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Precision nutrition: A review of current approaches and future endeavors

Katherine M. Livingstone [a,1], Omar Ramos-Lopez [b,*,1], Louis Pérusse [g,c], Hisanori Kato [d], Jose M. Ordovas [h,e], J. Alfredo Martínez [i,j,f]

[a] Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Geelong, Victoria, IUNS Task Force, Australia
[b] Medicine and Psychology School, Autonomous University of Baja California, Tijuana, Baja California, IUNS Task Force, Mexico
[c] Department of Kinesiology, Faculty of Medicine, Université Laval, Québec, Canada
[d] Health Nutrition, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan
[e] Nutrition and Genomics Laboratory, Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA, USA
[f] Precision Nutrition and Cardiometabolic Health, IMDEA- Food Institute, Madrid, Spain
[g] Centre Nutrition, Santé et Société (NUTRISS), Institute of Nutrition and Functional Foods (INAF), Québec, Canada
[h] IMDEA-Food Institute, Madrid, Spain
[i] CIBERobn Physiopathology of Obesity and Nutrition, Institute of Health Carlos III (ISCIII), Madrid, Spain
[j] Navarra Institute for Health Research (IdiSNa), Pamplona, Spain, IUNS Task Force

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ABSTRACT

Background: Precision and personalized nutrition approaches aim to leverage human variability to design tailored dietary interventions to improve health. With an extensive range of technological advances and opportunities for integrative precision nutrition, a review of current and future global trends is needed.

Scope and approach: The purpose of this review paper is to synthesize and critically appraise the latest developments, potential applications and future research needs in the field of precision nutrition. Selected examples of international studies that implement nutritional genetic, epigenetics, genomics, metabolomics and metagenomics approaches will be reviewed.

Key findings and conclusion: Precision nutrition integrates genetic, metagenomic, metabolomic, physiopathological, behavioral and sociocultural cues to understand metabolism and human wellbeing and implement health actions. Such wide-ranging measures require advances in 1) high-throughput multi-omics techniques, and 2) integrative big data systems. Over recent decades, research in the fields of nutritional genetic, epigenetics, genomics, metabolomics and metagenomics has accelerated exponentially. These approaches provide deep genotypic and phenotypic insights into human variability in response to diet, which has informed a new era of personalized and precision nutrition interventions. Moreover, advances in big data and machine learning have paved the way for integrated precision nutrition applications across research, industry and healthcare. This review will consider each of these areas in turn, such that the outcomes of this research will assist with understanding the latest developments and future consolidation trends in the field of precision nutrition.

1. Introduction

Suboptimal diet and nutritional imbalance are well established as contributors to the global burden of non-communicable diseaseswith a high incidence worldwide (Roth et al., 2018). Globally, in 2017, an estimated 11 million deaths were attributable to dietary risk factors, with more than half of these deaths associated with high sodium intake (Afshin et al., 2019). National dietary guidelines designed to influence consumers' nutritional behavior and dietary patterns have had minimal impact (Kalmpourtzidou, Eilander, & Talsma, 2020). Thus, health targets, as well as environmental targets, highlight the need for integrated population efforts to prioritize food-based guidelines that shift diets towards high intake of whole grains, fruit and vegetables, nuts and seeds and legumes (Springmann et al., 2020). However, the "one-size-fits-all" nature of national and international dietary guidelines does not account for the diverse biological and sociocultural factors that drive human conduct (Herforth et al., 2019). Human variability is wide-ranging, and

* Corresponding author. Medicine and Psychology School, Autonomous University of Baja California, Universidad 14418, UABC, Parque Internacional Industrial Tijuana, 22390, Tijuana, B.C, Mexico.
E-mail address: oscar.omar.ramos.lopez@uabc.edu.mx (O. Ramos-Lopez).
[1] Katherine M Livingstone and Omar Ramos-Lopez contributed equally and are joint first authors.

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Abbreviations

ApoE	Apolipoprotein E
BL	baseline;
DNAm	DNA methylation
FTO	Fat mass and obesity associated gene
FADS1	Fatty Acid Desaturase 1
HATs	histone acetyltransferases
HDACs	histone deacetylases
MTHFR	Methylenetetrahydrofolate reductase
miRNAs	microRNAs
ML:	machine learning
mo	month
RCT	randomized controlled trial
SNP	single nucleotide polymorphism
TCF7L2	Transcription Factor 7 Like 2
TL	telomere length

can include genetic, phenotypic, and physiological determinants, medical history, and lifestyle practices, such as dietary habits and physical activity, as well as sociocultural and socioeconomic factors, such as the food environment, gastronomy, and educational attainment (Ordovas, Ferguson, Tai, & Mathers, 2018). This range of potential dietary influences has led to the emergence of personalized and precision nutrition investigations to improve dietary patterns (Ordovas et al., 2018), which are now central pillars of many national and international nutrition research priorities and position statements (Ferguson et al., 2016; Kohlmeier et al., 2016).

The connections between nutrition and wellbeing are numerous and wide-ranging, concerning both health maintenance as well as disease prevention and management. To operationalize individualized interventions to improve population and planetary health, the measurement and scoring of dietary intake is required (Martínez-González et al., 2021). Nutritional status assessment has been routinely performed to identify and treat undernutrition, however efforts are now increasingly focused on quantifying the contributing factors to overnutrition and obesity (Martínez-González et al., 2021). Indeed, the concept of personalized nutrition has been a long-standing endeavor, which was first alluded to by the ancient Greeks, including Hippocrates ("your food is the base of your health), and Galen ("personal attitudes and unique responses to food"), and has since evolved to include nutriomics and the development of global tools to quantify and categorize individual dietary intakes (Ordovas et al., 2018).

The ultimate goal of personalized and precision nutrition is to preserve or ameliorate health and wellbeing using dietary interventions, products or services that leveraging human variability (Ferguson et al., 2016; Ordovas et al., 2018). However, there is no international consensus on the definition of these terms, and terminology varies depending on the country, health field and scope of the research question (Bush et al., 2020). For example, the terms precision public health and precision health have been coined to consider the needs of digital health interventions and data-driven public health systems to prevent non-communicable diseases (Canfell et al., 2022), as well as the social determinants of health inequity (Olstad & McIntyre, 2019) when designing precision nutrition approaches. For the purpose of this review, personalized nutrition will be defined as an approach in which genetic, metagenomic, physiological, phenotypic, nutritional, and other relevant information are used to design tailored nutritional advice and support for each individual (Jinnette et al., 2021). In turn, the overarching term of precision nutrition is defined as a methodology to integrate genetic, metabolic and environmental information at scale, which can utilize high-throughput metabolomics, metagenomic and epigenetic approaches (Ordovas et al., 2018). An overview of the components of precision nutrition harmonizing these health determinants is provided (Fig. 1).

The techniques and technologies used in precision nutrition research are rapidly expanding, with global implications for future research priorities, commercialization of products and services and implementation into health services and public health policy. Thus, the aim of this current document is to synthesize and critically appraise the latest developments, potential applications and future research needs in the field of precision nutrition. Within the scope of a narrative review, selected examples of studies that utilize nutritional genetic, epigenetics, genomics, metabolomics and metagenomics approaches will be identified and objectively analyzed based on their global relevance and health impact.

1.1. *Overview of precision and personalized nutrition approaches*

Personalized nutrition considers the differential response to dietary intake due to individual endogenous aspects that influence nutrient intake and uptake, metabolism, assimilation, and excretion (Ferguson et al., 2016). Therefore, tailor-made dietary prescription for the prevention and treatment of diverse metabolic disorders should include the phenotypic evaluation and bioinformatics processing of metabolic pathways and epi/genetic differences, lifestyle exposome heterogeneity, metagenomic variation, and psychological and behavioral features related to health (de Toro-Martín, Arsenault, Després, & Vohl, 2017).

Personalized nutrition strategies can involve not only the assessment of diet and health using questionnaire-based tools, but also the use of "omics" technologies (nutrigenomics, metagenomics, and metabolomics) to develop optimal and customized dietary support that promotes health maintenance and disease prevention for each individual (Ferguson et al., 2016). As described earlier, precision nutrition integrates information at scale to consider an individual's genomic background, including any nutrigenetic interactions identified from deep phenotyping, as well as socioeconomic and psychosocial characteristics, family history, perinatal feeding information, health status and other clinical features, such as circadian rhythm, physical activity, dietary patterns and eating behaviors, and food environments, with a wide spectrum of bioinformatics data on metabolic pathways (de Toro-Martín et al., 2017). An important distinction between both concepts is that personalized nutrition considers genomic and other "omics" features of an individual's diet and metabolism that are predominantly fixed and therefore don't change over time, whereas precision nutrition adopts an integrative, dynamic and holistic approach to developing comprehensive recommendations for individuals and population subgroups (National Institutes of Health, 2020).

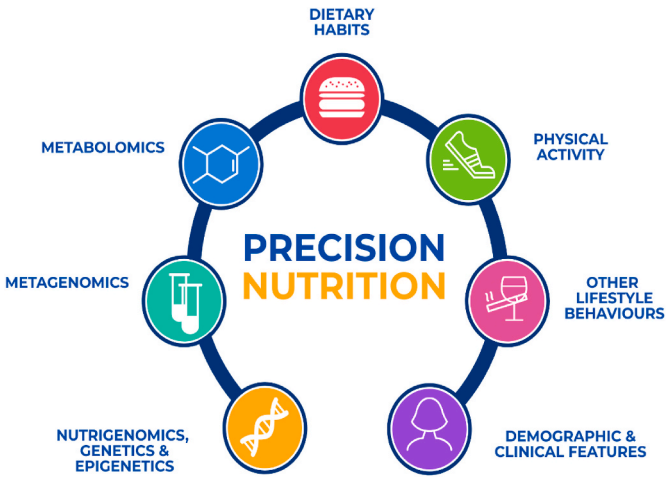

Fig. 1. Overview of the genetic, metabolic and diet and lifestyle components of an integrative precision nutrition approach.

The evidence base used to inform precision and personalized nutrition approaches is multidisciplinary, spanning *in vitro* and animal studies, high-resolution studies, epidemiology, and interventions, including randomized controlled trials (RCT). Many reviews of this field have been undertaken in recent years, which each focus on distinct techniques and scientific disciplines (Brennan & de Roos, 2021; Ferguson et al., 2016; Jinnette et al., 2021; Ordovas et al., 2018; Ramos-Lopez et al., 2017). For example, a 2021 systematic review of RCTs aimed to examine the evidence for whether dietary intake is improved to a greater extent in participants randomly assigned to receive personalized nutrition advice compared with generalized dietary advice (Jinnette et al., 2021). Outcomes from this review of eleven RCTs included a recommendation for a more comprehensive examination of the basis for personalization. While the majority of the included studies adopted a biological basis for personalization, the strategies to implement these interventions derived and delivered tailored dietary advice based on phenotypic or/and genotypic information. For example, some interventions selected genotypes known to influence chronic disease risk, such as disclosure of *HLA-DRB1*, which can increase rheumatoid arthritis risk three-fold (Sparks et al., 2018). In contrast, other studies selected genotypes known to impact on nutrient metabolism, such as the Apolipoprotein E, which regulates lipoprotein metabolism and is subsequently responsive to saturated fat intake (Celis-Morales et al., 2016; Nielsen & El-Sohemy, 2014). Other eminent reviews in the nutrition field have re-iterated that the successful design and delivery of precision nutrition interventions that incorporate biological data is likely to depend on advances in high-throughput biochemical assays, i.e., "omics" research focusing on reducing risk of obesity, diabetes and cancer (Ordovas et al., 2018).

Within the scope of this review, the high-throughput "omics" techniques of nutritional genomics, epigenetics, metabolomics, and metagenomics will be reviewed for their application in precision nutrition approaches (Fenech et al., 2011; Ferguson et al., 2016; Ramos-Lopez et al., 2017). These cutting-edge methodologies can be used separately, sequentially or integrated (e.g., multi-omics), for understanding human variability to improve or maintain optimal health and wellbeing. The computational and statistical methods for analysis of these high-throughput approaches is outside of the scope of this review, but has been covered elsewhere (Du et al., 2022). An overview of eleven selected studies employing precision and personalized nutrition approaches is summarized in this appraisal (Table 1). These studies range from RCTs (Arpón et al., 2016; Celis-Morales et al., 2016; Fragiadakis et al., 2020; Horne, Gilliland, O'Connor, Seabrook, & Madill, 2020; Roager et al., 2019; Ulven et al., 2019; Li et al., 2022) to observational studies (Smith et al., 2008; Vangay et al., 2018) and short-term postprandial studies (Berry et al., 2020), highlighting the multi-disciplinary applications of these approaches. The selected studies were undertaken in a range of European countries, including the UK, Ireland, Greece, Spain, Germany, The Netherlands, Finland, Sweden and Denmark, as well as Australia, Canada and the USA, including US immigrant Thai Hmong and Karen populations and Caribbean-origin Hispanics. High-throughput techniques used included shotgun sequencing-based metagenomics for characterizing microbiome diversity and function, and RT-qPCR for quantifying gene expression as well as metabolomic tools supported by big data analyses.

1.2. Nutrigenetic approaches

Nutritional genetics, or nutrigenetics, is broadly defined as the study of the effect of genetic variation on dietary response (Simopoulos, 2010). Many studies of single nucleotide polymorphisms (SNPs) exist, with classic examples including SNPs in the *MCM6*, *PAH* and *HLA-DQA1* and *HLA-DQB1* genes responsible for lactose intolerance (Enattah et al., 2002), Phenylketonuria (Blau, van Spronsen, & Levy, 2010) and celiac disease (Megiorni & Pizzuti, 2012), respectively. In more recent decades, the escalating global burden of obesity has led to the study of genes responsible for energy homeostasis, such as the fat mass and obesity associated (*FTO*) gene (Livingstone, Celis-Morales, Navas-Carretero, et al., 2016). Polymorphisms in *FTO* have been shown to influence energy homeostasis and body composition, and to interact with dietary factors in relation to adiposity phenotypes and therapeutic responsiveness (Ramos-Lopez, Milton-Laskibar, Martínez, 2021). Despite this, in an individual meta-analysis of 9564 individuals participating in weight loss RCTs, such as the Diabetes Prevention Program and the Look AHEAD study, carriage of the *FTO* minor allele was not associated with differential change in adiposity after the intervention. Moreover, Livingstone et al. demonstrated that individuals carrying the minor allele responded equally well to a weight loss intervention targeting diet or physical activity compared to those not carrying the risk variant (Livingstone, Celis-Morales, Navas-Carretero, et al., 2016). Thus, these investigations concluded that genetic predisposition to obesity associated with the *FTO* minor allele could be at least partly counteracted through such interventions, which is supported by observational research examining diet-gene interactions (Livingstone et al., 2022). As estimates for the proportion of variation explained by genetic for certain traits and conditions varies considerably depending on the population in question (Elks et al., 2012), such studies provide supportive evidence for diet and lifestyle interventions to improve health, in spite of genetic predispositions.

Selected studies of personalized and precision nutrition have used nutrigenetic approaches to design and deliver tailored dietary advice (Table 1). The Food4Me study, undertaken between 2012 and 2014, was the first proof-of-principle RCT of personalized nutrition (Celis-Morales et al., 2016). In this study, participants from across seven European countries self-collected biological samples at home using buccal swabs at baseline, and blood spot cards at baseline, month 3 and month 6. The former were used to measure 5 genotypes known to impact on nutrient metabolism, *FTO*, *FADS1*, *TCF7L2*, *ApoE*, and *MTHFR*, while the later were used to measure plasma concentrations of glucose, total cholesterol, carotenoids, n-3 fatty acid index, 32 other fatty acids and vitamin D (Celis-Morales et al., 2015). After 6 months of the intervention, Celis-Morales et al. concluded that greater improvement in diet quality (2010 Healthy Eating Index), intake of energy, red meat, salt, saturated fat, and folate were achieved in participants who received personalized advice compared to the control. Three levels of personalization were implemented and hierarchically compared, with no additional benefit of genotype-based advice observed (L3) compared to diet and phenotype-based advice (L2). However, in secondary analyses of the Food4Me Study, evidence for a benefit of genotype-based advice was identified for reducing intake of foods high in added salt, sugars and saturated fat (Livingstone et al., 2021), and improving adherence to the Mediterranean diet (MedDiet), as reported elsewhere (Livingstone, Celis-Morales, Navas-Carretero, et al., 2016). This study remains one of the largest and most comprehensive personalized nutrition RCTs conducted to date. The nutrigenetics component, however, was limited to genotypes with the most scientific evidence for potential to benefit from changes in diet and physical activity, and personalization was manually implemented by trained researchers. Thus, integration of polygenic and automated processes, such as multi-omics and machine learning (ML), will amplify the future design, delivery and potential for impact of personalized RCTs.

In the context of integrating polygenic and automated processes, a recent 4-month intervention incorporated genetic, phenotypic, and environmental information into a decision algorithm. This included the creation of genetic risk scores based on 95 SNPs related to energy homeostasis, enabling the personalized prescription of diets with different macronutrient distribution to over 200 Spanish subjects with overweight/obesity (Ramos-Lopez et al., 2020). Regarding the influence of the genotype on the dietary management of blood cholesterol, it was reported that an energy-restricted and moderately high-protein diet might be more beneficial than a low-fat diet to reduce serum cholesterol among subjects with obesity who were carriers of the *PPARGC1A*

Table 1
Overview of selected studies employing precision and personalized nutrition approaches.

Approach	Study, year	Methodology			Main findings
		Study design, duration, intervention	Population (n, age range, health; country)	Tool(s) used	
Nutrigenetics	Celis-Morales et al., 2016 (Celis-Morales et al., 2016) Food4Me	RCT; 6 mo; participants randomized to one of three levels of personalization: L1: dietary advice based on current diet; L2: dietary advice based on current diet and phenotype; L3: dietary advice based on current diet, phenotype, and genotype.	n = 1607; 18–79 y; healthy adults; seven European countries (UK, Ireland, Poland, Greece, Spain, Germany, NL)	Dry blood spot cards (glucose, total cholesterol, carotenoids, n-3 fatty acid index, 32 other fatty acids, vitamin D) - collected at BL, 3 mo, 6 mo. Buccal swabs (*FTO, FADS1, TCF7L2, ApoE,* and *MTHFR*) – collected at BL	Greater improvement in diet quality (2010 Healthy Eating Index), intake of energy, red meat, salt, saturated fat, and folate in participants who received personalized advice (L1+L2+L3) vs control
	Smith et al., 2008 (C. E. Smith et al., 2008)	Cohort study; 2 y	n = 920; 45–74 y; living in Boston, US	Genotyping from peripheral blood lymphocytes (*PLIN* 6209 T > C, *PLIN* 11482 G > A, PLIN 13041 A > G, PLIN 14995 A > T, *PPARG* Pro12Ala) – collected at BL	In subjects with higher complex carbohydrate intake, the minor *PLIN* allele was protective against obesity, whereas in subjects with lower carbohydrate intake, the minor allele was associated with increased obesity.
Nutrigenomics	Horne et al., 2020 (Horne et al., 2020) NOW	RCT; 12 mo; participants randomized to either the group lifestyle balance (GLF) program or the GLF + nutrigenomics program	n = 140; >18 years; health adults; Canada	Genotyping from Oragene ON-500 saliva collection kits (*UCP1, FTO, TCF7L2, APOA2, PPARγ2,* and *MC4R*)	Only the GLB + nutrigenomics group reduced their total fat intake at follow-up, suggesting nutrigenomics can motivate long-term improvements in dietary fat intake above and beyond gold-standard population-based interventions.
	Ulven et al., 2019 (Ulven et al., 2019) SYSDIET study	RCT; 12 w; subset of SYSDIET study	n = 88; 30–65 y; adults with metabolic syndrome; Finland and Sweden	Gene expression using RT-qPCR (inflammation and lipid metabolism-related genes of *PBMCs*)	The expression level of the gene tumor necrosis factor (*TNF*) receptor superfamily member 1A (*TNFRSF1A*) was down-regulated, whereas the nuclear factor kappa-light-chain-enhancer of activated B cells (*NF-κB*) subunit, *RELA* proto-oncogene, was up-regulated in the Nordic diet compared to the control.
	Dordevic et al., 2021 (Dordevic et al., 2021)	Randomized postprandial transcriptomic study; participants were randomized to consume two isocaloric high-fat breakfast meals in a cross-over design.	n = 19; 40–60 y; men with metabolic syndrome and age- and height-matched controls; Australia	Global adipose tissue gene expression was measured by RT-qPCR – collected before and 4 h postprandial.	In response to the high-fat meals, increases in genes related to cellular nutrient responses were observed in control participants, with blunted response in men with metabolic syndrome.
Nutriepigenetics	Arpón et al., 2016 (Arpón et al., 2016) PREDIMED	RCT; 5 y; participants randomized to one of three arms: a MedDiet supplemented with extra virgin olive oil (EVOO), a MedDiet supplemented with mixed nuts or a low-fat diet (control group). Subset of participants were analyzed for DNAm.	n = 36; 60–70 y; adults at risk of CVD; Spain	DNA methylation (eight CpGs methylation from venous blood samples) – collected at BL, 5 y	Following a MedDiet was associated with changes in the epigenome through differential methylation of >50 genes, including eight genes related to inflammation (*EEF2, COL18A1, IL4I1, LEPR, PPARGC1B, APKAPK2, IFRD1* and *PLAGL1).*
	Li et al., 2022 (Li et al., 2022) POUNDS lost trial	RCT; 2y; individuals were randomized to one of four diets that contained either 15% or 25% protein and 20% or 40% fat in a 2 × 2 factorial design	n = 639; 30–70 y; overweight or obese and in good health with a BMI of 25–40; living in Boston or Baton Rouge, US	BL blood DNAm levels were profiled by high-resolution methylC-capture sequencing	In participants with the highest tertile of regional DNAm at *TXNIP* gene, average protein (15%) intake was associated with a greater reduction in insulin and HOMA-IR than high protein (25%) intake.
Metabolomics	Berry et al., 2020 (Berry et al., 2020) PREDICT 1	Postprandial metabolic responses to sequential mixed-nutrient dietary challenges (during a clinic visit and 13 days at-home)	n = 1002; 18–65 y; healthy adults; UK	Stool sample (gut microbiome via 16S rRNA high-throughput sequencing) – collected at BL Dry blood spot cards (C-peptide, triglyceride) – collected at BL, day 1–3 Genotyping from blood samples (32 SNPs) – collected previously in TwinsUK study Continuous glucose monitoring – every 15 min	The gut microbiome had a greater influence (7.1% of variance) than meal macronutrients (3.6%) for postprandial lipemia, but not for postprandial glycemia (6.0% and 15.4% respectively); genetic variants had a modest impact on predictions (9.5% for glucose, 0.8% for triglyceride, 0.2% for c-peptide).
	Fragiadakis et al., 2020 (Fragiadakis	RCT; 12 mo; participants randomized to a low-carb or low-	n = 49; 18-50y; healthy individuals; US	Stool sample (gut microbiome via 16S rRNA high-throughput	While BL microbiota composition was not predictive of weight loss, each diet

(*continued on next page*)

Table 1 (*continued*)

Approach	Study, year	Methodology			Main findings
		Study design, duration, intervention	Population (n, age range, health; country)	Tool(s) used	
	et al., 2020) DIETFITS	fat diet. Subset of participants collected stool samples		sequencing) – collected at BL, 3 mo, 6 mo, 9 m, 12 mo	resulted in substantial changes in the microbiota at 3-mo; 14 taxonomic changes specific to low-carbohydrate diet, 12 taxonomic changes specific to low-fat diet.
Metagenomics	Roager et al., 2019 (Roager et al., 2019)	RCT; 8 wk; in a cross-over design participants were randomized to a whole grain or refined grain diet	n = 60; 20–65 y; individuals at risk of metabolic syndrome; Denmark	Stool sample (shotgun sequencing-based metagenomics and 16S rRNA amplicon profiling) – collected at BL, 8 wk (four visits in total) Urine sample (non-targeted metabolic profiling) – collected 4 h postprandial Fasting and postprandial venous blood samples – collected 30–180 min postprandial	Compared with the refined grain diet, the whole grain diet did not induce major changes in the faecal microbiome, nor did it alter insulin sensitivity, but it did reduce body weight and systemic low-grade inflammation.
	Vangay et al., 2018 (Vangay et al., 2018)	Cross-sectional study of United States immigrant populations	n = 514; >18 y; Hmong and Karen adults living in Thailand and the United States; this included first- and second-generation immigrants, 19 Karen adults sampled before and after immigration, and 36 U.S-born European American adults	Stool sample (shotgun sequencing-based metagenomics and 16S rRNA amplicon profiling) – collected at BL	Migration from a non-Western country to the U.S. is associated with immediate loss of gut microbiome diversity and function, in which U.S.-associated strains and functions displace native strains and functions.

ApoE, Apolipoprotein E*;* BL, baseline; DIETFITS, Diet Intervention Examining The Factors Interacting with Treatment Success; DNAm, DNA methylation; *FTO*, Fat mass and obesity associated gene*; FADS1*, Fatty Acid Desaturase 1; *MTHFR*, Methylenetetrahydrofolate reductase*;* mo, month; NOW, overweight/obesity and weight management trial; RCT, randomized controlled trial; RT-qPCR, Quantitative reverse transcription PCR; SNP, single nucleotide polymorphism; *TCF7L2*, Transcription Factor 7 Like 2.

Gly482Gly genotype (Ramos-Lopez, Samblas, et al., 2018). Likewise, the *APOA1* (rs670) gene polymorphism showed important differential effects on adiposity, cholesterol levels and insulin resistance after 12 weeks on a hypocaloric diet in an intervention study comprised of one arm (de Luis, Izaola, Primo, & Aller, 2018). These findings highlight the potential for a holistic decision algorithm approach encompassing genetic, phenotypic and exogenous data that can be used to personalize dietary advice for improving or maintaining health.

The scientific literature on diet-gene interactions in non-Caucasian populations remains under-represented. In a 2-year cohort study, 920 Caribbean-origin Hispanics adults were genotyped for the Perilipin (*PLIN*) gene to examine whether dietary macronutrients, including foods high in complex carbohydrate, such as whole grains and vegetables, modulated the associations of the *PLIN* SNP with obesity (Smith et al., 2008). Findings from this study identified that in subjects with higher complex carbohydrate intake, the minor *PLIN* allele was protective against obesity, whereas in subjects with lower complex carbohydrate intake, the minor allele was associated with increased risk of obesity. Plausible mechanisms identified in Caucasian populations (Smith et al., 2008) are likely to apply here, including modulation of postprandial insulin and glucose responses, with downstream effects on lipolysis and energy homeostasis of adipocytes (Perez-Martinez et al., 2008). Findings for a *PLIN*-complex carbohydrate interaction in this cohort of Caribbean-origin Hispanic adults support the targeting of dietary advice based on genotypes. However, extending nutrigenetic research by examining a broader range of multi-race populations is needed to ensure that precision nutrition approaches are equitable, with the potential to be effective for every individual. Genome-wide association studies (GWAS) have contributed to the identification of a number of variants influencing individual responses to dietary counseling, which are located in or near genes related to energy intake, appetite, adipogenesis/lipid metabolism, inflammation, and insulin resistance (Goni, Cuervo, Milagro, & Martínez, 2015).

1.3. Nutrigenomic approaches

Nutritional genomics, or nutrigenomics, refers to the study of the effect of bioactive dietary components on gene expression and function, consequently, on the proteome and the metabolome (Ramos-Lopez et al., 2017). In this sense, nutrient-gene expression interactions are defined as dietary intake exerting an influence on the expression of genes that regulate critical metabolic pathways (Fenech et al., 2011). This assertion statement contrasts with nutrigenetic approaches, where the genotype influences the dietary response (Brennan & de Roos, 2021). Advances in nutrigenomics have provided a greater understanding of the role of different bioactive foods and nutrients on metabolic pathways and homeostatic control (Ramos-Lopez et al., 2017). Notable examples of such diet-gene-metabolic homeostasis pathways include the role of sugars on the carbohydrate-responsive element binding protein (*ChREBP*) gene on glycolysis, fat intake on peroxisome proliferator-activated receptors (*PPARs*) on lipid metabolism and protein on wGCN2/activating transcription factor 4 (*ATF4*) and mTORC1 pathways that regulate lipogenesis (Haro, Marrero, & Relat, 2019). Alterations in these pathways are often responsible for the onset of metabolic disturbances such as obesity, insulin resistance, type 2 diabetes, CVD and cancer (Haro et al., 2019).

Several studies of personalized and precision nutrition have used nutrigenomic approaches to design and deliver tailored dietary advice, with select examples (Table 1). In the NOW study, a 12-month RCT of 140 Canadian adults, participants in the group lifestyle balance with nutrigenomics program received information related to their resting metabolism and were advised to focus on the macronutrient recommendation(s) highlighted in their genetic report to enhance their weight loss response (Horne et al., 2020). For example, an individual with the AA variant of *FTO* (rs9939609) was advised to follow a higher protein dietary plan to optimize weight loss. Horne et al. demonstrated that only participants randomized to receive the group lifestyle balance with

nutrigenomics program significantly reduced their total fat intake at 12-months. Together with other nutrigenomic-based interventions (Hietaranta-Luoma, Tahvonen, Iso-Touru, Puolijoki, & Hopia, 2014; Nielsen & El-Sohemy, 2014), there has been some evidence to support the potential for nutrigenomic-based interventions to motivate long-term changes in specific nutrients, such as total fat intake. However, recent reviews of RCTs highlight important gaps in the evidence-base for the effective integration of nutrigenomics and behavior science approaches (Hollands et al., 2016; Jinnette et al., 2021). In particular, although an increasing number of studies have incorporated behavior change techniques, such as the theory of planned behavior (Horne et al., 2020), the motivators of behavior change are likely to be specific to the nature of the intervention and the target population, thus interventions targeting weight management in mid-aged adults may be a more amenable to nutrigenomic messaging compared to interventions in young adults, who may be less motivated to improve their health (Munt, Partridge, & Allman-Farinelli, 2017).

Building on animal and *in vitro* research, an increasing number of postprandial human intervention studies have been conducted globally to examine the impact of meals and snacks on gene expression pathways (Jakubowicz et al., 2017; Lopez-Miranda, Williams, & Lairon, 2007; Ramos-Lopez et al., 2017). For example, in a recent randomized postprandial cross-over study of 19 Australian men, Dordevic et al. investigated transcriptomic regulation of adipose tissue following a high-fat meal in men with and without metabolic syndrome (Dordevic et al., 2021). Outcomes demonstrated increases in gene expression related to cellular nutrient responses in control participants following a high-fat meal, whereas blunted response were observed in men with metabolic syndrome. Specifically, in healthy males, genes related to activation of cellular metabolism and nutrient response pathways were up regulated, such as mTOR regulation via activation of *MAPK1*, *STAT3*, and *TGFB3* genes. Insights from such mechanistic studies provide new knowledge of potential therapeutic and precision nutrition targets to improve health.

1.4. Nutriepigenetic approaches

Nutrition is one of the most studied and better understood lifestyle factors associated with epigenetic modifications (Milagro, Mansego, De Miguel, & Martínez, 2013). In this context, nutriepigenetic research encompasses the study of the effect of foods and nutrients that may impact on the epigenetic landscape and cell phenotypes (Ramos-Lopez et al., 2017). Selected studies of personalized and precision nutrition are presented (Table 1), which have used nutriepigenetic approaches to design and deliver tailored dietary advice.

Knowledge of the range of bioactive foods and subsequent dietary patterns identified as exerting epigenetic effects is growing. For example, low intake of folate has been associated with hypomethylation of the *CAMKK2* gene and more instances of insulin resistance in participants with metabolic syndrome (Ramos-Lopez, Samblas, et al., 2018). Interestingly, changes in the DNA methylation (DNAm) levels of the circadian *BMAL1* gene were associated with the effects of a weight loss intervention on blood lipids levels in women (Samblas, Milagro, Gómez-Abellán, Martínez, & Garaulet, 2016). Similarly, adherence to a MedDiet was associated with changes in DNAm levels of genes related to inflammation in high cardiovascular risk volunteers (Arpón et al., 2016). Besides, higher regional DNAm level at *TXNIP* gene was significantly associated with insulin resistance improvements by taking the average-protein (20%) weight-loss diet (Li et al., 2022). Regarding the effect of maternal diet on the methylome concerning pregnancy outcomes and newborns' health, genome-scale analyses have revealed that prenatal famine exposure was related to DNAm signatures in pathways associated with growth and metabolism (Tobi et al., 2014). In addition, findings from the MANOE study showed that maternal dietary and supplemental intake of methyl-group donors may influence infant's DNAm landscape in genes related to appetite regulation, growth and development, and maintenance of DNAm reactions (Pauwels et al., 2017).

In addition to effects on DNA, several microRNAs (miRNAs) have been identified as being modified by dietary intake. Several miRNAs implicated in the control of cellular processes such as inflammation or apoptosis, have been shown to be modulated by dietary polyphenols found in fruits, vegetables, tea, coffee, and wine (Milenkovic, Jude, & Morand, 2013). Furthermore, several miRNAs have been identified as potential biomarkers in response to different diets and foods (Garcia--Lacarte, Mansego, Zulet, Martinez, & Milagro, 2019). For instance, 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 the response to a low-fat diet intervention prescribed to aid weight loss (Assmann, Riezu-Boj, Milagro, & Martínez, 2020). Similarly, plasma miR-23a-3p expression levels positively correlated with sodium intake, and negatively correlated dietary vitamin E, whereas the consumption of vitamin D negatively correlated with the expression of miR-1277-5p and miR-144-3p in healthy European volunteers (Ferrero et al., 2021).

The health benefits of consuming dietary bioactive compounds (such as genistein, sulforaphane, curcumin, resveratrol, and epigallocatechin-3-gallate) are thought to be mediated, at least in part, by epigenetic mechanisms including the regulation of histone acetyltransferases (HATs) and deacetylases (HDACs) activities (Vahid, Zand, Nosrat-Mirshekarlou, Najafi, & Hekmatdoost, 2015). Specifically, it was shown that the consumption of 68 g of broccoli (which is equivalent to a daily dietary intake of 105 mg of the HDACs inhibitor sulforaphane) showed hyperacetylation of histones H3 and H4 in circulating blood cells in healthy human volunteers (Myzak, Tong, Dashwood, Dashwood, & Ho, 2007). Also, *in vitro* experiments revealed that quercetin (a dietary polyphenol found in many fruits, vegetables, nuts, and red wine) exerted anti-inflammatory and antitumoral effects via inhibition of HATs activity (Xiao et al., 2011). Other bioactive food constituents with potential HDACs inhibitory activities (a promising therapeutic approach in the clinical setting) include short chain fatty acids, isoflavones, indoles, organosulfur/organoselenium agents, and sesquiterpene lactones (Kim et al., 2016).

Interestingly, various nutrients influence telomere length (TL) through mechanisms reflecting potential roles in cellular functions including inflammation, oxidative stress, DNA integrity, and telomerase activity (Paul, 2011). For example, sugar-sweetened soda consumption was associated with shorter leukocyte TL in a nationally representative sample of American healthy adults (Leung et al., 2014). Within the Multi-Ethnic Study of Atherosclerosis (including white, black, and Hispanic adults), processed meat intake was associated with shorter TL (Nettleton, Diez-Roux, Jenny, Fitzpatrick, & Jacobs, 2008). Meanwhile, a prudent dietary pattern (characterized by high intake of whole grains, seafood, legumes, vegetables and seaweed) was associated with longer leukocyte TL in middle-aged and older Korean adults from a population-based cohort (Lee, Jun, Yoon, Shin, & Baik, 2015). Moreover, findings from the PREDIMED-NAVARRA trial showed that better adherence to MedDiet was associated with longer basal telomeres in women, whereas the opposite was observed in men (García-Calzón et al., 2016).

1.5. Metabolomic approaches

Metabolomic research implements the profiling of metabolites in biofluids, cells and tissues and is routinely applied as a tool for biomarker description and target discovery (Johnson, Ivanisevic, & Siuzdak, 2016). Advances in analytical technologies and informatics have led to the rapid uptake of metabolomic research to investigate physiological conditions and chronic diseases (Mastrangelo & Barbas, 2017). In particular, application of metabolomics approaches has shown promise for improving the accuracy of dietary assessment through the identification of biomarkers of food intake, and identifying metabolites and metabolic signatures that can serve as targets for interventions

(Brennan & de Roos, 2021). Two distinct metabolomic methodologies have been implemented: untargeted metabolomics, an intended comprehensive screening of all the measurable metabolites in a sample, including chemical unknowns); and targeted metabolomics, the measurement of chemically described and biochemically characterized metabolites (Johnson et al., 2016).

In recent compilations of future perspectives in "omics" research, three opportunities for metabolomics were identified to improve the accuracy of dietary assessment in the field of nutritional epidemiology: 1) determination of food intake based on levels of biomarkers and calibration equations from feeding studies, 2) classification of individuals into dietary patterns based on urinary metabolic profiles, and 3) application of metabolome wide–association studies (Brennan & de Roos, 2021; Brennan & Hu, 2019). Many of these endeavors require rapid and effective data integration. For example, in a recent guide to integration of microbiome and dietary pattern data, Choi et al. recommended using methods currently applied to microbiome datasets, such as dietary tree-of-foods and data adjustment for compositionality, to better incorporate dietary patterns research into existing microbiome analysis pipelines (Choi, Hoops, Thoma, & Johnson, 2022). Furthermore, research on dietary metabolites has traditionally focused on single metabolites, such as 2-hydroxy-3-methylbutyric acid as a candidate biomarker of habitual alcohol (Loftfield et al., 2021). However, recent research has identified combinations of metabolites, known as metabolic signatures that are associated with specific dietary exposures and disease outcomes (E. Smith et al., 2022). As proposed by Smith et al., if metabolic signatures can be used to identify population groups at risk on chronic disease, a single plasma sample could be sufficient for estimating disease risk in clinical settings, without the need to self-report dietary intake (E. Smith et al., 2022).

State-of-the-art studies have used metabolomic approaches to understand individualized responses to dietary intake (Table 1). One such example is the PREDICT 1 study, led by Berry et al., which examined the postprandial metabolic responses to sequential mixed-nutrient dietary challenges in 1002 healthy UK adults aged 18–65 years (Berry et al., 2020). Stool samples, dry blood spot cards and continuous glucose monitoring were used to determining the extent of influence of the gut microbiome on postprandial lipemia and glycemia. Outcomes from this research showed that the gut microbiome had a greater influence (7.1% of variance) than meal macronutrients (3.6%) for postprandial lipemia, but not for postprandial glycemia (6.0% and 15.4%, respectively). In contrast, the heritability of postprandial traits was modest, highlighting the importance of meal composition and context, such as meal timing, exercise, sleep and circadian rhythm, as core determinants of postprandial metabolism (Berry et al., 2020). Integrative precision nutrition approaches thus have significant potential for combining physiological, behavioral and contextual factors into targeted dietary advice and support (Ramos-Lopez, Milton-Laskibar, Martínez, 2021).

One of the first and most comprehensive studies of individual variability, the DIETFITS study, was a 12-month RCT that aimed to identify whether individual differences in insulin secretion explained inter-individual variation in weight loss (Ebbeling, Leidig, Feldman, Lovesky, & Ludwig, 2007). In this study, average weight loss was comparable between groups, yet considerable variations were observed within groups. In a sub-study of 49 18–50 year old US adults from the DIETFITS study, Fragiadakis et al. aimed to extend this research by determining if baseline microbiota composition or diversity was associated with weight-loss success (Fragiadakis et al., 2020). Findings from this study indicated that while baseline microbiota composition was not predictive of weight loss, each diet resulted in substantial changes in the microbiota 3 months after the start of the intervention, most notably due to changes specific to the healthy low-carbohydrate diet, although these changes were not sustained at 12-months (Fragiadakis et al., 2020). The authors speculate that this could be the result of a microbiome-based "memory" of obesity, in which there is resilience of the microbiota to dietary and host physiological change and presence of a homeostatic corrective force on the microbial community to return to a long-established state (Thaiss et al., 2016). This microbial resistance could have important implications for precision nutrition approaches that aim to achieve sustained changes in diet, gut microbiota and health in individuals with obesity, and warrants further investigation (Thaiss et al., 2016).

1.6. Metagenomic approaches

Metagenomics is defined as the comprehensive study of microbial and host genetic material (DNA and RNA) in samples from patients without prior need for culturing (Chiu & Miller, 2019). The human gastrointestinal tract is estimated to harbor ~1013 microorganisms, referred to as the gut microbiome (Bäckhed, Ley, Sonnenburg, Peterson, & Gordon, 2005). The gut microbiome has a vast genetic potential to contribute to host physiology, and has been increasingly studied in relation its impact on biological pathways that regulate immunity, energy homeostasis and its potential to explain human variability in dietary response (Mills, Stanton, Lane, Smith, & Ross, 2019). As a result, advances in next generation sequencing have allowed for shotgun metagenomics, which is low-cost high-throughput sequencing that can analyze all genomes within an ecosystem sample, and marker gene metagenomics, which describes the taxa within a specific community by sequencing conserved marker genes, without the need to cultivate the clonal cultures (Oulas et al., 2015).

Landmark studies have shown the potential for metagenomic approaches to be utilized at a population-level. This includes the Belgium Flemish Gut Flora Project (FGFP), which has generated one of the largest and best characterized fecal microbiota databases currently available (Falony et al., 2016). As part of the project, Falony et al. have investigated the extent to which anthropometrics, health, lifestyle, bowel habits, medication, and diet explained variation in the gut microbiome, and its association with health outcomes. With fiber consumption identified as the strongest dietary influence on gut microbiome (Falony et al., 2016), many subsequent studies have built upon this research (Hughes et al., 2020), which would not be possible without advances in metagenomic tools.

As shown in the select examples (Table 1), metabolomic approaches have been applied to understand individualized responses to dietary intake. In 8-week RCT of 60 Danish adults at risk of metabolic syndrome, shotgun sequencing-based metagenomics was employed to investigate whether a whole grain diet altered the gut microbiome and insulin sensitivity, as well as biomarkers of metabolic health and gut functionality (Roager et al., 2019). Contrary to the author's hypothesis, the whole grain diet did not induce major changes in the fecal microbiome compared with the refined grain diet. However, the metagenomics-based examination of the microbiome response at both species and functional levels did identify some minor changes in the microbiome. In particular, the whole grain diet induced a reduction in *E. ramosum*, which has been reported to promote obesity in high-fat mice models, thus potentially contributing to the observed reduction in weight and low-grade inflammation observed in the trial. The combination of metagenomics with urine and postprandial blood sampling in this study showcases the advantage of a multi-omics perspective for the comprehensive study of biological mechanisms of health and disease.

The use of metagenomics tools has considerable potential for use in population-based studies, which explains why an increasing number of studies have collected fecal samples. In a pioneering study, Vangay et al. collected stool, dietary recalls, and anthropometrics from 514 Hmong and Karen individuals living in Thailand and the U.S., including first- and second-generation immigrants and 19 Karen individuals sampled before and after immigration, as well as from 36 US-born European American individuals (Vangay et al., 2018). Using 16S and deep shotgun metagenomic DNA sequencing, the authors found that migration to the US was associated with rapid displacement of native gut microbiome diversity and function by US-associated strains and functions.

Subsequent studies have since used similar metagenomic approaches in longitudinal studies, including a study of 144 Chinese adults, where a healthy dietary pattern was associated with greater diversity of microbial gene families and metabolic pathways, as well as altered symbiotic functions relevant to human health (Yu et al., 2021). These studies provide important insights into the racial considerations when implementing precision nutrition approaches in different population groups, with further research needed to better understand how these align with sociocultural influences on diet.

1.7. Integrative precision nutrition: big data and machine learning

The evolution of "omics" technologies and emerging big data analyses has deepened the understanding and characterization of nutrition-related chronic diseases by applying ML and artificial intelligence methods. ML refers to the ability of algorithms and other categorization/clustering strategies to produce inferences or find patterns from statistical analysis of very large datasets, which is expressed as the likelihood of a relationship between variables (Baştanlar & Ozuysal, 2014). In other words, ML provides techniques that can automatically build a computational model by processing the available data and maximizing a problem dependent performance criterion, which can be used to make predictions or classifications for advanced exploratory data analysis (Baştanlar & Ozuysal, 2014). Thus, ML encompasses linear and logistic regression, data clustering, artificial neural networks, association rule learning, feature engineering and dimensionality reduction, deep learning and decision tree testing, principal component analysis, and topological data assessment (DeGregory et al., 2018).

Here, we review machine learning methods that predict and/or classify such as linear and logistic regression, artificial neural networks, deep learning and decision tree analysis. We also review methods that describe and characterize data such as cluster analysis, principal component analysis, network science and topological data analysis.

These approaches are able to capture large and complex matrices of data, incorporating potential interactions and identifying both linear and non-linear associations (Vilne et al., 2022). Generally, the performance of a ML model in various application areas depends on the amount, quality, nature, and characteristics of the data, the complexity and form of the relationships between variables and the target outcome, as well as the application of suitable bioinformatics instruments (Sarker, 2021).

Extracting valuable knowledge from "omics" data remains a challenge in bioinformatics, often needing more innovative methods for efficient handlings and effective results (Khorraminezhad, Leclercq, Droit, Bilodeau, & Rudkowska, 2020). In this regards, ML play a major role in the integration and interpretation of multi-"omics" techniques in nutrition research (including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and metagenomics) since they can be used for computational modeling, data mining, sample clustering, and classification in response to dietary intake (Khorraminezhad et al., 2020). The combination of these tools can be translated into practical clinical nutrition applications such as decision support and diet optimization schemes (Limketkai, Mauldin, Manitius, Jalilian, & Salonen, 2021). Fig. 2 provides an overview of integrative precision nutrition, where quantitative nutri-indices/scores and decision trees/algorithms designed to categorize and cluster interventions are devised. ML could facilitate the analysis of many complex features, contributing to the development of high-performance precision nutrition recommendations (Limketkai et al., 2021).

Indeed, one common application of precision nutrition is the creation of ML algorithms. For instance, an integrative approach with ML algorithms was performed to predict obesity using genetic (402,793 SNPs), epigenetic (415,202 DNAm sites), and environmental data (397 dietary and lifestyle factors) and exploring gene-gene and gene-diet interactions (Lee et al., 2022). Also, a ML model based on routine, quantitative, and easily measured variables (such as age, systolic blood pressure, blood/urine tests and dietary intake values) was able to detect the presence and extent of subclinical atherosclerosis in young, asymptomatic individuals (Sánchez-Cabo et al., 2020). Of note, ML techniques (Random Forest and Gradient Boosting Machine models) were employed to predict the BMI from a wide set of 190 multidomain variables including age, sex, genetic polymorphisms, lifestyle, socio-economic position, diet, exercise, and gestation features in children (Marcos-Pasero et al., 2021). As detailed in Table 1, another example of ML applications includes the findings from the PREDICT 1 clinical trial, reporting individual variations in postprandial triglyceride and glucose responses to standardized meals using genetic, metabolic, microbiome, and meal context data, which could help to customize nutrition recommendations for cardiometabolic health (Berry et al., 2020). Likewise, a ML algorithm that integrated blood markers, dietary habits, anthropometrics, physical activity, and gut microbiota composition was fitted to accurately predict individual glycemic responses to real-life meals (Zeevi et al., 2015).

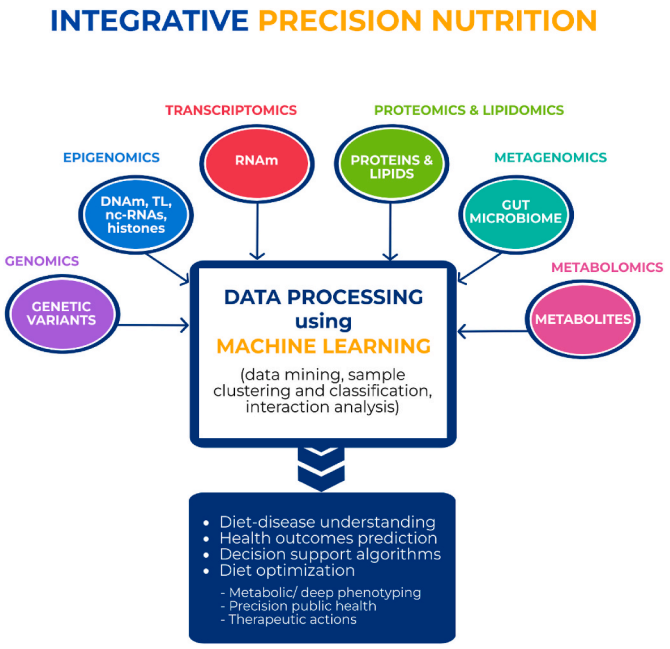

Fig. 2. Integrative precision nutrition: use of biomarkers from OMICS technologies for data processing and clinical applications.

The application of big data and ML has significant potential to advance nutritional epidemiology. Specifically, as detailed earlier, ML can be used to improve the precision and validity of dietary measurements and offer more tools to model the complexity of diet and its relationship with diseases (Morgenstern, Rosella, Costa, de Souza, & Anderson, 2021). Interestingly, findings from the ATTICA study revealed that ML techniques (k-nearest-neighbor's algorithm and random-forests decision tree) were superior to linear regression models in evaluating the association between dietary patterns and 10-year cardiometabolic risk, leading to more accurate disease-risk evaluation (Panaretos et al., 2018). Such advances in the application of ML and other artificial intelligence approximates to nutritional epidemiology have been encouraged by concurrent developments in dietary monitoring. These include the use of mobile applications (i.e., food photography and related artificial intelligence processing), wearable and handheld sensors capable of detecting temporal variations in intake of foods and supplements, and chemical sensors to estimate the macronutrient composition of diets and specific meals (Mortazavi & Gutierrez-Osuna, 2021). In fact, digital advances have the potential to revolutionize dietary behavior change research by providing timely (previously unavailable) dietary information. This information can then be used in just-in-time adaptive dietary interventions, paving the way

for the design of more effective precision nutrition strategies that use ML to tailor and adapt advice and support at scale (Sempionatto, Montiel, Vargas, Teymourian, & Wang, 2021).

In addition to the aforementioned applications, another important tool in ML and big data analysis is the use of biomarkers. Potential applications of biomarkers include to quantify dietary intake; analyze physiopathological responses to food components or diets; characterize therapeutic targets; identify individuals with specific nutritional deficiencies; provide information on inter-individual variations in response to diets; and to help design personalized nutritional recommendations for particular metabolic phenotypes to achieve optimal health (Picó, Serra, Rodríguez, Keijer, & Palou, 2019).

Overall, ML modeling in precision nutrition may contribute to a greater understanding of human health and disease, individual risk prediction, case triage diagnosis and interpretation, and personalized patient prognosis and management. Nevertheless, some of the most important challenges include the lack of data availability with large enough sample sizes to ensure high reliability and reproducibility, and the interpretability and practical application of the ML approaches to bedside settings (Habehh & Gohel, 2021). The involvement of healthcare professionals in the development, implementation, and testing of ML-based methods may help to increase the adoption rates of these innovative approaches as well as improve the clinical applicability and real-world impact of the results on health monitoring procedures (Habehh & Gohel, 2021).

1.8. Challenges for the development of precision nutrition

While the opportunities for integrative precision nutrition are vast, the challenges of developing and implementing such approaches require consideration. The ethical, legal and social issues of using genetic information, and other highly sensitive personal information, has been reviewed within the content of human rights requirements in and outside the EU (Slokenberga et al., 2019), and specifically within the context of precision nutrition (Kohlmeier et al., 2016). Although the legal framework surrounding genetic testing remains complex, and country and region-specific (Slokenberga et al., 2019), there is an increasing understanding of the importance of ethical and social issues. Above all else, the responsible handling of genetic information is critical, as results may have far-reaching implications for the health and legal status of the consumer and their family. As a result, consumers undergoing genetic testing must provide informed consent, where they are aware of any benefits and risks associated with such testing. However, consumer protection goes beyond personal approval, as the responsible handling of genetic information should also consider the quality of these tests. Quality control includes ensuring the databases used and personalized advice provided by laboratories, companies, and health care professionals are appropriate. Upskilling of non-genetic healthcare professionals has been identified as an unmet need in recent years, with an increasing number of training resources now being developed and tested, which is critical to meet the rise in commercialization of genetic testing (Talwar, Tseng, Foster, Xu, & Chen, 2016).

Many frameworks have been developed, which can help navigate the challenges of precision nutrition. One such example is a precision public health ethics background that aims to ensure the benefit of precision approaches based on advances in genomics research outweigh any possible public health risks to individuals, families, and vulnerable members of the population (Juengst & Van Rie, 2020). Within this framework, four intersectional elements of precision public health ethics are proposed: community health priority, shared authority, least intrusive data use and proactive transparency. As such, a key principle of this endeavor is a commitment to confidentiality of information, responsible governance of data, and the consent of individuals or groups involved (San-Cristobal, Milagro, & Martínez, 2013). Future research should continue to strengthen ethical, legal and social solutions for the integration of genetic, and other sensitive biological, cultural or behavioral information, into precision nutrition approaches for a personalized attention (Ferguson et al., 2016).

2. Conclusions

As outlined in this document, personalized and precision nutrition approaches are being increasingly adopted in nutrition research. While closely related terms, there are distinct differences. Personalized nutrition encompasses the application of “omics” technologies such as nutrigenomics, metagenomics, and metabolomics to the prescription of individualized diets for health and wellbeing. Information used in the prescription of such advice is predominantly fixed and therefore doesn’t change over time. In contrast, precision nutrition adopts an integrative, dynamic and holistic approach to developing comprehensive recommendations for individuals and population subgroup. Precision nutrition can involve the analysis of complex gene-environment interactions and deep phenotyping, the screening and integration of behavioral and sociocultural factors, health characteristics, and perinatal feeding information. However, precision nutrition combines such information at scale, thus requiring the use of bioinformatics, ML and artificial intelligence approaches for integrative purposes.

This review provides an overview of current trends in “omics” technologies that are likely to underpin the future success of integrative precision nutrition approaches. As outlined in this review, inter-individual variations in genetics only partially explain the heterogeneity in the response to a given diet. Over the last two decades, the study of the gut microbiota and metabolomics have increased exponentially, creating a better understanding of metabolic pathways through which dietary intakes may impact on health and disease. These emerging fields of research require the use of high-throughput technologies and deep phenotyping, which provide physiological and genetic insights into the metabolic pathways of bioactive foods and nutrients. In turn, such insights will help inform the optimal design of precision dietary interventions to improve and maintain health in individuals. New frontiers in big data and machine learning will undoubtedly pave the way for delivering integrated precision nutrition, where multi-omics approaches can be combined with lifestyle and behavioral determinants of diet and health to improve population diets at scale. Indeed, genotypical and phenotypical data as well as perinatal, clinical history, and demographic/socioeconomic determinants need to be accorded.

The outcomes of this review will assist with understanding trends in the design and application of precision nutrition approaches for use in research, healthcare and industry. The global application of precision nutrition requires understanding of the population health, political will and technological and digital landscape of the region and country in question, prior to implementation of such approaches. Moreover, multidisciplinary collaborations between researchers, health care professionals and industry are likely to become even more important to aid the generation, interpretation and implementation of integrative precision nutrition data.

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Author contributions

All authors designed the study and developed the search strategy. KML, OR and JAM drafted the manuscript with all co-authors contributing critical review to drafts of the manuscript. All authors approved the final manuscript.

Declaration of competing interest

None.

Data availability

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References

Afshin, A., Sur, P. J., Fay, K. A., Cornaby, L., Ferrara, G., Salama, J. S., et al. (2019). Health effects of dietary risks in 195 countries, 1990-2017: A systematic analysis for the global burden of disease study 2017. *The Lancet, 393*(10184), 1958–1972. https://doi.org/10.1016/S0140-6736(19)30041-8

Arpón, A., Riezu-Boj, J. I., Milagro, F. I., Marti, A., Razquin, C., Martínez-González, M. A., et al. (2016). Adherence to Mediterranean diet is associated with methylation changes in inflammation-related genes in peripheral blood cells. *Journal of Physiology & Biochemistry, 73*(3), 445–455. https://doi.org/10.1007/s13105-017-0552-6

Assmann, T. S., Riezu-Boj, J. I., Milagro, F. I., & Martínez, J. A. (2020). Circulating adiposity-related microRNAs as predictors of the response to a low-fat diet in subjects with obesity. *Journal of Cellular and Molecular Medicine, 24*(5), 2956–2967. https://doi.org/10.1111/jcmm.14920

Bäckhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A., & Gordon, J. I. (2005). Host-bacterial mutualism in the human intestine. *Science, 307*(5717), 1915–1920. https://doi.org/10.1126/science.1104816

Baştanlar, Y., & Ozuysal, M. (2014). Introduction to machine learning. *Methods in molecular biology (Clifton, N.J.), 1107*, 105–128. https://doi.org/10.1007/978-1-62703-748-8_7

Berry, S. E., Valdes, A. M., Drew, D. A., Asnicar, F., Mazidi, M., Wolf, J., et al. (2020). Human postprandial responses to food and potential for precision nutrition. *Nature Medicine, 26*(6), 964–973. https://doi.org/10.1038/s41591-020-0934-0

Blau, N., van Spronsen, F. J., & Levy, H. L. (2010). Phenylketonuria. *Lancet, 376*(9750), 1417–1427. https://doi.org/10.1016/s0140-6736(10)60961-0

Brennan, L., & de Roos, B. (2021). Nutrigenomics: Lessons learned and future perspectives. *The American Journal of Clinical Nutrition, 113*(3), 503–516. https://doi.org/10.1093/ajcn/nqaa366

Brennan, L., & Hu, F. B. (2019). Metabolomics-based dietary biomarkers in nutritional epidemiology—current status and future opportunities. *Molecular Nutrition & Food Research, 63*(1), Article 1701064. https://doi.org/10.1002/mnfr.201701064

Bush, C. L., Blumberg, J. B., El-Sohemy, A., Minich, D. M., Ordovás, J. M., Reed, D. G., et al. (2020). Toward the definition of personalized nutrition: A proposal by the American nutrition association. *Journal of the American College of Nutrition, 39*(1), 5–15. https://doi.org/10.1080/07315724.2019.1685332

Canfell, O. J., Davidson, K., Woods, L., Sullivan, C., Cocoros, N. M., Klompas, M., et al. (2022). Precision public health for non-communicable diseases: An emerging strategic roadmap and multinational use cases. *Frontiers in Public Health, 10*. https://doi.org/10.3389/fpubh.2022.854525

Celis-Morales, C., Livingstone, K. M., Marsaux, C. F. M., Forster, H., O'Donovan, C. B., Woolhead, C., et al. (2015). Design and baseline characteristics of the Food4Me study: A web-based randomised controlled trial of personalised nutrition in seven European countries. *Genes & Nutrition, 10*(1), 450. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4261071/.

Celis-Morales, C., Livingstone, K. M., Marsaux, C. F. M., Macready, A. L., Fallaize, R., O'Donovan, C. B., et al. (2016). Effect of personalized nutrition on health-related behaviour change: Evidence from the Food4me European randomized controlled trial. *International Journal of Epidemiology, 46*(2), 578–588. https://doi.org/10.1093/ije/dyw186

Chiu, C. Y., & Miller, S. A. (2019). Clinical metagenomics. *Nature Reviews Genetics, 20*(6), 341–355. https://doi.org/10.1038/s41576-019-0113-7

Choi, Y., Hoops, S. L., Thoma, C. J., & Johnson, A. J. (2022). A guide to dietary pattern-microbiome data integration. *Journal of Nutrition, 152*(5), 1187–1199. https://doi.org/10.1093/jn/nxac033

DeGregory, K. W., Kuiper, P., DeSilvio, T., Pleuss, J. D., Miller, R., Roginski, J. W., et al. (2018). A review of machine learning in obesity. *Obesity Reviews : An Official Journal of the International Association for the Study of Obesity, 19*(5), 668–685. https://doi.org/10.1111/obr.12667

Dordevic, A. L., Coort, S. L., Evelo, C. T., Murgia, C., Sinclair, A. J., Bonham, M. P., et al. (2021). Blunted nutrient-response pathways in adipose tissue following high fat meals in men with metabolic syndrome: A randomized postprandial transcriptomic study. *Clinical Nutrition, 40*(3), 1355–1366. https://doi.org/10.1016/j.clnu.2020.08.024

Du, X., Aristizabal-Henao, J. J., Garrett, T. J., Brochhausen, M., Hogan, W. R., & Lemas, D. J. (2022). A checklist for reproducible computational analysis in clinical metabolomics research. *Metabolites, 12*(1), 87. https://doi.org/10.3390/metabo12010087

Ebbeling, C. B., Leidig, M. M., Feldman, H. A., Lovesky, M. M., & Ludwig, D. S. (2007). Effects of a low-glycemic load vs low-fat diet in obese young adults: A randomized trial. *JAMA, 297*(19), 2092–2102. https://doi.org/10.1001/jama.297.19.2092

Elks, C. E., den Hoed, M., Zhao, J. H., Sharp, S. J., Wareham, N. J., Loos, R. J., et al. (2012). Variability in the heritability of body mass index: A systematic review and meta-regression. *Frontiers in Endocrinology, 3*, 29. https://doi.org/10.3389/fendo.2012.00029

Enattah, N. S., Sahi, T., Savilahti, E., Terwilliger, J. D., Peltonen, L., & Järvelä, I. (2002). Identification of a variant associated with adult-type hypolactasia. *Nature Genetics, 30*(2), 233–237. https://doi.org/10.1038/ng826

Falony, G., Joossens, M., Vieira-Silva, S., Wang, J., Darzi, Y., Faust, K., et al. (2016). Population-level analysis of gut microbiome variation. *Science, 352*(6285), 560–564. https://doi.org/10.1126/science.aad3503

Fenech, M., El-Sohemy, A., Cahill, L., Ferguson, L. R., French, T. A., Tai, E. S., et al. (2011). Nutrigenetics and nutrigenomics: Viewpoints on the current status and applications in nutrition research and practice. *Journal of Nutrigenetics and Nutrigenomics, 4*(2), 69–89. https://doi.org/10.1159/000327772

Ferguson, L. R., De Caterina, R., Görman, U., Allayee, H., Kohlmeier, M., Prasad, C., et al. (2016). Guide and position of the international society of nutrigenetics/nutrigenomics on personalised nutrition: Part 1 - fields of precision nutrition. *Journal of Nutrigenetics and Nutrigenomics, 9*(1), 12–27. Retrieved from https://www.karger.com/DOI/10.1159/000445350.

Ferrero, G., Carpi, S., Polini, B., Pardini, B., Nieri, P., Impeduglia, A., et al. (2021). Intake of natural compounds and circulating microRNA expression levels: Their relationship investigated in healthy subjects with different dietary habits. *Frontiers in Pharmacology, 11*, Article 619200. https://doi.org/10.3389/fphar.2020.619200

Fragiadakis, G. K., Wastyk, H. C., Robinson, J. L., Sonnenburg, E. D., Sonnenburg, J. L., & Gardner, C. D. (2020). Long-term dietary intervention reveals resilience of the gut microbiota despite changes in diet and weight. *The American Journal of Clinical Nutrition, 111*(6), 1127–1136. https://doi.org/10.1093/ajcn/nqaa046

García-Calzón, S., Martínez-González, M. A., Razquin, C., Arós, F., Lapetra, J., Martínez, J. A., et al. (2016). Mediterranean diet and telomere length in high cardiovascular risk subjects from the PREDIMED-NAVARRA study. *Clinical nutrition (Edinburgh, Scotland), 35*(6), 1399–1405. https://doi.org/10.1016/j.clnu.2016.03.013

Garcia-Lacarte, M., Mansego, M. L., Zulet, M. A., Martinez, J. A., & Milagro, F. I. (2019). miR-1185-1 and miR-548q are biomarkers of response to weight loss and regulate the expression of GSK3B. *Cells, 8*(12), 1548. https://doi.org/10.3390/cells8121548

Goni, L., Cuervo, M., Milagro, F. I., & Martínez, J. A. (2015). Future perspectives of personalized weight loss interventions based on nutrigenetic, epigenetic, and metagenomic data. *Journal of Nutrition, 146*(4), 905S–912S. https://doi.org/10.3945/jn.115.218354

Habehh, H., & Gohel, S. (2021). Machine learning in healthcare. *Current Genomics, 22*(4), 291–300. https://doi.org/10.2174/1389202922666210705124359

Haro, D., Marrero, P. F., & Relat, J. (2019). Nutritional regulation of gene expression: Carbohydrate-, fat- and amino acid-dependent modulation of transcriptional activity. *International Journal of Molecular Sciences, 20*(6), 1386. Retrieved from https://www.mdpi.com/1422-0067/20/6/1386.

Herforth, A., Arimond, M., Álvarez-Sánchez, C., Coates, J., Christianson, K., & Muehlhoff, E. (2019). A global review of food-based dietary guidelines. *Advances in Nutrition, 10*(4), 590–605. https://doi.org/10.1093/advances/nmy130

Hietaranta-Luoma, H. L., Tahvonen, R., Iso-Touru, T., Puolijoki, H., & Hopia, A. (2014). An intervention study of individual, apoE genotype-based dietary and physical-activity advice: Impact on health behavior. *Journal of Nutrigenetics and Nutrigenomics, 7*(3), 161–174. https://doi.org/10.1159/000371743

Hollands, G. J., French, D. P., Griffin, S. J., Prevost, A. T., Sutton, S., King, S., et al. (2016). The impact of communicating genetic risks of disease on risk-reducing health behaviour: Systematic review with meta-analysis. *BMJ, 352*. https://doi.org/10.1136/bmj.i1102

Horne, J., Gilliland, J., O'Connor, C., Seabrook, J., & Madill, J. (2020). 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 Nutrition, Prevention & Health*. https://doi.org/10.1136/bmjnph-2020-000073. bmjnph-2020-000073.

Hughes, D. A., Bacigalupe, R., Wang, J., Rühlemann, M. C., Tito, R. Y., Falony, G., … Raes, J. (2020). Genome-wide associations of human gut microbiome variation and implications for causal inference analyses. *Nature microbiology, 5*(9), 1079–1087. https://doi.org/10.1038/s41564-020-0743-8

Jakubowicz, D., Wainstein, J., Landau, Z., Raz, I., Ahren, B., Chapnik, N., … Froy, O. (2017). Influences of breakfast on clock gene expression and postprandial glycemia in healthy individuals and individuals with diabetes: A randomized clinical trial. *Diabetes Care, 40*(11), 1573–1579. https://doi.org/10.2337/dc16-2753

Jinnette, R., Narita, A., Manning, B., McNaughton, S. A., Mathers, J. C., & Livingstone, K. M. (2021). Does personalized nutrition advice improve dietary intake in healthy adults? A systematic review of randomized controlled trials. *Advances in Nutrition, 12*(3), 657–669. https://doi.org/10.1093/advances/nmaa144

Johnson, C. H., Ivanisevic, J., & Siuzdak, G. (2016). Metabolomics: Beyond biomarkers and towards mechanisms. *Nature Reviews Molecular Cell Biology, 17*(7), 451–459. https://doi.org/10.1038/nrm.2016.25

Juengst, E. T., & Van Rie, A. (2020). Transparency, trust, and community welfare: Towards a precision public health ethics framework for the genomics era. *Genome Medicine, 12*, 98. https://doi.org/10.1186/s13073-020-00800-y

Kalmpourtzidou, A., Eilander, A., & Talsma, E. F. (2020). Global vegetable intake and supply compared to recommendations: A systematic review. *Nutrients, 12*(6), 1558. Retrieved from https://www.mdpi.com/2072-6643/12/6/1558.

Khorraminezhad, L., Leclercq, M., Droit, A., Bilodeau, J. F., & Rudkowska, I. (2020). Statistical and machine-learning analyses in nutritional genomics studies. *Nutrients, 12*(10), 3140. https://doi.org/10.3390/nu12103140

Kim, E., Bisson, W. H., Löhr, C. V., Williams, D. E., Ho, E., Dashwood, R. H., et al. (2016). Histone and non-histone targets of dietary deacetylase inhibitors. *Current Topics in Medicinal Chemistry, 16*(7), 714–731. https://doi.org/10.2174/1568026615666150825125857

Kohlmeier, M., De Caterina, R., Ferguson, L. R., Görman, U., Allayee, H., Prasad, C., et al. (2016). Guide and position of the international society of nutrigenetics/nutrigenomics on personalized nutrition: Part 2 - ethics, challenges and endeavors of precision nutrition. *Lifestyle Genomics, 9*(1), 28–46. https://doi.org/10.1159/000446347

Lee, Y. C., Christensen, J. J., Parnell, L. D., Smith, C. E., Shao, J., McKeown, N. M., et al. (2022). Using machine learning to predict obesity based on genome-wide and epigenome-wide gene-gene and gene-diet interactions. *Frontiers in Genetics, 12*, Article 783845. https://doi.org/10.3389/fgene.2021.783845

Lee, J. Y., Jun, N. R., Yoon, D., Shin, C., & Baik, I. (2015). Association between dietary patterns in the remote past and telomere length. *European Journal of Clinical Nutrition, 69*(9), 1048–1052. https://doi.org/10.1038/ejcn.2015.58

Leung, C. W., Laraia, B. A., Needham, B. L., Rehkopf, D. H., Adler, N. E., Lin, J., et al. (2014). Soda and cell aging: Associations between sugar-sweetened beverage consumption and leukocyte telomere length in healthy adults from the national health and nutrition examination surveys. *American Journal of Public Health, 104*(12), 2425–2431. https://doi.org/10.2105/AJPH.2014.302151

Limketkai, B. N., Mauldin, K., Manitius, N., Jalilian, L., & Salonen, B. R. (2021). The age of artificial intelligence: Use of digital technology in clinical nutrition. *Current surgery reports, 9*(7), 20. https://doi.org/10.1007/s40137-021-00297-3

Li, X., Shao, X., Bazzano, L. A., Xue, Q., Koseva, B. S., Grundberg, E., et al. (2022). Blood DNA methylation at TXNIP and glycemic changes in response to weight-loss diet interventions: The POUNDS lost trial. *International Journal of Obesity, 46*(6), 1122–1127. https://doi.org/10.1038/s41366-022-01084-5, 2005.

Livingstone, K. M., Brayner, B., Celis-Morales, C., Ward, J., Mathers, J. C., & Bowe, S. J. (2022). Dietary patterns, genetic risk, and incidence of obesity: Application of reduced rank regression in 11,735 adults from the UK Biobank study. *Preventive Medicine, 158*, Article 107035. https://doi.org/10.1016/j.ypmed.2022.107035

Livingstone, K. M., Celis-Morales, C., Navas-Carretero, S., San-Cristobal, R., Forster, H., Woolhead, C., & on behalf of the Food4Me, S. (2021). Personalised nutrition advice reduces intake of discretionary foods and beverages: Findings from the Food4Me randomised controlled trial. *International Journal of Behavioral Nutrition and Physical Activity, 18*(1), 70. https://doi.org/10.1186/s12966-021-01136-5

Livingstone, K. M., Celis-Morales, C., Navas-Carretero, S., San-Cristobal, R., Macready, A. L., Fallaize, R., et al. (2016). Effect of an internet-based, personalized nutrition randomized trial on dietary changes associated with the mediterranean diet: The Food4Me study. *American Journal of Clinical Nutrition*. https://doi.org/10.3945/ajcn.115.129049

Loftfield, E., Stepien, M., Viallon, V., Trijsburg, L., Rothwell, J. A., Robinot, N., et al. (2021). Novel biomarkers of habitual alcohol intake and associations with risk of pancreatic and liver cancers and liver disease mortality. *Journal of the National Cancer Institute: Journal of the National Cancer Institute, 113*(11), 1542–1550. https://doi.org/10.1093/jnci/djab078

Lopez-Miranda, J., Williams, C., & Lairon, D. (2007). Dietary, physiological, genetic and pathological influences on postprandial lipid metabolism. *British Journal of Nutrition, 98*(3), 458–473. https://doi.org/10.1017/S000711450774268X

de Luis, D. A., Izaola, O., Primo, D., & Aller, R. (2018). Role of rs670 variant of APOA1 gene on lipid profile, insulin resistance and adipokine levels in obese subjects after weight loss with a dietary intervention. *Diabetes Research and Clinical Practice, 142*, 139–145. https://doi.org/10.1016/j.diabres.2018.05.040

Marcos-Pasero, H., Colmenarejo, G., Aguilar-Aguilar, E., Ramírez de Molina, A., Reglero, G., & Loria-Kohen, V. (2021). Ranking of a wide multidomain set of predictor variables of children obesity by machine learning variable importance techniques. *Scientific Reports, 11*(1), 1910. https://doi.org/10.1038/s41598-021-81205-8

Martínez-González, M. A., Kim, H.-S., Prakash, V., Ramos-Lopez, O., Zotor, F., & Martinez, J. A. (2021). Personalised, population and planetary nutrition for precision health. *BMJ Nutrition, Prevention & Health, 4*(1), 355–358. https://doi.org/10.1136/bmjnph-2021-000235

Mastrangelo, A., & Barbas, C. (2017). Chronic diseases and lifestyle biomarkers identification by metabolomics. *Advances in Experimental Medicine & Biology, 965*, 235–263. https://doi.org/10.1007/978-3-319-47656-8_10

Megiorni, F., & Pizzuti, A. (2012). HLA-DQA1 and HLA-DQB1 in celiac disease predisposition: Practical implications of the HLA molecular typing. *Journal of Biomedical Science, 19*(1), 88. https://doi.org/10.1186/1423-0127-19-88

Milagro, F. I., Mansego, M. L., De Miguel, C., & Martínez, J. A. (2013). Dietary factors, epigenetic modifications and obesity outcomes: Progresses and perspectives. *Molecular Aspects of Medicine, 34*(4), 782–812. https://doi.org/10.1016/j.mam.2012.06.010

Milenkovic, D., Jude, B., & Morand, C. (2013). miRNA as molecular target of polyphenols underlying their biological effects. *Free Radical Biology and Medicine, 64*, 40–51. https://doi.org/10.1016/j.freeradbiomed.2013.05.046

Mills, S., Stanton, C., Lane, J. A., Smith, G. J., & Ross, R. P. (2019). Precision nutrition and the microbiome, Part I: Current state of the science. *Nutrients, 11*(4), 923. Retrieved from https://www.mdpi.com/2072-6643/11/4/923.

Morgenstern, J. D., Rosella, L. C., Costa, A. P., de Souza, R. J., & Anderson, L. N. (2021). Perspective: Big data and machine learning could help advance nutritional epidemiology. *Advances in nutrition (Bethesda, Md, 12*(3), 621–631. https://doi.org/10.1093/advances/nmaa183

Mortazavi, B. J., & Gutierrez-Osuna, R. (2021). A review of digital innovations for diet monitoring and precision nutrition. *Journal of diabetes science and technology*, 1–7. https://doi.org/10.1177/19322968211041356, 19322968211041356. Advance online publication.

Munt, A. E., Partridge, S. R., & Allman-Farinelli, M. (2017). The barriers and enablers of healthy eating among young adults: A missing piece of the obesity puzzle: A scoping review. *Obesity Reviews, 18*(1), 1–17. https://doi.org/10.1111/obr.12472

Myzak, M. C., Tong, P., Dashwood, W. M., Dashwood, R. H., & Ho, E. (2007). Sulforaphane retards the growth of human PC-3 xenografts and inhibits HDAC activity in human subjects. *Experimental biology and medicine (Maywood, N.J.), 232*(2), 227–234.

National Institutes of Health. (2020). 2020–2030 strategic plan for NIH nutrition research. A report of the NIH nutrition research Task force. Retrieved from https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/strategic-plan-nih-nutrition-research.

Nettleton, J. A., Diez-Roux, A., Jenny, N. S., Fitzpatrick, A. L., & Jacobs, D. R., Jr. (2008). Dietary patterns, food groups, and telomere length in the Multi-Ethnic Study of Atherosclerosis (MESA). *The American Journal of Clinical Nutrition, 88*(5), 1405–1412. https://doi.org/10.3945/ajcn.2008.26429

Nielsen, D. E., & El-Sohemy, A. (2014). Disclosure of genetic information and change in dietary intake: A randomized controlled trial. *PLoS One, 9*(11), Article e112665. https://doi.org/10.1371/journal.pone.0112665

Olstad, D. L., & McIntyre, L. (2019). Reconceptualising precision public health. *BMJ Open, 9*(9). https://doi.org/10.1136/bmjopen-2019-030279. e030279-e030279.

Ordovas, J. M., Ferguson, L. R., Tai, E. S., & Mathers, J. C. (2018). Personalised nutrition and health. *BMJ*, 361. https://doi.org/10.1136/bmj.k2173

Oulas, A., Pavloudi, C., Polymenakou, P., Pavlopoulos, G. A., Papanikolaou, N., Kotoulas, G., … Iliopoulos, l. (2015). Metagenomics: Tools and insights for analyzing next-generation sequencing data derived from biodiversity studies. *Bioinformatics and Biology Insights, 9*, Article S12462. https://doi.org/10.4137/bbi.S12462. BBI.

Panaretos, D., Koloverou, E., Dimopoulos, A. C., Kouli, G. M., Vamvakari, M., Tzavelas, G., et al. (2018). 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. *British Journal of Nutrition, 120*(3), 326–334. https://doi.org/10.1017/S0007114518001150

Paul, L. (2011). Diet, nutrition and telomere length. *The Journal of Nutritional Biochemistry, 22*(10), 895–901. https://doi.org/10.1016/j.jnutbio.2010.12.001

Pauwels, S., Ghosh, M., Duca, R. C., Bekaert, B., Freson, K., Huybrechts, I., et al. (2017). Maternal intake of methyl-group donors affects DNA methylation of metabolic genes in infants. *Clinical Epigenetics, 9*, 16. https://doi.org/10.1186/s13148-017-0321-y

Perez-Martinez, P., Yiannakouris, N., Lopez-Miranda, J., Arnett, D., Tsai, M., Galan, E., et al. (2008). Postprandial triacylglycerol metabolism is modified by the presence of genetic variation at the perilipin (PLIN) locus in 2 white populations. *American Journal of Clinical Nutrition, 87*(3), 744–752. https://doi.org/10.1093/ajcn/87.3.744

Picó, C., Serra, F., Rodríguez, A. M., Keijer, J., & Palou, A. (2019). Biomarkers of nutrition and health: New tools for new approaches. *Nutrients, 11*(5), 1092. https://doi.org/10.3390/nu11051092

Ramos-Lopez, O., Cuervo, M., Goni, L., Milagro, F. I., Riezu-Boj, J. I., & Martinez, J. A. (2020). Modeling of an integrative prototype based on genetic, phenotypic, and environmental information for personalized prescription of energy-restricted diets in overweight/obese subjects. *The American Journal of Clinical Nutrition, 111*(2), 459–470. https://doi.org/10.1093/ajcn/nqz286

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

Ramos-Lopez, O., Milton-Laskibar, I., Martínez, J. A., San-Cristobal, C. R., & Portillo, M. P. (2021). Precision nutrition based on phenotypical traits and the (epi) genotype: Nutrigenetic and nutrigenomic approaches for obesity care. *Current Opinion in Clinical Nutrition and Metabolic Care, 24*(4), 315–325. https://doi.org/10.1097/mco.0000000000000754

Ramos-Lopez, O., Samblas, M., Milagro, F. I., Zulet, M. A., Mansego, M. L., Riezu-Boj, J. I., et al. (2018). Association of low dietary folate intake with lower CAMKK2 gene methylation, adiposity, and insulin resistance in obese subjects. *Nutrition research (New York, N.Y.), 50*, 53–62. https://doi.org/10.1016/j.nutres.2017.11.007

Roager, H. M., Vogt, J. K., Kristensen, M., Hansen, L. B. S., Ibrügger, S., Mærkedahl, R. B., et al. (2019). 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, 68*(1), 83–93. https://doi.org/10.1136/gutjnl-2017-314786

Roth, G. A., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., et al. (2018). Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: A systematic analysis for the global burden of disease study 2017. *The Lancet, 392*(10159), 1736–1788. https://doi.org/10.1016/S0140-6736(18)32203-7

San-Cristobal, R., Milagro, F. I., & Martínez, J. A. (2013). Future challenges and present ethical considerations in the use of personalized nutrition based on genetic advice. *Journal of the Academy of Nutrition and Dietetics, 113*(11), 1447–1454. https://doi.org/10.1016/j.jand.2013.05.028

Samblas, M., Milagro, F. I., Gómez-Abellán, P., Martínez, J. A., & Garaulet, M. (2016). Methylation on the Circadian Gene BMAL1 Is Associated with the Effects of a Weight Loss Intervention on Serum Lipid Levels. *Journal of biological rhythms, 31*(3), 308–317. https://doi.org/10.1177/0748730416629247.

Sánchez-Cabo, F., Rossello, X., Fuster, V., Benito, F., Manzano, J. P., Silla, J. C., et al. (2020). Machine learning improves cardiovascular risk definition for young, asymptomatic individuals. *Journal of the American College of Cardiology, 76*(14), 1674–1685. https://doi.org/10.1016/j.jacc.2020.08.017

Sarker, I. H. (2021). Machine learning: Algorithms, real-world applications and research directions. *SN computer science, 2*(3), 160. https://doi.org/10.1007/s42979-021-00592-x

Sempionatto, J. R., Montiel, V. R., Vargas, E., Teymourian, H., & Wang, J. (2021). Wearable and mobile sensors for personalized nutrition. *ACS Sensors, 6*(5), 1745–1760. https://doi.org/10.1021/acssensors.1c00553

Simopoulos, A. P. (2010). Nutrigenetics/nutrigenomics. *Annual Review of Public Health, 31*, 53–68. https://doi.org/10.1146/annurev.publhealth.031809.130844

Slokenberga, S., Tzortzatou, O., Howard, H. C., Romano, V., Soulier, A., & Niemiec, E. (2019). *Analysis of the legal and human rights requirements for genomics in and outside the EU*. https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5c2e1586f&appId=PPGMS.

Smith, E., Ericson, U., Hellstrand, S., Orho-Melander, M., Nilsson, P. M., Fernandez, C., et al. (2022). A healthy dietary metabolic signature is associated with a lower risk for type 2 diabetes and coronary artery disease. *BMC Medicine, 20*(1), 122. https://doi.org/10.1186/s12916-022-02326-z

Smith, C. E., Tucker, K. L., Yiannakouris, N., Garcia-Bailo, B., Mattei, J., Lai, C.-Q., et al. (2008). Perilipin polymorphism interacts with dietary carbohydrates to modulate anthropometric traits in Hispanics of caribbean origin. *Journal of Nutrition, 138*(10), 1852–1858. https://doi.org/10.1093/jn/138.10.1852

Sparks, J. A., Iversen, M. D., Yu, Z., Triedman, N. A., Prado, M. G., Miller Kroouze, R., et al. (2018). Disclosure of personalized rheumatoid arthritis risk using genetics, biomarkers, and lifestyle factors to motivate health behavior improvements: A randomized controlled trial. *Arthritis Care & Research, 70*(6), 823–833. https://doi.org/10.1002/acr.23411

Springmann, M., Spajic, L., Clark, M. A., Poore, J., Herforth, A., Webb, P., et al. (2020). The healthiness and sustainability of national and global food based dietary guidelines: Modelling study. *BMJ, 370*, m2322. https://doi.org/10.1136/bmj.m2322

Talwar, D., Tseng, T.-S., Foster, M., Xu, L., & Chen, L.-S. (2016). Genetics/genomics education for nongenetic health professionals: A systematic literature review. *Genetics in Medicine, 19*, 725. https://doi.org/10.1038/gim.2016.156

Thaiss, C. A., Itav, S., Rothschild, D., Meijer, M. T., Levy, M., Moresi, C., et al. (2016). Persistent microbiome alterations modulate the rate of post-dieting weight regain. *Nature, 540*(7634), 544–551. https://doi.org/10.1038/nature20796

Tobi, E. W., Goeman, J. J., Monajemi, R., Gu, H., Putter, H., Zhang, Y., et al. (2014). DNA methylation signatures link prenatal famine exposure to growth and metabolism. *Nature Communications, 5*, 5592. https://doi.org/10.1038/ncomms6592

de Toro-Martín, J., Arsenault, B. J., Després, J. P., & Vohl, M. C. (2017). Precision nutrition: A review of personalized nutritional approaches for the prevention and management of metabolic syndrome. *Nutrients, 9*(8), 913. https://doi.org/10.3390/nu9080913

Ulven, S. M., Holven, K. B., Rundblad, A., Myhrstad, M. C. W., Leder, L., Dahlman, I., et al. (2019). An isocaloric nordic diet modulates RELA and TNFRSF1A gene expression in peripheral blood mononuclear cells in individuals with metabolic syndrome—a SYSDIET sub-study. *Nutrients, 11*(12), 2932. Retrieved from https://www.mdpi.com/2072-6643/11/12/2932.

Vahid, F., Zand, H., Nosrat-Mirshekarlou, E., Najafi, R., & Hekmatdoost, A. (2015). The role dietary of bioactive compounds on the regulation of histone acetylases and deacetylases: A review. *Gene, 562*(1), 8–15. https://doi.org/10.1016/j.gene.2015.02.045

Vangay, P., Johnson, A. J., Ward, T. L., Al-Ghalith, G. A., Shields-Cutler, R. R., Hillmann, B. M., et al. (2018). US immigration westernizes the human gut microbiome. *Cell, 175*(4). https://doi.org/10.1016/j.cell.2018.10.029, 962-972. e910.

Vilne, B., Ķibilds, J., Siksna, I., Lazda, I., Valciņa, O., & Krūmiņa, A. (2022). Could artificial intelligence/machine learning and inclusion of diet-gut microbiome interactions improve disease risk prediction? Case study: Coronary artery disease. *Frontiers in Microbiology, 13*, Article 627892. https://doi.org/10.3389/fmicb.2022.627892

Xiao, X., Shi, D., Liu, L., Wang, J., Xie, X., Kang, T., et al. (2011). Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. *PLoS One, 6*(8), Article e22934. https://doi.org/10.1371/journal.pone.0022934

Yu, D., Yang, Y., Long, J., Xu, W., Cai, Q., Wu, J., et al. (2021). Long-term diet quality and gut microbiome functionality: A prospective, shotgun metagenomic study among urban Chinese adults. *Current Developments in Nutrition, 5*(4). https://doi.org/10.1093/cdn/nzab026. nzab026-nzab026.

Zeevi, D., Korem, T., Zmora, N., Israeli, D., Rothschild, D., Weinberger, A., et al. (2015). Personalized nutrition by prediction of glycemic responses. *Cell, 163*(5), 1079–1094. https://doi.org/10.1016/j.cell.2015.11.001