessment of dietary intake. Clin Chem. 2018;64(1):82–98. https://doi.org/10.1373/clinchem.2017.272344
83 Navgire GS, Goel N, Sawhney G, Sharma M, Kaushik P, Mohanta YK, et al. Analysis and Interpretation of metagenomics data: an approach. Biol Proced Online. 2022;24(1):18. https://doi.org/10.1186/s12575-022-00179-7
84 Ramos-Lopez O. Multi-omics nutritional approaches targeting metabolic-associated fatty liver disease. Genes. 2022;13(11):2142. https://doi.org/10.3390/genes13112142
85 Cuevas-Sierra A, Ramos-Lopez O, Riezu-Boj JI, Milagro FI, Martinez JA. Diet, gut microbiota, and obesity: links with host genetics and epigenetics and potential applications. Adv Nutr. 2019;10(Suppl l_1):S17–30. https://doi.org/10.1093/advances/nmy078
86 Melo NCO, Cuevas-Sierra A, Fernández-Cruz E, de la O V, Martínez JA. Fecal microbiota composition as a metagenomic biomarker of dietary intake. Int J Mol Sci. 2023;24(5):4918. https://doi.org/10.3390/ijms24054918
87 Falony G, Joossens M, Vieira-Silva S, Wang J, Darzi Y, Faust K, et al. Population-level analysis of gut microbiome variation. Science. 2016;352(6285):560–4. https://doi.org/10.1126/science.aad3503
88 Yu D, Yang Y, Long J, Xu W, Cai Q, Wu J, et al. Long-term diet quality and gut microbiome functionality: a prospective, shotgun metagenomic study among urban Chinese adults. Curr Dev Nutr. 2021;5(4):nzab026. https://doi.org/10.1093/cdn/nzab026
89 Roager HM, Vogt JK, Kristensen M, Hansen LBS, Ibrügger S, Mærkedahl RB, et al. Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial. Gut. 2019;68(1):83–93. https://doi.org/10.1136/gutjnl-2017-314786
90 Kelly Souza Silveira B, Mayumi Usuda Prado Rocha D, Stampini Duarte Martino H, Grancieri M, Juste Contin Gomes M, Cuquetto Mantovani H, et al. Daily cashew and Brazil nut consumption modifies intestinal health in overweight women on energy-restricted intervention: a randomized controlled trial (Brazilian Nuts Study). J Nutr. 2024;154(3):962–77. https://doi.org/10.1016/j.tjnut.2023.12.022
91 Fragiadakis GK, Wastyk HC, Robinson JL, Sonnenburg ED, Sonnenburg JL, Gardner CD. Long-term dietary intervention reveals resilience of the gut microbiota despite changes in diet and weight. Am J Clin Nutr. 2020;111(6):1127–36. https://doi.org/10.1093/ajcn/nqaa046
92 Mendes-Soares H, Raveh-Sadka T, Azulay S, Ben-Shlomo Y, Cohen Y, Ofek T, et al. Model of personalized postprandial glycemic response to food developed for an Israeli cohort predicts responses in Midwestern American individuals. Am J Clin Nutr. 2019;110(1):63–75. https://doi.org/10.1093/ajcn/nqz028
93 Berciano S, Figueiredo J, Brisbois TD, Alford S, Koecher K, Eckhouse S, et al. Precision nutrition: maintaining scientific integrity while realizing market potential. Front Nutr. 2022;9:979665. https://doi.org/10.3389/fnut.2022.979665
94 Liang Y, Xiao R, Huang F, Lin Q, Guo J, Zeng W, et al. AI nutritionist: intelligent software as the next generation pioneer of precision nutrition. Comput Biol Med. 2024;178:108711. https://doi.org/10.1016/j.compbiomed.2024.108711
95 Zhang B, Li J, Zhou J, Chow L, Zhao G, Huang Y, et al. A three-dimensional liquid diode for soft, integrated permeable electronics. Nature. 2024;628(8006):84–92. https://doi.org/10.1038/s41586-024-07161-1
96 Jaromy M, Miller JD. Potential clinical applications for continuous ketone monitoring in the hospitalized patient with diabetes. Curr Diab Rep. 2022;22(10):501–10. https://doi.org/10.1007/s11892-022-01489-6
97 Kirk D, Kok E, Tufano M, Tekinerdogan B, Feskens EJM, Camps G. Machine learning in nutrition research. Adv Nutr. 2022;13(6):2573–89. https://doi.org/10.1093/advances/nmac103
98 Verma AA, Murray J, Greiner R, Cohen JP, Shojania KG, Ghassemi M, et al. Implementing machine learning in medicine. CMAJ. 2021;193(34):E1351–7. https://doi.org/10.1503/cmaj.202434
99 de Cuevillas B, Álvarez Álvarez I, Cuervo M, Fernández Montero A, Navas Carretero S, Martínez JA. Definition of nutritionally qualitative categorizing (proto)nutritypes and a pilot quantitative nutrimeter for mirroring nutritional well-being based on a quality of life health related questionnaire. Nutr Hosp. 2019;36(4):862–74. https://doi.org/10.20960/nh.02532
100 Martínez JA, Alonso-Bernáldez M, Martínez-Urbistondo D, Vargas-Nuñez JA, Ramírez de Molina A, Dávalos A, et al. Machine learning insights concerning inflammatory and liver-related risk comorbidities in non-communicable and viral diseases. World J Gastroenterol. 2022;28(44):6230–48. https://doi.org/10.3748/wjg.v28.i44.6230
101 Martínez-García M, Hernández-Lemus E. Data integration challenges for machine learning in precision medicine. Front Med. 2021;8:784455. https://doi.org/10.3389/fmed.2021.784455
102 Lee YC, Christensen JJ, Parnell LD, Smith CE, Shao J, McKeown NM, et al. Using machine learning to predict obesity based on genome-wide and epigenome-wide gene-gene and gene-diet interactions. Front Genet. 2021;12:783845. https://doi.org/10.3389/fgene.2021.783845
103 Sánchez-Cabo F, Rossello X, Fuster V, Benito F, Manzano JP, Silla JC, et al. Machine learning improves cardiovascular risk definition for young, asymptomatic individuals. J Am Coll Cardiol. 2020;76(14):1674–85. https://doi.org/10.1016/j.jacc.2020.08.017
104 Berry SE, Valdes AM, Drew DA, Asnicar F, Mazidi M, Wolf J, et al. Human postprandial responses to food and potential for precision nutrition. Nat Med. 2020;26(6):964–73. https://doi.org/10.1038/s41591-020-0934-0
105 Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015;163(5):1079–94. https://doi.org/10.1016/j.cell.2015.11.001
106 Ramos-Lopez O, Cuervo M, Goni L, Milagro FI, Riezu-Boj JI, Martinez JA. Modeling of an integrative prototype based on genetic, phenotypic, and environmental information for personalized prescription of energy-restricted diets in overweight/obese subjects. Am J Clin Nutr. 2020;111(2):459–70. https://doi.org/10.1093/ajcn/nqz286
107 Panaretos D, Koloverou E, Dimopoulos AC, Kouli GM, Vamvakari M, Tzavelas G, et al. A comparison of statistical and machine-learning techniques in evaluating the association between dietary patterns and 10-year cardiometabolic risk (2002-2012): the ATTICA study. Br J Nutr. 2018;120(3):326–34. https://doi.org/10.1017/S0007114518001150
108 Abeltino A, Riente A, Bianchetti G, Serantoni C, De Spirito M, Capezzone S, et al. Digital applications for diet monitoring, planning, and precision nutrition for citizens and professionals: a state of the art. Nutr Rev. 2024;9:nuae035. https://doi.org/10.1093/nutrit/nuae035
109 Cuparencu C, Bulmuş-Tüccar T, Stanstrup J, La Barbera G, Roager HM, Dragsted LO. Towards nutrition with precision: unlocking biomarkers as dietary assessment tools. Nat Metab. 2024;6(8):1438–53. https://doi.org/10.1038/s42255-024-01067-y

110 Kohlmeier M, De Caterina R, Ferguson LR, Görman U, Allayee H, Prasad C, et al. Guide and position of the international society of nutrigenetics/nutrigenomics on personalized nutrition: Part 2 – ethics, challenges and endeavors of precision nutrition. J Nutrigenet Nutrigenomics. 2016;9(1):28–46. https://doi.org/10.1159/000446347
111 Kurnat-Thoma E. Educational and ethical considerations for genetic test implementation within health care systems. Netw Syst Med. 2020;3(1):58–66. https://doi.org/10.1089/nsm.2019.0010
112 Newson AJ. The promise of public health ethics for precision medicine: the case of newborn preventive genomic sequencing. Hum Genet. 2022;141(5):1035–43. https://doi.org/10.1007/s00439-021-02269-0
113 de la Garza AL, Zonenszain-Laiter Y. Análisis bioético del uso de la biotecnología genómica en la nutrición traslacional. pers bioet. 2023;26(2):1–13. https://doi.org/10.5294/pebi.2022.26.2.4
114 Babu M, Snyder M. Multi-omics profiling for health. Mol Cell Proteomics. 2023;22(6):100561. https://doi.org/10.1016/j.mcpro.2023.100561
115 Ramos-Lopez O, Milton-Laskibar I, Martínez JA; Collaborators Rodrigo San-Cristobal and Maria P Portillo. Precision nutrition based on phenotypical traits and the (epi) genotype: nutrigenetic and nutrigenomic approaches for obesity care. Curr Opin Clin Nutr Metab Care. 2021;24(4):315–25. https://doi.org/10.1097/MCO.0000000000000754
116 Oldoni E, Saunders G, Bietrix F, Garcia Bermejo ML, Niehues A, Hoen PAC, et al. Tackling the translational challenges of multi-omics research in the realm of European personalised medicine: a workshop report. Front Mol Biosci. 2022;9:974799. https://doi.org/10.3389/fmolb.2022.974799
117 de Roos B, Brennan L. Personalised interventions-A precision approach for the next generation of dietary intervention studies. Nutrients. 2017;9(8):847. https://doi.org/10.3390/nu9080847
118 Poore J, Nemecek T. Reducing food's environmental impacts through producers and consumers. Science. 2018;360(6392):987–92. https://doi.org/10.1126/science.aaq0216
119 Zhao C, Liu B, Piao S, Wang X, Lobell DB, Huang Y, et al. Temperature increase reduces global yields of major crops in four independent estimates. Proc Natl Acad Sci U S A. 2017;114(35):9326–31. https://doi.org/10.1073/pnas.1701762114
120 Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. Lancet. 2019;393(10170):447–92. https://doi.org/10.1016/S0140-6736(18)31788-4
121 Vaidyanathan G. What humanity should eat to stay healthy and save the planet. Nature. 2021;600(7887):22–5. https://doi.org/10.1038/d41586-021-03565-5
122 Marchioni DM, Cacau LT, De Carli E, Carvalho AM, Rulli MC. Low adherence to the EAT-lancet sustainable reference diet in the Brazilian population: findings from the national dietary survey 2017-2018. Nutrients. 2022;14(6):1187. https://doi.org/10.3390/nu14061187
123 Sawicki CM, Ramesh G, Bui L, Nair NK, Hu FB, Rimm EB, et al. Planetary health diet and cardiovascular disease: results from three large prospective cohort studies in the USA. Lancet Planet Health. 2024;8(9):e666–74. https://doi.org/10.1016/S2542-5196(24)00170-0
124 Cacau LT, Benseñor IM, Goulart AC, Cardoso LO, Santos IS, Lotufo PA, et al. Adherence to the EAT-Lancet sustainable reference diet and cardiometabolic risk profile: cross-sectional results from the ELSA-Brasil cohort study. Eur J Nutr. 2023;62(2):807–17. https://doi.org/10.1007/s00394-022-03032-5