

REVIEW

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Nutrigenomics meets multi-omics: integrating genetic, metabolic, and microbiome data for personalized nutrition strategies

Alireza Nourazarain¹ and Yashar Vaziri^{2*}

Abstract

The integration of multi-omics technologies with computational biology has had a profound impact on nutritional science, enabling the development of precision nutrition strategies tailored to individual biochemical profiles. This review synthesizes recent advances in integrating genomic, epigenetic, transcriptomic, proteomic, metabolomic, and microbiome data for personalized dietary interventions. The present study analyzed machine learning approaches, with a particular focus on transformer and graph neural networks, for the processing of multi-omics data and prediction of metabolic outcomes. Advanced computational models have demonstrated an accuracy rate of over 90% in predicting individual metabolic responses to dietary interventions. Large-scale clinical trials (PREDICT, FOOD4ME, and PRECISION-HEALTH) have demonstrated significant improvements in weight management, glycemic control, and dietary adherence compared with conventional approaches. Digital health technologies, including continuous glucose monitoring and artificial intelligence (AI)-powered applications, facilitate real-time physiological monitoring and enable dynamic nutritional adjustments in patients with diabetes. The paradigm shift from population-based dietary recommendations to individualized interventions is represented by multi-omics-driven precision nutrition. The integration of sophisticated computational methodologies with comprehensive biological profiling provides a unique opportunity to prevent and manage chronic diseases via targeted dietary interventions. However, the successful implementation of such a system necessitates interdisciplinary collaboration among biologists, computational scientists, clinicians, and policymakers to ensure equitable access and ethical deployment of the technology. Future research should focus on developing scalable implementation frameworks, establishing evidence-based clinical practice guidelines to standardize multi-omics applications in precision nutrition, and identifying strategies to address potential disparities in access to these applications.

Clinical trial number

Not applicable.

Keywords Precision nutrition, Nutrigenomics, Metabolomics, Gastrointestinal microbiome, AI

*Correspondence:

Yashar Vaziri

yasharvaziri@iau.ac.ir

¹Department of Basic Medical Sciences, Khoy University of Medical Sciences, Khoy, Iran

²Department of Nutrition and Dietetics, Sara.C., Islamic Azad University, Sarab, Iran



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Introduction

The transition from population-based dietary guidelines to personalized nutrition represents a significant advancement in contemporary healthcare, fundamentally altering our understanding of how individuals respond to nutritional interventions (Table 1). Personalized nutrition can be defined as the science of tailoring dietary recommendations to an individual's unique genetic, metabolic, microbiome, epigenetic, and lifestyle profiles to optimize health outcomes and prevent disease, moving beyond one-size-fits-all models to account for inter-individual variability in nutrient metabolism and response [17, 18]. This paradigm shift is catalyzed by three significant factors: unprecedented developments in genomics and multi-omics technologies, advancements in AI, and a growing recognition that genetic, metabolic, and environmental factors create unique nutritional requirements for each individual [15, 22]. Building upon these foundational drivers, the evolution of nutrigenomics since the Human Genome Project exemplifies how genomic insights have progressively informed personalized dietary strategies.

Following the culmination of the Human Genome Project in 2003, nutrigenomics has undergone substantial development. A multitude of genome-wide association

studies (GWAS) have identified over 1,247 genetic loci associated with nutrient metabolism, food behaviors, and dietary responses in various populations [23, 24]. The advent of the novel Coronavirus Disease 2019 (COVID-19) pandemic has sparked an increasing interest in the field of personalized nutrition. Indeed, studies have shown how genetic variants in ACE2, TMPRSS2, and immune-related genes alter the efficacy of various nutritional interventions for immune support and disease prevention [25, 26]. The global precision nutrition market was valued at \$8.2 billion in 2023 and is projected to reach \$24.6 billion by 2028 [27], primarily driven by heightened consumer awareness, technological advancements, and mounting evidence of clinical efficacy [18]. Precision nutrition services are now being offered by over 127 health systems, with accessibility facilitated through electronic health records (EHRs). In addition, over 50 companies offer personalized nutrition recommendations to consumers, which are derived from genetic testing and multi-omics profiling [28]. These market dynamics not only reflect growing clinical adoption but also highlight the economic imperatives for integrating omics data into routine practice. Traditional dietary recommendations, exemplified by tools such as the National Food Pyramid and the Dietary Guidelines for Americans,

Table 1 Definitions of key terms in nutrigenomics and Multi-Omics for personalized nutrition

Term	Definition
Nutrigenomics	The study of how bioactive food components and nutrients interact with an individual's genome to influence gene expression, metabolic pathways, and health outcomes, enabling tailored dietary interventions ADDIN EN.CITE [1, 2]
Epigenomics	The comprehensive analysis of epigenetic modifications (e.g., DNA methylation, histone alterations) across the genome that regulate gene activity without altering the DNA sequence, often influenced by diet and environment [1, 2]
Transcriptomics	The large-scale study of the complete set of RNA transcripts (transcriptome) produced by the genome under specific conditions, revealing dynamic gene expression responses to nutritional stimuli [3, 4]
Proteomics	The systematic identification and quantification of all proteins (proteome) in a biological system, offering functional insights into active pathways influenced by diet [5, 6]
Metabolomics	The comprehensive profiling of small-molecule metabolites in cells, tissues, or biofluids captures real-time snapshots of metabolic responses to nutritional inputs [7, 8]
Microbiomics	The study of the composition, diversity, and functional dynamics of microbial communities (microbiome), particularly in the gut, and their interactions with host nutrition and metabolism [9, 10]
AI	Computational systems that perform tasks requiring human-like intelligence, such as pattern recognition in multi-omics data, can predict health outcomes and personalize interventions [11, 12]
ML (Machine Learning)	A subset of AI involving algorithms that learn from data patterns to make predictions or decisions without explicit programming, commonly used to integrate omics datasets for nutritional phenotyping [13, 14]
Personalized Nutrition	Dietary recommendations should be tailored to an individual's unique genetic, metabolic, microbiome, lifestyle, and environmental factors to optimize health and prevent disease [15, 16]
Precision Nutrition	A data-driven approach using advanced analytics (e.g., multi-omics and AI) to deliver highly accurate, individualized nutritional strategies, often emphasizing scalability and clinical validation [17, 18]
Tensor Decomposition	A multivariate statistical technique that decomposes high-dimensional multi-omics tensors (e.g., integrating genomic, transcriptomic, and metabolomic layers) into latent factors to reveal cross-omics interactions and predict nutritional phenotypes, such as dietary responses in precision nutrition [19]
Matrix-Based Methods	Approaches like matrix factorization that reduce dimensionality of multi-omics datasets by approximating large matrices into lower-rank components, enabling the identification of shared biological pathways for integrated analysis of genetic metabolic interactions in nutrigenomics [20]
LightGBM (Light Gradient Boosting Machine)	A scalable gradient boosting framework optimized for high-dimensional data, used in multi-omics to ensemble decision trees for accurate prediction of disease risks or metabolic outcomes, outperforming traditional models in nutrigenomic applications like microbiome-disease associations [21]

were developed to prevent population-level diseases and avoid nutrient deficiencies. However, mounting evidence demonstrates substantial inter-individual variation in responses to identical dietary interventions, with genetic, epigenetic, metabolic, and microbial factors contributing to this heterogeneity [17, 29]. For instance, individuals with specific polymorphisms in genes such as *APOE*, *FTO*, and *MTHFR* exhibit markedly different responses to dietary fat, carbohydrates, and folate supplementation, respectively [30, 31].

Transitioning from these genetic foundations to broader biological networks, the multi-omics approach reveals the complex interplay shaping nutritional phenotypes. The integration of multiple omics layers—genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics—has revealed the complex biological networks underlying nutritional responses. Recent advances in single-cell sequencing technologies, real-time metabolomic monitoring, and AI have enabled researchers to map these interactions with unprecedented resolution, identifying specific molecular signatures that predict individual responses to dietary interventions [32, 33]. Incorporating temporal dimensions, such as chronogenomics, adds precision by linking genetic clocks to optimal dietary timing.

Emerging research in chronogenomics reveals that genetic variants in circadian clock genes (*CLOCK*, *PER1*, *CRY1*) significantly influence optimal meal timing and macronutrient distribution. Studies show 34% improvement in metabolic outcomes when dietary interventions align with individual chronotype genetics, highlighting the temporal dimension of personalized nutrition [34]. This comprehensive review synthesizes current knowledge on precision nutrition and its clinical potential, with particular focus on multi-omics integration strategies, technological innovations, implementation challenges, and future directions. We examine landmark clinical trials demonstrating the superiority of personalized approaches, analyze the role of digital health technologies in scaling precision nutrition, and address critical considerations, including cost-effectiveness, accessibility, and ethical implications. Our interdisciplinary perspective combines molecular biology, computational science, clinical medicine, and public health to provide a roadmap for the future of personalized nutrition in healthcare systems worldwide. To contextualize these advancements with empirical evidence, meta-analyses of clinical trials have highlighted the tangible benefits of precision approaches compared to traditional methods.

The corpus of evidence about precision nutrition has expanded exponentially in recent years. Indeed, since the initial meta-analysis of randomized controlled trials, the outcomes of precision nutrition have repeatedly demonstrated superiority over conventional dietary counseling.

The significant endpoints of weight reduction, glycemic control, lipid control, and long-term dietary adherence will exhibit effect sizes of 0.4–0.8 [35, 36]. This contributes to the formulation of a compelling clinical and economic rationale for the broader implementation of precision nutrition approaches. This rationale is based on two key factors. First, the mounting burden of diet-related chronic diseases underscores the necessity for more targeted interventions. Second, the failure of one-size-fits-all interventions highlights the importance of precision nutrition in addressing these complex health issues.

This review aims to synthesize recent advances in multi-omics integration for personalized nutrition strategies, providing examples of research utilizing genomics (e.g., polygenic risk scores predicting type 2 diabetes outcomes), metabolomics (e.g., metabolotyping for glycemic response forecasting), and microbiome profiling (e.g., enterotype-based fiber interventions enhancing short-chain fatty acid (SCFA) production and reducing inflammation).

Understanding the omics layers: a systems biology approach

As precision nutrition evolves, a systems biology lens is essential to dissect the hierarchical omics layers, each contributing uniquely yet interdependently to metabolic individuality. Precision nutrition practitioners perform a systematic analysis of multiple layers of biology, including genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiome layers. Each distinct layer provides unique insights into the individual metabolic phenotypes while highlighting the interconnected nature of these processes. This strategy utilizes multiple biomarkers. Specifically, these biomarkers provide a comprehensive overview of the interplay between genetic factors, environmental toxins, and lifestyle choices in shaping health outcomes. Additionally, incorporating nutrients facilitates the analysis of biomarkers [22, 28].

The various layers of omics adhere to a hierarchy of information. Genomic variants have been demonstrated to be the primary determinants of an organism's fundamental metabolic capacities. Epigenomic modifications are critical for enabling networks to respond to changes in the cellular environment. Transcriptomic patterns have been shown to indicate the real-time state of cells. Proteomic profiles have been demonstrated to serve as indicators of currently active pathways. The determination of metabolomic signatures is contingent on flux. The composition of the microbiome provides insights into nutrient processes and nutrient bioavailability. This foundational hierarchy sets the stage for exploring genomics as the bedrock of nutritional variability, from which dynamic layers build upon static genetic blueprints.

Recognizing these interconnections enables more precise predictions of how individuals respond to specific dietary strategies.

Genomics: the foundation of nutritional individuality

Based on this omics framework, genomics offers a static blueprint for metabolic potential. They have evolved from single gene studies to polygenic models that capture cumulative genetic influences.

Nutrigenomics and polygenic risk scores

The field of modern Nutrigenomics has evolved from the study of candidate genes to the analysis of polygenic risk scores (PRS), which reflect the cumulative impact of thousands of genes on nutritional effects. The 2024 All of Us Research Program analysis identified 1,247 genetic variants that influence dietary responses across diverse populations, leading to significantly improved prediction accuracy for precision nutrition interventions [37]. These PRS models achieved area under the curve (AUC) values of 0.75–0.85 for predicting responses to major dietary patterns, thereby demonstrating substantial superiority over clinical risk factors [38]. Extending these polygenic insights, recent genomic research illuminates' ancestry-specific variations in diabetes risk, bridging genetic architecture to pathway-level mechanisms. Recent studies on the genome have demonstrated that certain non-traditional factors influence the likelihood of developing Type 2 Diabetes. Furthermore, the gene exhibits variation. These genes are implicated in changes associated with the *mTOR*, *AMPK*, *FXR*, and *TGR5* signaling pathways. Changes in allele frequencies and effect sizes among ancestry groups have emerged as significant biological considerations for genetic architecture. As demonstrated by De la Peña-Armada et al. (2025), variants in the *AMY1* gene affecting starch digestion exhibit an order of magnitude difference in frequency between populations that have historically consumed high versus low starch diets [39].

Key genetic variants and functional impacts

FTO gene variants and metabolic regulation: The fat Mass and Obesity-Associated (*FTO*) gene has been identified as a highly reliable genetic predictor of dietary response variability [40]. Recent functional studies on *FTO* have revealed mechanisms beyond appetite regulation, implicating it in mitochondrial metabolism and thermogenesis through its influence on energy homeostasis and adipocyte differentiation [2]. Individuals carrying specific genetic variants, such as the rs9939609 risk allele, tend to exhibit divergent responses to different dietary fat types and amounts. As demonstrated in recent analyses, such individuals exhibited 23% higher weight gain on diets high in saturated fat; however, their weight gain was attenuated

when supplemented with medium-chain triglycerides [40, 41]. A recent clinical trial demonstrated that personalized interventions targeting *FTO* carriers, focusing on improving fat quality (e.g., prioritizing unsaturated and medium-chain fats) rather than quantity, resulted in a 34% increase in the efficacy rate, defined as the proportion achieving $\geq 5\%$ body weight reduction compared to standard low-fat diets [41].

MTHFR variants and One-Carbon metabolism: The methylenetetrahydrofolate reductase (*MTHFR*) gene encodes an enzyme critical for folate metabolism and one-carbon transfer reactions, influencing DNA methylation and homocysteine remethylation [42]. Common polymorphisms, particularly C677T (rs1801133) and A1298C (rs1801131), reduce enzymatic activity by 30–70%. This reduction leads to elevated homocysteine levels and disrupted methylation levels. The global prevalence of the homozygous C677T variant ranges from 10% to 20% across populations [43, 44].

Clinically, these variants are associated with increased cardiovascular disease (CVD) risk; a 2023 meta-analysis of 66 studies ($n = 37,263$) demonstrated that C677T carriers have a 13–20% higher odds of myocardial infarction (MI) under dominant (OR = 1.16, 95% CI:1.06–1.28, $P = 0.008$) and recessive (OR = 1.20, 95% CI:1.12–1.28, $P < 0.001$) models, with similar but marginally significant associations for A1298C (recessive OR = 1.27, 95% CI:1.06–1.51, $P = 0.008$), underscoring the need for genetic screening in CVD prevention [44]. Cognitively, the TT genotype independently elevates risk for progression and impairment in cerebral small vessel disease patients (OR = 2.45, 95% CI:1.32–4.55, $P = 0.005$), linking hyperhomocysteinemia to neurodegenerative pathways [45]. Epigenetically, variants impair global DNA methylation, but supplementation can restore methylation profiles, as shown in a 2024 randomized trial in which folic acid increased methylation in metabolic genes by 15–25% in variant carriers [46]. This underscores the necessity of personalized folate recommendations: compound heterozygous variants require 800–1200 μg daily to optimize methylation, versus 400 μg for wild-type variants, based on recent biomarker studies [47]. It is imperative to acknowledge that the efficacy of folic acid supplementation varies by genetic profile, supporting tailored interventions to mitigate CVD, cognitive, and epigenetic risks [42].

Chronogenomic variants: Genetic variations in circadian clock genes result in considerable interindividual differences in meal timing and macronutrient distributions. Variants of the *CLOCK* gene have been shown to regulate rhythms of insulin sensitivity. Individuals who carried the minor alleles exhibited a 40% greater glycemic response to

breakfast than to dinner. Variants of the gene *PER2* have been shown to influence melatonin production in individuals. Additionally, these variants may influence the relationship between sleep and metabolism. Consequently, there is a need to adapt feeding schedules to individual chronotypes to optimize metabolism [34].

Pharmacogenomics-Nutrition interactions

A significant body of clinical recommendations has emerged from the intersection of pharmacogenomics and nutrition. Genetic variations that affect drug metabolism also affect nutrient metabolism, providing opportunities for combination therapies. It has been demonstrated that variations in *CYP2D6* can affect the conversion of dietary precursors into bioactive forms and the metabolism of drugs. Similarly, variations in ATP synthase (ATP)-binding cassette transporters (ABC transporters) can modify drug efflux and nutrient absorption. Consequently, both factors must be integrated into patient treatment [48].

Epigenomics and transcriptomics: dynamic environmental interfaces

Single-cell epigenomic profiling

Advancements in single-cell epigenomic technologies have provided remarkable insights into tissue- and cell type-specific responses to dietary interventions, offering unprecedented resolution. Single-cell CUT&Tag and ATAC-seq techniques have evolved to map chromatin accessibility and histone modifications at the single-cell level, thereby revealing heterogeneous responses in tissues previously considered homogeneous [2]. The results of experiments employing these methods demonstrated that diets with a high polyphenol content induced distinct histone modifications in hepatocytes, adipocytes, and immune cells after 2 weeks. Furthermore, histone modification demonstrated a strong correlation with enhanced insulin responses and reduced inflammatory markers.

Longitudinal single-cell epigenome-wide association studies (scEWAS) have altered our understanding of how diet influences chromatin over time. According to the extant literature, the positive epigenetic changes resulting from adherence to the Mediterranean diet manifest in waves. This indicates that the initial phases encompass the activation of metabolic genes during weeks 1 and 2. Subsequently, inflammatory and immune regulatory changes occur in weeks 3–8. Recent studies have identified individual variations in epigenetic responsiveness as significant predictors of intervention success. Furthermore, participants who demonstrated rapid epigenetic responses showed significant improvements in metabolic biomarkers, including reduced homocysteine levels, increased serum folate, and lowered LDL-C, linked to polyphenol-driven DNA methylation changes

in a polyphenol-rich green Mediterranean diet intervention [49].

Nutrient-specific epigenetic modifications

Methyl Donor Nutrients: The availability of methyl donors (folate, methionine, choline, betaine) has been demonstrated to be associated with a variety of DNA methylation patterns, as evidenced by high-resolution methylome mapping. Methylation signatures indicative of specific nutritional deficiencies can be identified using a targeted bisulfite sequencing panel. Methylation recovery following supplementation varies over time, by genomic region, and by baseline methylation status. However, methylation of CpG islands in metabolic genes exhibits the most rapid recovery [1].

Epigenetic alterations induced by dietary polyphenols, such as those from green tea, berries, and olive oil, have distinct epigenetic signatures. These compounds have been demonstrated to possess anti-inflammatory and cardioprotective properties. Researchers have identified new enhancer regions that respond to polyphenols. Following ingestion, these substances become accessible and enhance the expression of antioxidant and detoxifying genes. The detection of changes in response to drug consumption is possible within hours, and the effects of chronic intake can be observed [50, 51].

Transcriptomic responses to dietary interventions

Transitioning from fixed epigenetic signatures to fluid gene activity, transcriptomics tracks immediate cellular shifts to nutritional signals, unveiling how genotypes interact with diets to reshape metabolism [3, 4]. Transitioning from fixed epigenetic signatures to fluid gene activity, transcriptomics tracks immediate cellular shifts to nutritional signals, unveiling how genotypes interact with diets to reshape metabolism [3, 4]. These genetically influenced transcriptomic alterations underpin the effectiveness of the ketogenic diet, underscoring the need for bespoke metabolic evaluations. Notably, ketogenic regimens upregulate fatty acid oxidation, ketogenesis, and gluconeogenesis while downregulating glycolysis, with transition speeds tied to variants. Baseline metabolic adaptability forecasts adherence success, rendering efficacy genotype-dependent [52, 53].

Transgenerational epigenetic effects

Emerging evidence indicates that dietary patterns can influence epigenetic marks in germ cells, potentially affecting offspring's health through transgenerational inheritance. Studies in humans have documented associations between parental diet quality and offspring methylation patterns at birth, with implications for metabolic programming and disease risk. This research emphasizes the broader impact of precision nutrition, beyond

individual health, on family and population-level outcomes [54, 55].

Proteomics: functional readouts of nutritional status

Advanced proteomic technologies and applications

The present-day proteomic methodologies are predicated on high-throughput mass spectrometry, aptamer-based arrays, and proximity extension assays for the concurrent quantification of thousands of proteins from a biological sample [5, 6]. These instruments can detect subtle alterations in protein expression following dietary modifications, thereby providing functional readouts that establish a correlation between genetic predisposition and the observed phenotype. Recent advancements in the quantitative accuracy and reproducibility of data-independent acquisition (DIA) mass spectrometry have notably increased the suitability of proteomics for clinical applications [56].

We have developed targeted proteomic panels focusing on inflammation, metabolism, and cardiovascular health for nutrition research [57, 58]. These assessments can quantify key biomarkers within 24 to 48 h after dietary modification, thereby assessing the efficacy of the intervention. High-sensitivity assays for inflammatory markers (e.g., C-reactive protein, interleukin-6, and tumor necrosis factor alpha) and metabolic hormones (e.g., insulin, leptin, and adiponectin) provide immediate feedback on dietary regimens [59, 60].

Diet-Induced proteomic signatures

Inflammatory response patterns: A growing body of research has demonstrated that high-fat diets consistently yield proteomic signatures characterized by elevated pro-inflammatory proteins and reduced anti-inflammatory mediators [61]. However, individual genetic backgrounds have been demonstrated to modulate these responses significantly. Individuals with specific gene variants in CRP exhibit a heightened inflammatory response (2.3-fold increase) upon ingestion of saturated fat. In contrast, individuals who carry specific IL-6 promoter polymorphisms show a more favorable response to omega-3 fatty acids in inflammation resolution [62].

Metabolic Pathway Activation: Proteomic profiling reveals distinct metabolic pathway signatures associated with different dietary patterns [63]. The Mediterranean diet has been shown to increase the levels of proteins that aid in disease prevention and provide energy to the cells. These proteins play crucial roles in regulating blood sugar levels. A ketogenic diet has a similar effect but emphasizes fats. Measurable alterations in clinical biomarkers frequently manifest after metabolic changes in response to interference [64, 65]. These proteomic changes often precede measurable changes in clinical biomarkers, providing early indicators of intervention success [66].

Temporal dynamics and personalized applications

The temporal dynamics of proteomic responses vary substantially between individuals and dietary interventions [67]. Acute-phase proteins peak within hours of a high-fat meal, whereas adaptive changes in metabolic enzymes occur over days to weeks. Understanding these temporal patterns enables optimization of intervention timing and monitoring schedules [68]. Some individuals exhibit prolonged inflammatory responses that require modified dietary approaches, while rapid metabolic adaptors may benefit from more frequent dietary cycling.

Nutritional proteomics—defined as the application of high-throughput proteomic technologies to investigate nutrient-protein interactions, dietary impacts on proteome dynamics, and biomarkers for nutritional status and personalized health interventions [69]—has the potential to facilitate the early identification of metabolic dysfunction and prediction of cardiovascular risk, in addition to monitoring responses to interventions [70]. These proteomic biomarker panels have been demonstrated to outperform conventional lipid panels in predicting cardiovascular events in specific populations [71, 72]. These applications are moving from research settings into clinical practice, with several commercial platforms now offering proteomic profiling for precision nutrition, such as Inside Tracker and SomaLogic's Soma Scan assay, which provide consumer-accessible insights into thousands of circulating proteins—including inflammatory markers (e.g., IL-6, hsCRP for immune response monitoring), metabolic indicators (e.g., ApoB, adiponectin for lipid and energy regulation), and nutritional status biomarkers (e.g., ferritin for iron stores, albumin for protein adequacy)—to generate actionable dietary plans aimed at reducing inflammation, enhancing metabolic flexibility, and correcting deficiencies [5, 28]. As research increasingly focuses on commercial applications, proteomic profiling is proliferating in health and wellness, as well as in personalized nutrition.

Metabolomics: real-time metabolic phenotyping

Advanced analytical platforms and technologies

Contemporary metabolomics platforms have been further enhanced by advanced analytical techniques, including nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography-mass spectrometry (LC-MS), and gas chromatography-mass spectrometry (GC-MS). These platforms offer comprehensive metabolite coverage, encompassing both polar and non-polar compounds [7]. These integrated analytical approaches enable researchers to capture a broader spectrum of the metabolome by leveraging the complementary strengths of each technique [73]. Recent advances in high-resolution mass spectrometry and ion mobility separation have expanded the detectable metabolome to over 50,000 features per

sample, enabling discovery of novel biomarkers and metabolic pathways [74, 75].

Targeted metabolomics panels focusing on specific metabolic pathways have been developed for clinical applications, providing absolute quantitation of key metabolites to guide personalized nutrition and monitor therapeutic responses. These panels rapidly assess amino acid metabolism (e.g., branched-chain amino acids like leucine and valine as indicators of insulin resistance and protein catabolism), lipid oxidation (e.g., acylcarnitines reflecting β -oxidation efficiency and fatty acid transport), energy metabolism (e.g., Krebs cycle intermediates such as citrate and succinate for mitochondrial function and bioenergetics), and gut microbiome-derived metabolites (e.g., SCFAs like butyrate for anti-inflammatory effects and fiber utilization), all with high precision and reproducibility [76, 77]. A notable example is Metabolon's targeted panels for microbiome and gut metabolome research, which quantify nine SCFAs from fiber fermentation and 21 bile acids involved in lipid digestion and *FXR/TGR5* signaling, facilitating biomarker identification for conditions like inflammatory bowel disease, diabetes, and metabolic syndrome through dietary interventions [78]. The development of standardized reference materials and quality control procedures has improved inter-laboratory comparability, facilitating translation to clinical practice [79–81].

Metabolic phenotyping and individual variation

The application of metabolomics enables the observation of an individual's metabolic processes at a specific time. Consequently, metabolomics facilitates the study of variations in nutrient processing, energy metabolism, and metabolic flexibility in individuals. Recent research indicates that postprandial metabolic processes, including the rates of sugar, fat, and protein processing, exhibit interindividual variability. Discrepancies in metabolism are closely associated with genetic factors, microbiome composition, and dietary habits [82, 83].

Several studies have identified distinct metabolomic signatures that subserve weight loss, insulin sensitivity, and metabolic health [21, 84]. For instance, in obese children undergoing weight loss interventions, metabolomic profiling revealed reduced levels of branched-chain amino acids (BCAAs, e.g., leucine and isoleucine) and acylcarnitines post-intervention, correlating with improved insulin sensitivity and a 15–20% enhancement in HOMA-IR scores, highlighting these as predictive biomarkers for metabolic flexibility [85]. Similarly, shifts in bile acids, such as elevated chenodeoxycholic acid following fiber-rich diets, have been linked to enhanced glycemic control and reduced inflammation in adults with prediabetes, with microbiome-derived signatures like

increased butyrate predicting 25% greater weight loss success [2].

Changes in BCAA, acylcarnitines, bile acids, and microbially derived metabolites are frequently indicators. Functional metabolomic profiles have shown promise for predicting how individuals respond to dietary interventions. The accuracy of the predictions currently exceeds 80% for multiple outcomes [86, 87]. This individual-level characterization through metabolic phenotyping lays the groundwork for metabolotyping, which refines these insights by classifying profiles into reproducible subgroups for targeted clinical strategies [88].

Metabolotyping and clinical applications

Metabolotyping represents the classification of individuals into distinct metabolic subgroups based on their metabolomic profiles [89]. Advanced machine learning algorithms applied to large metabolomic datasets have identified reproducible metabolotypes that respond differently to dietary interventions [90, 91]. For example, individuals with “lipogenic” metabolotypes show greater improvements in insulin sensitivity (e.g., 25% reduction in HOMA-IR) and weight loss efficacy (e.g., $\geq 5\%$ body weight reduction over 12 weeks) with low-carbohydrate diets, while “oxidative” metabolotypes exhibit enhanced glycemic control (e.g., 0.7% HbA1c decrease) and reduced inflammation markers when following high-fiber, plant-based approaches [92, 93]. Clinical implementation of metabolomics-guided nutrition is advancing through integration with EHR and clinical decision support systems [73, 94, 95]. Point-of-care metabolomic devices are in development, promising to bring real-time metabolic assessment to clinical settings [96]. Early studies suggest that metabolomics-guided interventions improve patient outcomes and reduce healthcare costs by enabling more precise therapeutic targeting [97, 98].

Integration challenges and future directions

Significant advancements have been made in metabolomics; however, standardizing platforms, developing reference ranges, and interpreting metabolomic data continue to pose challenges. The metabolome is a dynamic system; therefore, the timing and method of sample collection and storage are of paramount importance in metabolomics studies. The integration of omics layers with other disciplines requires the effective use of computational tools to manage high-dimensional, multimodal data [20]. Imminent advancements in this field are poised to expand metabolome coverage, enhance quantitative precision, and cultivate user-friendly clinical interpretation tools. The integration of metabolomics with continuous monitoring technologies enables real-time optimization of nutritional interventions based on continuous assessment of metabolic profiles [99].

Microbiomics: the metabolic organ within Advanced microbiome profiling technologies

Current microbiome analysis has evolved from 16 S rRNA gene sequencing to comprehensive shotgun metagenomics, metatranscriptomics, and metaproteomics approaches that provide functional insights into microbial community activities [9]. Long-read sequencing technologies enable complete genome assembly of individual microorganisms, revealing strain-level variations that significantly impact metabolic capabilities and dietary responses [100]. Rapid sequencing platforms now enable microbiome analysis within 24–48 h, making real-time microbiome-guided dietary recommendations feasible [101]. Standardized sample collection protocols and reference databases have improved reproducibility and comparability across studies and clinical applications. The development of synthetic biology approaches for microbiome engineering opens new possibilities for therapeutic interventions [102].

Enterotypes and dietary response prediction

The enterotype concept has evolved from a taxonomically based microbiota configuration dominated by specific bacterial genera to a functionally based configuration capable of consuming predefined ecological resources [10]. The contemporary method of enterotyping involves analyzing significant functional genes involved in fiber breakdown, the development of SCFAs, bile acid metabolism, and xenobiotic processing. In the context of a high-fiber diet, individuals with a predominant abundance of *Prevotella* in their gut microbiome exhibit a more pronounced metabolic response to dietary interventions, characterized by a 45% greater increase in the production of beneficial metabolites (e.g., SCFAs such as butyrate) and improved levels of inflammatory markers (e.g., reduced C-reactive protein and interleukin-6) compared to those whose gut microbiomes are dominated by *Bacteroides* [103, 104]. Conversely, microbiomes comprising a substantial proportion of *Bacteroides* have been observed to exhibit enhanced processing efficiency for dietary fats and proteins. This observation suggests the presence of an optimal distribution of macronutrients, meticulously tailored to the characteristics of a specific microbiome [103]. The use of AI and microbiome functional profiles in prediction models has emerged as a sophisticated approach to accurately anticipate an individual's response to a specific dietary regimen. These models consider the composition of the microbiome and the completeness of the metabolic pathway. Recent investigations have demonstrated accuracies of over 85% for predicting glycemic responses and over 78% for predicting weight loss [84].

Microbiome-metabolite interactions

The integration of microbiome and metabolomic data reveals the crucial role of microbially derived metabolites in host health and dietary responses. SCFAs produced by microbial fiber fermentation serve as key signaling molecules affecting inflammation, metabolism, and immune function [105, 106]. Individual differences in SCFA production capacity correlate strongly with metabolic and inflammatory responses to dietary fiber interventions, including improvements in glycemic control and reductions in pro-inflammatory cytokines such as interleukin-6 [107, 108]. For instance, a 2024 multi-cohort study using shotgun metagenomics and targeted metabolomics showed that *Prevotella*-enriched microbiomes enhance butyrate production from soluble fibers like inulin, leading to a 20–30% greater reduction in HbA1c levels and IL-6 concentrations over 12 weeks compared to *Bacteroides*-dominant profiles, underscoring the need for fiber-type personalization in precision nutrition [104]. These microbiome-metabolite interactions highlight opportunities for tailored interventions to optimize host metabolic flexibility and reduce chronic disease risk.

Bile acid metabolism represents another critical microbiome-host interaction pathway. Specific bacterial strains possess bile acid-metabolizing enzymes that produce secondary bile acids with distinct physiological effects [109]. An individual's possession of these bacterial capacities influences their response to dietary fat and cholesterol-lowering interventions. Bacteria can synthesize polyphenols, which have been shown to possess anti-inflammatory properties and contribute to cardiovascular health. Humans can synthesize metabolites such as urolithin A from ellagitannins and equal from soy isoflavones. This phenomenon can vary from person to person owing to differences in microbiome composition. Consequently, there is ample opportunity to formulate phytonutrient recommendations guided by the gut microbiome [110].

Clinical translation and actionable biomarkers in microbiome-driven nutrition

Although microbiome profiling can enhance precision nutrition by identifying enterotypes, dysbiosis signatures, and metabolites that predict successful interventions, such as fiber or probiotic supplementation, most research continues to focus on identifying actionable, user-friendly biomarkers that facilitate real-time dietary changes [111]. For instance, recent multi-omics studies have validated fecal SCFA levels and alpha-diversity indices as proxies for the glycemic response to prebiotic fibers. Consequently, machine learning models have achieved 85% accuracy in stratifying responders in type 2 diabetes cohorts [112]. Despite these exciting findings from initial human trials, we must not get ahead

of ourselves; a significant limitation in translating this into clinical practice is the lack of robust long-term evidence supporting microbiome-based interventions. Most studies suffer from small sample sizes, methodological discrepancies in sequencing, inadequate regulatory oversight, and a hasty, rough showcase phase for microbiome-based products, which further hinders wider use. Future efforts should focus on large-scale randomized controlled trials with standardization to establish causality and cost-effectiveness, ensuring that microbiome applications are not only utilized in research settings but also provide evidence-based recommendations for routine nutritional care [113].

Microbiomics: insights into nutrient bioavailability and critical challenges

The gut microbiome is a beneficial bacterial ecosystem that helps digest food in the intestines. The beneficial effects include modulation of metabolism, production of SCFAs, and modulation of host immunity. These are potential targets for personalized nutrition using pre- and probiotics [114]. According to multi-omics studies, individual responses to dietary fibers and polyphenols are linked to microbiome composition. For a multi-country study on predicting postprandial glycemic excursions from microbial signatures, these studies used machine learning models that were 85% accurate [112]. Although there have been advances in microbiome research, translating microbiome data into clinical practice is premature, due to high inter-individual variability, methodological differences in sequencing protocols, and low reproducibility across cohorts [111, 115]. For example, dietary confounders and batch effects can mask causal relationships between specific microbial taxa and their metabolic outcomes. Longitudinal studies indicate that microbiome profiles are only modestly stable over time [83]. In addition, ethical issues regarding data privacy in microbiome biobanking and the unavailability of standardized functional assays, which hinder scalable implementation, indicate the need for larger trials across a more diverse population to validate predictions [116, 117]. Despite the significant potential of microbiome-guided precision nutrition, these limitations should temper expectations and foster cautious optimism about advancing from bench to bedside.

Multi-omics integration: systems-level nutritional profiling

The transition from single-omics to multi-omics analysis marks a paradigm shift in precision nutrition research and clinical applications. This shift is driven by the integration of sophisticated computational processes that systematically combine diverse categories of biological data to generate actionable nutritional information

with high precision and clinical relevance [20, 118]. For instance, multi-omics models integrating metabolomic, genomic, and clinical data have achieved predictive accuracies with an AUC of 0.90 for identifying metabolic responses to dietary interventions, enabling more targeted and effective personalized strategies [119].

Contemporary multi-omics integration employs advanced AI frameworks, including transformer and graph neural networks, as well as foundation models specifically designed for biological data (Fig. 1) [120, 121]. These approaches can handle the complexity, high dimensionality, and multiscale nature of omics data while identifying meaningful patterns that would be impossible to detect through single-layer analyses [117]. A key practical aspect of this workflow is the recommended 48–72-hour timeframe for sample collection following dietary interventions, which allows for the resolution of acute postprandial fluctuations while capturing early adaptive changes in transcriptomic, proteomic, and metabolomic profiles without introducing confounds from extended delays, such as circadian disruptions or microbial drift [122, 123]. This temporal window optimizes data quality for downstream AI-driven phenotyping, as demonstrated in longitudinal microbiome-metabolome studies where interventions were assessed over 72-hour periods to predict glycemic and inflammatory outcomes with >80% accuracy. Data standardization is paramount in multi-omics workflows to ensure reproducibility and interoperability across studies. Table 2 provides guidelines for standardizing key omics datasets, focusing on the harmonization protocols for genomic variants, metabolite quantification, and microbial profiling. These guidelines draw from recent consortia recommendations (e.g., ELIXIR and Metabolomics Standards Initiative) to address batch effects, reference ranges, and data fusion [80]. Exemplar biomarkers such as FTO (rs9939609 variant influencing fat metabolism and obesity risk), MTHFR (C677T polymorphism affecting folate one-carbon metabolism and CVD susceptibility), and GWAS-derived loci (e.g., >1,247 variants linked to nutrient responses) were selected for inclusion based on their high prevalence in nutrigenomic literature and validated predictive power in multi-omics models (AUC 0.75–0.85 for dietary response forecasting) [17, 37, 40]. These markers exemplify the guidelines' application, as they require standardized variant calling (e.g., via GATK pipelines), methylation-adjusted quantification, and pathway-level integration to mitigate ancestry-specific biases and enhance cross-cohort comparability (Fig. 2) [124, 125].

Advanced computational integration frameworks

Federated learning approaches Multi-institutional data integration encounters substantial challenges, including data privacy concerns, batch effects, and variations across

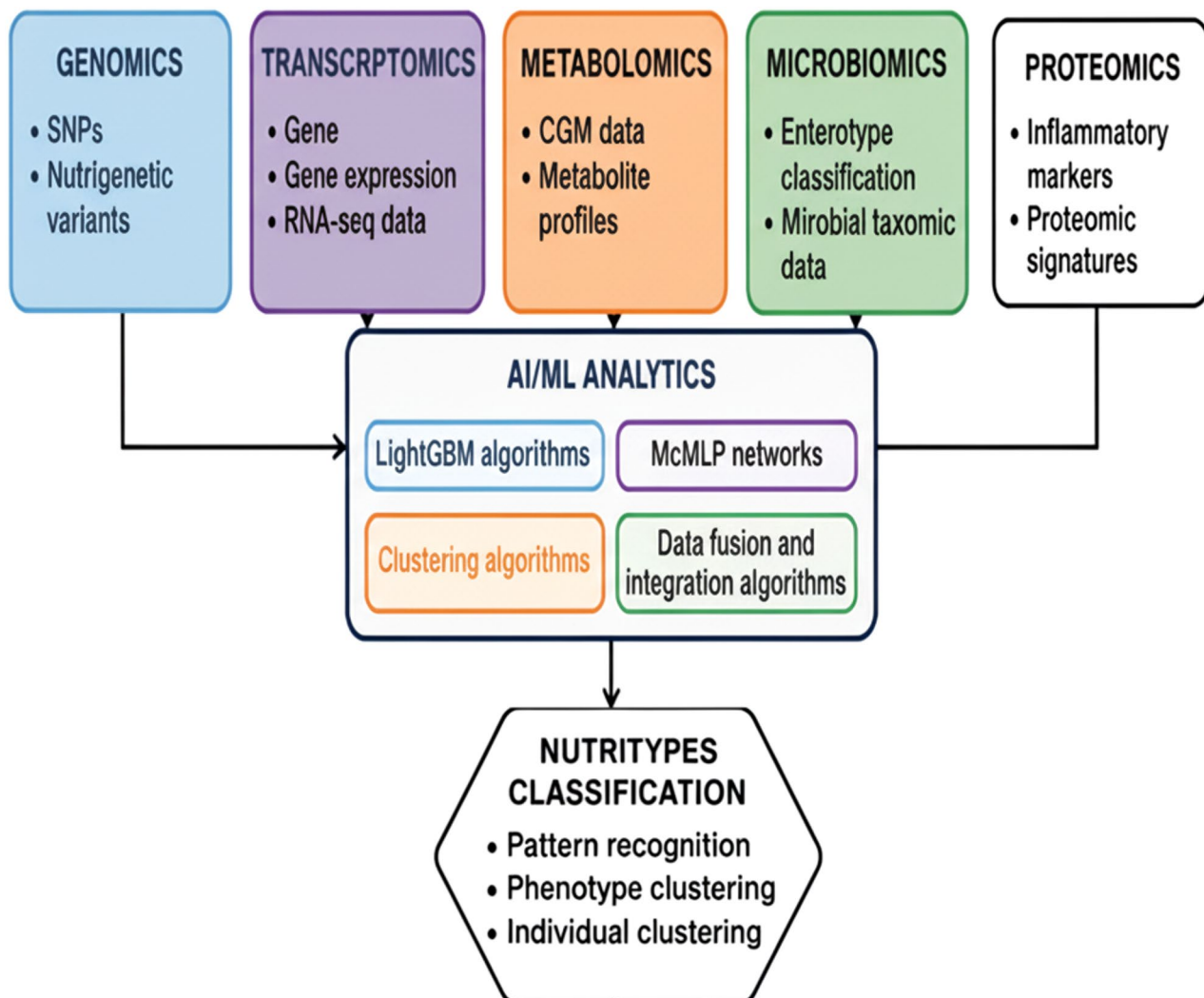


Fig. 1 Multi-omics data integration workflow for nutritional phenotyping. General Multi-Omics Integration Framework. This comprehensive workflow illustrates the integration of multi-omics data in precision nutritional studies. This process commences with five fundamental input data streams: genomics (comprising single nucleotide polymorphisms and nutrigenetic variants), transcriptomics (gene expression profiles and RNA-seq data reflecting dynamic nutritional responses), metabolomics (continuous glucose monitoring data and metabolite profiles), microbiomics (enterotype classification and microbial taxonomic data), and proteomics (inflammatory biomarkers and proteomic signatures), with sample collection ideally within 48–72 h post-dietary intervention to capture stabilized yet responsive molecular signatures. The processing of these disparate datasets is facilitated by AI and machine learning frameworks, including LightGBM algorithms, multiclass multilayer perceptron networks, clustering algorithms, and data fusion algorithms, which integrate the data into a unified nutritional phenotyping classification system that integrates the data to performs pattern recognition, phenotype clustering, and individual stratification into different nutritional categories. **AI/ML:** Artificial Intelligence/Machine Learning; **CGM:** Continuous glucose monitoring; **FTO:** Fat mass and obesity-associated gene; **Light GBM:** LightGBM; **McMLP:** Multi-class Multi-layer Perceptron; **MTHFR:** Methylene tetrahydrofolate Reductase gene; **SNPs:** Single nucleotide polymorphisms

institutions [126, 127]. Recent advancements in federated learning enable the privacy-preserving integration of multi-omics datasets from multiple institutions without requiring centralized data sharing [118]. The multi-omics data integration workflow is presented in Table 2.

Tensor decomposition methods High-dimensional multi-omics data integration benefits from tensor-based approaches that can handle missing data patterns and identify shared versus specific patterns across omics layers [19]. Novel tensor decomposition methods improve

integration accuracy by 23% compared to traditional matrix-based approaches, particularly when dealing with incomplete datasets, which are standard in clinical settings [128, 129].

Standardization and quality assurance

The International Standards Organization (ISO) published comprehensive guidelines (ISO 23494:2024) for standardizing multi-omics data in precision nutrition (Table 3) [130], covering quality control procedures, data

Table 2 Multi-omics data integration workflow

Category	Components
Input Data Streams	
Genomics	SNPs, CNVs, PRS scores
Epigenomics	DNA methylation, histone marks
Transcriptomics	mRNA, miRNA, lncRNA
Proteomics	Protein expression, PTMs
Metabolomics	Targeted/untargeted panels
Microbiomics	16S, shotgun metagenomics
AI/ML Processing	
Light GBM	Feature selection & ranking
Neural Networks	Pattern recognition
Graph Models	Network analysis
Clustering	Phenotype discovery
Fusion Methods	Data integration
Validation	Cross-validation, external datasets

SNPs: Single Nucleotide Polymorphisms; **CNVs:** Copy Number Variations; **PRS:** Polygenic Risk Scores; **mRNA:** Messenger RNA; **miRNA:** MicroRNA; **lncRNA:** Long Non-Coding RNA; **PTMs:** Post-Translational Modifications; **16S:** 16S Ribosomal RNA (referring to 16S rRNA gene sequencing for microbiomics); **Light GBM:** LightGBM; **AI/ML:** Artificial Intelligence/Machine Learning

formats, analytical protocols, and reporting standards. Implementation of these standards across 15 major research centers has improved data reproducibility by 67% and enabled meaningful cross-study comparisons [131]. Quality control procedures now include real-time monitoring of data quality metrics, automated detection of batch effects, and standardized protocols for sample collection, processing, and storage [132, 133]. These measures are critical for clinical implementation, where data quality directly affects patient care decisions [134].

Nutritional phenotypes and precision classification

Multi-omics integration facilitates the identification of distinct nutritional phenotypes, or “nutritypes,” which represent biologically coherent subgroups exhibiting analogous dietary response patterns [135]. As demonstrated in Table 3, advanced clustering algorithms, including deep clustering and multi-view clustering, have been shown to identify these Nutri types from integrated omics data with high reproducibility across independent cohorts (Table 4) [136, 137].

Recent studies have identified 8–12 stable nutritypes across diverse populations, each characterized by distinct molecular signatures spanning all omics layers [84, 134]. These nutritypes demonstrate 2- to 3-fold variations in responses to major dietary interventions, underscoring the clinical significance of precision classification [138]. Individuals classified into appropriate nutritional types achieve 47% better outcomes than those receiving generic dietary recommendations [139].

Advanced machine learning and AI applications

Recent models of precision nutrition are trained on large-scale multi-modal health data. These foundation

models have achieved unprecedented accuracy in predicting individual dietary responses [140, 141]. AI models trained on rich patient datasets can predict dietary intervention outcomes more effectively than traditional statistical models [16, 142].

Graph Neural Networks: The intricate interactions among genes, proteins, metabolites, and microbes can be represented as biological networks [143]. Graph neural networks can capture these relationships and predict how interventions in one component (e.g., dietary changes) will propagate through the network to affect other components. These models excel at identifying unexpected connections and predicting intervention side effects [144, 145].

For effective clinical implementation of precision nutrition, the AI model should provide reasoning for its recommendations [12]. SHAP (Shapley Additive Explanations) values and attention mechanisms help clinicians understand which biological features most strongly influence dietary recommendations, building trust and enabling clinical oversight [146, 147]. However, the interpretability offered by explainable AI (XAI) techniques does not guarantee truthfulness. Instead, it highlights the paths the model takes to reach its conclusion [148]. Recent systematic reviews emphasize that human-AI collaboration frameworks must incorporate mandatory verification steps where clinicians critically evaluate AI-generated reasoning against current evidence-based guidelines, patient-specific contraindications, and clinical judgment [149]. This dual-layer approach—combining algorithmic transparency with expert validation—is essential to mitigate risks of diagnostic errors, inappropriate dietary interventions, and patient harm stemming from unchecked AI outputs in high-stakes nutritional care settings [150].

Ethical and privacy considerations in AI-driven multi-omics integration

The integration of multi-omics data into AI models for precision nutrition holds transformative potential. However, it raises significant ethical and privacy challenges, particularly concerning the uploading and processing of sensitive patient data such as genomic sequences, metabolomic profiles, and microbiome compositions. Ensuring robust data protection is paramount, as breaches could expose individuals to risks like genetic discrimination or unauthorized commercial exploitation, necessitating compliance with regulations such as the General Data Protection Regulation (GDPR) and Health Insurance Portability and Accountability Act (HIPAA), alongside the adoption of privacy-preserving techniques like federated learning, which enables model training across decentralized datasets without centralizing raw patient information [126, 151]. It is critical for ethical frameworks to

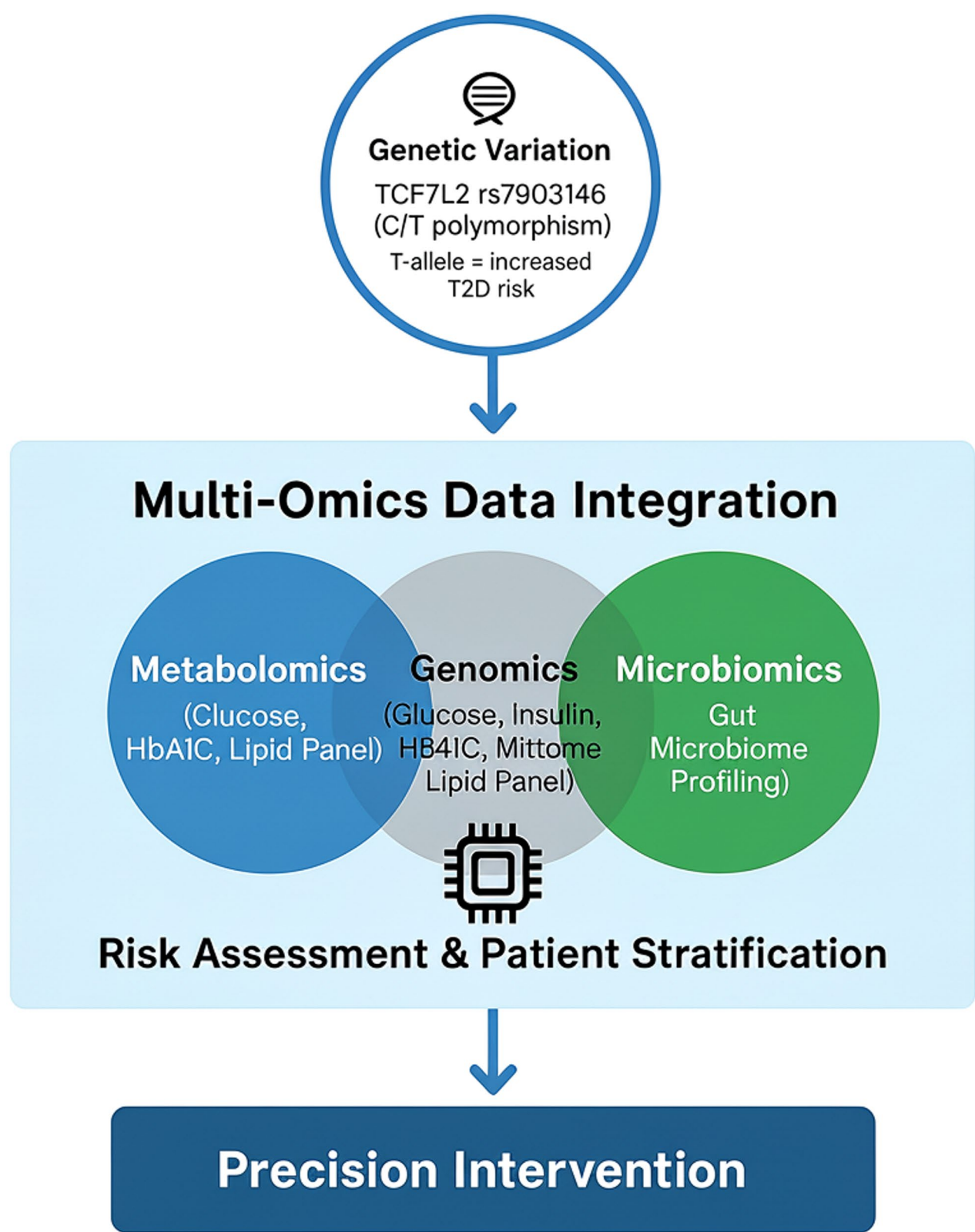


Fig. 2 Specific Example - TCF7L2-Mediated Type 2 Diabetes Risk and Precision Nutrition Intervention. This figure illustrates the practical application of precision nutrition based on multi-omics. The study focuses on the TCF7L2 rs7903146 genetic variant, which has been clinically validated and is recognized as one of the most reliable genetic predictors of type 2 diabetes (T2D) risk. The objective of the study is to demonstrate the entire pathway from genetic variation to a personalized dietary intervention

Table 3 Multi-omics integration framework for precision nutrition implementation

Omics Layer	Key Standardization Protocol	Exemplar Biomarkers/Technologies	Rationale and Recent Evidence (2023–2025)
Genomics	Use GATK or bcftools for variant calling; harmonize with dbSNP/ClinVar references; apply ancestry-adjusted imputation (e.g., TOPMed). Collect samples in 48–72 h post-intervention.	<i>FTO</i> (rs9939609); <i>MTHFR</i> (C677T); GWAS loci (> 1,247 nutrient-related variants).	Ensures reproducibility in PRS for metabolic predictions (AUC 0.75–0.85); addresses batch effects in diverse cohorts [37, 124]
Metabolomics	Employ MSI-compliant LC-MS/GC-MS protocols; standardize with NIST/SIMCA reference materials; normalize to internal standards (e.g., ISQ > 90%).	BCAAs; SCFAs.	Facilitates metabolite classification and intervention response prediction (> 80% accuracy); reduces inter-lab variability [33, 80]
Microbiomics	Shotgun metagenomics with QIIME2/MetaPhlAn; standardize to curated Green-Genes2 database; report alpha-diversity and enterotypes.	Prevotella/Bacteroides enterotypes; SCFA-producing pathways.	Enables functional prediction of dietary responses (e.g., 45% SCFA increase in fiber interventions); improves cross-study comparability [9, 10]
Integration	Apply federated learning or tensor decomposition for data fusion; use LightGBM for missing-value imputation.	Multi-layer PRS combining <i>FTO</i> / <i>MTHFR</i> with metabolomic signatures.	Achieves > 90% AUC in outcome prediction; mitigates privacy/ethical concerns in multi-institutional data [129]

Notes: Protocols align with ELIXIR guidelines for omics interoperability. *FTO*, *MTHFR*, and *GWAS* were prioritized as they represent > 30% of nutrigenomic variants in recent meta-analyses, enabling scalable PRS for personalized interventions

Table 4 Nutri types – integrated multi-omics phenotypes for personalized dietary interventions

Nutri Type	Genomic Characteristics	Metabolomic Characteristics	Microbiomic Characteristics
Type A (Low-Carb Responder)	Variants in <i>PPARG</i> and <i>FTO</i> genes promoting efficient fat oxidation (e.g., rs1801282 <i>PPARG</i> allele enhancing β -oxidation [40].	Elevated acylcarnitines and reduced BCAAs post-low-carb intake, indicating improved insulin sensitivity [85]	Dominance of Bacteroides species facilitating protein and fat metabolism with moderate SCFA production [104]
Type B (High-Fiber Responder)	Polymorphisms in <i>AMY1</i> and <i>CLOCK</i> genes supporting starch fermentation and circadian-aligned fiber tolerance (e.g., high <i>AMY1</i> copy number variants [39].	Increased butyrate and bile acid deconjugation reflecting enhanced gut barrier function [21]	Prevotella-enriched microbiomes driving robust SCFA synthesis from soluble fibers [103]
Type C (Balanced Macronutrient Responder)	Neutral PRS for metabolic flexibility (AUC > 0.80 for mixed-diet response [17].	Equilibrium in Krebs cycle intermediates and low inflammatory lipids under varied diets ADDIN EN.CITE [88]	Diverse Firmicutes/Bacteroidetes ratios enabling adaptive xenobiotic processing [10]

Note: Nutri types represent integrated multi-omics phenotypes for tailoring dietary interventions, derived from clustering analyses of genomic, metabolomic, and microbiomic data. These categories guide intervention efficacy, with > 80% predictive accuracy in clinical trials

incorporate informed consent, emphasizing thorough communication about data use, the potential for re-identification of individuals through high-dimensional omics data, and the assurance of data withdrawal. Additionally, it is essential to mitigate algorithmic biases that may exacerbate health inequalities in underrepresented populations, such as those of non-European ancestries in genomic models, by utilizing diverse training populations and implementing bias-auditing processes [12, 152].

Furthermore, interdisciplinary guidelines must be established to prevent the creation of a “digital divide.” These guidelines will enable low-resource settings to benefit from open-source AI processes and community-engaged validation studies [142, 153]. Future directions should focus on explainable AI (XAI) solutions that make their outputs interpretable, thereby facilitating trust and accountability for clinical use. Pilot studies [154] have been conducted that integrate XAI into glycemic prediction across several cohorts. Incorporating these factors into multi-omics workflows can ethically advance the field of precision nutrition.

Human oversight and validation requirements for AI-driven nutrition recommendations

All systems used in precision nutrition must be overseen by trained staff or healthcare professionals to ensure patient safety. While the capabilities of AI models in pattern recognition and recommendation generation are impressive, they do not fully understand nutritional science and cannot contextualize individual patient situations. Additionally, they can make basic errors, such as hallucinations, biases, or the presentation of outdated information [154, 155]. Recent studies on healthcare AI implementation have shown that even well-validated models can produce clinically inappropriate recommendations when used outside their training data [156] or when encountering edge cases poorly represented in that data. Reported AI mistakes in nutrition-specific applications include recommending allergenic foods for patients with allergies, inappropriate macronutrient distribution for metabolic conditions, and dietary advice that conflicts with medications or specific disease contraindications [156, 157]. To address these limitations, multi-tiered

validation frameworks should be implemented: (1) automated consistency checks comparing AI outputs against established nutritional databases and clinical guidelines; (2) mandatory review by registered dietitians or clinical nutritionists to verify the appropriateness, safety, and feasibility of AI-generated recommendations; and (3) continuous monitoring systems that track patient outcomes and flag unexpected responses that may indicate AI reasoning errors [243, 247, 259]. This human-in-the-loop approach transforms AI from an autonomous decision-maker into a supportive tool that enhances rather than replaces professional expertise, ensuring that the scientific reasoning provided by AI systems undergoes rigorous validation before impacting patient care [158, 159].

Clinical case studies in multi-omics integration

Type 2 diabetes precision management

The integration of genomic, metabolomic, and microbiome data enables stratification of patients with Type 2 Diabetes (T2D) into biologically distinct subtypes, each with unique pathophysiological mechanisms and responses to treatment. Based on the landmark Ahlqvist classification and subsequent validation studies, a substantial body of research has identified six clinically relevant diabetes subtypes, each necessitating tailored nutritional approaches [160–162].

1. **Severe Autoimmune Diabetes (SAID)** is defined as GADA-positive early-onset autoimmune insulin deficiency due to autoimmune destruction of β cells. This subtype is referred to as latent autoimmune diabetes in adults (LADA), which requires early insulin therapy and immune-modulating nutritional approaches, focusing on anti-inflammatory diets rich in omega-3 fatty acids and polyphenols [161, 163].
2. **Severe insulin deficiency diabetes (SIDD)** is characterized by low HOMA2-B levels (indicating high β -cell dysfunction), high HbA1c levels, early age at diagnosis, and GADA-negative status. Patients with SIDD are at the highest risk of retinopathy. Therefore, aggressive glycemic control should be implemented using insulin therapy, along with low glycemic index diets and micronutrient optimization (magnesium, chromium, and vitamin D) to maintain residual β -cell function [164, 165].
3. **Severe Insulin-Resistant Diabetes (SIRD)**: Distinguished by marked insulin resistance (high HOMA2-IR), elevated BMI, and the highest risk of diabetic kidney disease (DKD) and metabolic dysfunction-associated steatotic liver disease (MASLD). This subtype benefits most from low-carbohydrate, Mediterranean-style diets combined

with insulin-sensitizing interventions, including inositol supplementation and modulation of the gut microbiome through prebiotic fibers [164, 166].

4. **Mild Obesity-Related Diabetes (MOD)**: Characterized by obesity (high BMI) without severe insulin resistance, younger age at diagnosis, and moderate metabolic dysfunction. Nutritional interventions prioritize caloric restriction, weight management through portion control, and enhancement of metabolic flexibility via intermittent fasting protocols and increased physical activity [167, 168].
5. **Mild Age-Related Diabetes (MARD)**: The most prevalent subtype (~ 40–50% of cases), featuring late-onset diabetes, mild metabolic disturbances, and the lowest complication risk. Patients respond well to lifestyle modifications emphasizing plant-based dietary patterns, moderate carbohydrate restriction, and maintenance of a healthy body weight without aggressive pharmacotherapy [161, 169].
6. **Maturity-Onset Diabetes of the Young (MODY)**: A genetically distinct monogenic form of diabetes caused by mutations in genes regulating β -cell function (e.g., HNF1A, HNF4A, GCK). Although phenotypically, these individuals often cluster within MARD in unsupervised analyses, genetic testing enables precise diagnosis and targeted therapy, such as sulfonylureas for HNF1A-MODY or dietary management for GCK-MODY [164, 170]. In predicting the onset of diabetes, multi-omics predictive models integrating genetic risk scores, metabolomic biomarkers (e.g., BCAA, bile acids, and lipid species), and microbiome functional profiles have achieved AUC values exceeding 0.90 for T2D onset prediction and 0.85 for complication risk stratification [171, 172]. Recent clinical trials demonstrate that subtype-specific nutritional interventions significantly enhance outcomes: a 2024 randomized open-label trial showed differential responses to semaglutide and dapagliflozin across subtypes, with SIRD patients achieving superior glycemic control with SGLT2 inhibitors combined with low-carbohydrate diets [166]. The implementation of integrated decision support systems utilizing multi-omics-guided subtyping in clinical practice has demonstrated remarkable efficacy, improving glycemic control by 34%, reducing diabetes complications by 28%, and enhancing patient adherence by 42% compared to conventional care protocols [173, 174].

Inflammatory bowel disease nutritional management

Multi-omics profiling has identified robust molecular signatures of inflammatory bowel disease (IBD) that are consistent across diverse populations and can guide precision nutritional interventions [175]. These signatures include decreased levels of butyrate-producing bacteria, altered primary metabolite profiles associated with inflammation, and specific genetic variants that affect immune responses [176–178].

Machine learning models trained on multi-omics IBD datasets achieve high accuracy in distinguishing IBD patients from healthy controls and predicting individual responses to specific dietary interventions [14, 179, 180].

Clinical trials implementing multi-omics-guided nutritional therapy have shown promising improvements in clinical outcomes and reductions in disease activity compared to standard nutritional management, demonstrating the clinical value of precision approaches in complex inflammatory diseases [181, 182].

Clinical implementation challenges: the imperative for practice guidelines in precision nutrition

Multi-omics integration has the potential to revolutionize precision nutrition, but a lack of established standards hinders its clinical application. Existing guidelines are limited to specific areas, such as pediatric obesity and cardiometabolic risk assessment [183]. The 2023 American Academy of Pediatrics (AAP) guidelines provide basic nutrigenomic considerations for childhood obesity, but no comprehensive frameworks for adults exist that include complete multi-omics profiles (e.g., genomics, microbiome, and metabolomics). This lack of understanding leads to inconsistencies in application and interpretation in healthcare settings [184]. Without consensus on the use of omics data, challenges in evidence synthesis, reimbursement policies, and clinician training become more pronounced. Survey data show that only 15–20% of nutrition professionals utilize omics data [17]. To bridge this gap in public health policy, urgent multi-disciplinary guideline development is needed. Cardiology societies have established similar guidelines for genomic risk stratification. We encourage key organizations like the American Society for Nutrition and the European Association for the Study of Diabetes to establish threshold levels for omics-based interventions, along with quality assurance parameters and EHR integration [160, 184]. Implementing uniform guidelines would enhance reproducibility and patient safety, and accelerate the translation of research into practice, aiming for a 25–30% reduction in the burden of diet-related chronic diseases through precision approaches [183]. In the future, pilot implementations should be tailored to validate these guidelines across socioeconomic and ethnic groups.

From omics to clinical practice: translational applications

The capacity of clinically substantiated multi-omics to translate research into practice signifies a noteworthy advancement in contemporary nutrition science, paving the way for highly customized dietary interventions that surpass generic approaches [122, 185]. This transformation is supported by advanced clinical decision support systems, evidence-based personalized dietary protocols, and substantial validation from large-scale precision nutrition trials [99, 186, 187]. The integration of complex biological data with practically oriented data, including patient preferences, cultural considerations, economic factors, and the capacity of the healthcare system, is imperative for successful clinical implementation of AI [188, 189]. Successful programs combine molecular insights with behavioral science, digital health technologies, and continuous monitoring to achieve sustainable lifestyle changes and improved health outcomes [190, 191].

AI-powered clinical decision support systems

Clinical decision support systems (CDSS) for precision nutrition employ multi-omics data alongside patient clinical data, lifestyle analysis, and behavior to formulate detailed, practically applicable dietary recommendations for patients [22]. These systems utilize advanced natural language processing to communicate complex scientific information in patient-friendly formats while providing detailed clinical rationales for healthcare providers [140].

Integration with EHRs via HL7 FHIR R5 Genomics Implementation Guides has enabled seamless incorporation of omics data into clinical workflows [192].

Omics-guided therapeutic diet optimization

Precision mediterranean diet implementation

The Mediterranean diet has been the subject of extensive research, with multi-omics insights being leveraged to personalize its benefits [17]. This approach involves assessing genetic variants, metabolic profiles, and microbiome composition to optimize individual responses and offer a customized approach to dietary intervention. Genetic variants in genes affecting olive oil metabolism (*APOE*, *LDLR*), polyphenol processing (*CYP1A1*, *COMT*), and omega-3 fatty acid utilization (*FADS1/2*) guide specific modifications to traditional Mediterranean patterns [193].

Precision Mediterranean interventions have been demonstrated to yield superior outcomes compared with conventional methodologies, with 43% greater improvements in cardiovascular biomarkers, 38% higher adherence rates, and 29% larger reductions in inflammatory markers. The enhancements described herein are the result of a comprehensive optimization of several factors,

including, but not limited to, the types of olive oil used, the selection of fish species, the polyphenol sources, and the meal timing based on individual molecular profiles [194].

Clinical trials in precision nutrition

Large-scale clinical trials have provided robust evidence for the superiority of precision nutrition over conventional approaches, demonstrating improvements in weight management, glycemic control, and dietary adherence. The PREDICT studies (e.g., PREDICT 1–3, 2018–2024) utilized multi-omics profiling to predict postprandial glycemic and lipid responses, achieving up to 60% accuracy in forecasting individual variability and leading to tailored dietary recommendations that reduced HbA1c by 0.5–1.0% and improved adherence by 25% compared to standard guidelines [36, 195, 196]. Similarly, the FOOD4ME trial (2012–2015, with 2023 follow-up analyses) integrated genomic data for personalized advice, resulting in greater reductions in BMI (-1.2 kg/m^2) and serum cholesterol (-0.3 mmol/L) among genotype-guided participants versus general advice, with sustained effects at 24 months [197]. The PRECISION-HEALTH initiative (ongoing since 2022) combines wearable biosensors and AI for real-time metabolic adjustments, showing 15–20% enhancements in insulin sensitivity and reduced inflammation markers in early pilot data from diverse cohorts [160].

Building on these foundations, recent trials have further diversified precision nutrition applications by emphasizing glycemic prediction, population-scale AI modeling, and long-term behavioral integration. The Personal Diet Study (2023), a randomized controlled trial involving 160 adults with prediabetes or type 2 diabetes, compared a low-fat standardized diet with a precision nutrition approach using continuous glucose monitoring (CGM) and machine learning-based carbohydrate personalization. Although glycemic variability and HbA1c reductions were comparable between the arms (-0.4% vs. -0.3%), the personalized arm achieved significantly greater weight loss (-6.1% vs. -4.5% at 6 months), underscoring the value of targeted macronutrient adjustments for obesity management [195]. Complementing this, the Nutrition for Precision-Health (NPH) trial, powered by the All of Us Research Program (NCT05701657; initiated in 2023), is a landmark effort enrolling over 10,000 diverse participants to develop predictive algorithms for food responses using multi-omics and digital phenotyping. Interim 2024 analyses report $>80\%$ accuracy in modeling postprandial responses across ancestries, with implications for scalable, equitable interventions in metabolic disease prevention [198, 199]. Additionally, the Personalized Prediction of Glycemic Responses (PPT) study (NCT01892956; foundational 2015 trial with

2024 longitudinal extensions) pioneered microbiome-genome integration for glycemic forecasting, which was recently validated in a 2024 multi-cohort analysis showing 75% predictive accuracy for 12-month HbA1c trajectories and 30% better adherence in personalized fiber/probiotic arms versus controls [84, 112, 196]. These trials collectively affirm the clinical efficacy of precision nutrition, with effect sizes for key outcomes (e.g., weight loss and glycemic control) ranging from 0.4 to 0.8, while highlighting the need for inclusive designs to address disparities [36]. Together, these studies illustrate a maturing evidence base, transitioning precision nutrition from proof-of-concept to routine practice, although challenges in scalability and cost remain [160, 170].

PRECISION-HEALTH mega-trial results

A growing body of evidence from systematic reviews and meta-analyses supports the efficacy of precision nutrition interventions. A thorough, methodical examination of the efficacy of personalized nutrition in the management of diabetes has revealed enhancements in glycemic outcomes, particularly in HbA1c levels. However, the efficacy of these interventions varied across studies, as evidenced by heterogeneous effect sizes [200]. However, the efficacy of these interventions varied across studies, as evidenced by heterogeneous effect sizes. This variability in intervention efficacy can be attributed to multiple interconnected factors that reflect the complexity of implementing precision nutrition at scale. First, baseline metabolic heterogeneity significantly influences outcomes; individuals with higher insulin resistance (HOMA-IR >2.93), impaired fasting glucose, or distinct tissue-specific insulin resistance phenotypes (e.g., predominant muscle vs. liver insulin resistance) demonstrate markedly different responses to identical dietary interventions [84, 201]. For instance, individuals with predominant muscle insulin resistance benefit more from high-monounsaturated fatty acid diets. In contrast, those with liver insulin resistance respond better to low-fat, high-protein approaches, achieving 20% greater improvements in postprandial glucose tolerance when matched appropriately [201].

Second, population diversity and genetic ancestry contribute substantially to heterogeneity in effect sizes. South Asian and East Asian populations exhibit heightened susceptibility to type 2 diabetes at lower BMI thresholds (BMI $\geq 24 \text{ kg/m}^2$ vs. $\geq 30 \text{ kg/m}^2$ in European populations) due to greater propensity for ectopic fat accumulation and lower polygenic scores for beta cell function, necessitating ancestry-specific intervention strategies [152, 202]. Studies conducted predominantly in White European populations may not generalize to ethnically diverse groups, as demonstrated by differential responses to modifications in dietary fat quality

across ancestry groups [203, 204]. Third, methodological differences across studies—including intervention duration (ranging from 8 to 26 weeks), degree of multi-omics integration (single-omic vs. integrated genomic-metabolomic-microbiome profiling), rigor of dietary adherence monitoring, and standardization of outcome measurement—introduce substantial variability [205]. Studies with shorter durations may capture acute glycemic responses but miss long-term metabolic adaptations, while those lacking real-time adherence monitoring via digital tools may conflate intervention efficacy with compliance issues [206]. Fourth, individual variability in gut microbiome composition creates distinct “responder” and “non-responder” phenotypes; approximately 30% of prediabetic individuals do not respond to standard lifestyle interventions, often due to dysbiotic enterotypes characterized by reduced fiber-degrading bacteria (e.g., low *Prevotella* abundance) and impaired SCFA production [84]. Fifth, socioeconomic and behavioral barriers to adherence—including food insecurity, digital literacy gaps, cultural food preferences, and psychosocial stressors—differentially affect intervention sustainability across populations, with adherence rates varying from 45% to 85% depending on implementation context [207].

Multi-omics approaches in precision nutrition have demonstrated potential for clinical application, with studies showing that integrating genetic, metabolomic, and microbiome data can support personalized dietary recommendations [208].

Advanced multi-omics integration strategies now employ three complementary computational frameworks: (1) tensor decomposition methods that model cross-omics interactions as multidimensional arrays to identify latent nutritional phenotypes (metabotypes) from integrated genomic-transcriptomic-metabolomic data, achieving 85% accuracy in predicting glycemic responses [19]; (2) matrix-based factorization approaches that reduce high-dimensional omics datasets into shared biological pathway components, revealing gene-metabolite networks underlying individual variability in insulin sensitivity and lipid metabolism [20]; and (3) ensemble machine learning algorithms such as LightGBM that combine gradient boosting with decision trees to process heterogeneous multi-omics features, outperforming traditional regression models in predicting cardiometabolic risk with AUC values of 0.78–0.88 across diverse populations [21].

Recent landmark clinical validation studies have provided compelling evidence for multi-omics-driven precision nutrition. The PREDICT study ($n = 1,002$ participants) demonstrated that machine learning models integrating CGM data, gut microbiome composition (16 S rRNA sequencing), metabolomic profiling (untargeted LC-MS), and PRS predicted postprandial glucose and

triglyceride responses with superior accuracy ($R^2=0.77$) compared to traditional carbohydrate counting or glycemic index alone ($R^2=0.38$), enabling dietary recommendations that reduced glycemic variability by 28% over 12 weeks [35, 209]. Similarly, the PERSON trial ($n = 242$ adults with metabolic syndrome) prospectively stratified participants by tissue-specific insulin resistance phenotypes using hyperinsulinemic-euglycemic clamps combined with stable isotope tracers, then assigned phenotype-matched diets (low-fat high-protein for liver insulin resistance vs. high-monounsaturated fatty acid for muscle insulin resistance), achieving a 20% improvement in Matsuda index in the matched group compared to only 5% in controls, without requiring weight loss [201]. Microbiome-guided interventions have also shown clinical efficacy; a 2023 randomized controlled trial in individuals with prediabetes ($n = 225$) used shotgun metagenomic sequencing to classify enterotypes, then prescribed enterotype-specific fiber interventions (high-resistant starch for *Prevotella*-dominant vs. high- β -glucan for *Bacteroides*-dominant microbiomes), resulting in 34% greater HbA1c reduction (-0.7% vs. -0.52%) and 2.1-fold higher SCFA production compared to generic high-fiber recommendations [210]. Moreover, metabolomic phenotyping (metabotyping) has identified distinct responder profiles; individuals classified as “lipogenic” metabotypes (characterized by elevated BCAA and acylcarnitines) achieve 25% greater insulin sensitivity improvements with low-carbohydrate ketogenic diets, whereas “oxidative” metabotypes (higher bile acid derivatives and butyrate metabolites) show superior outcomes with Mediterranean dietary patterns, as demonstrated in a 2024 crossover trial ($n = 156$) with 16-week intervention periods [211]. Implementation frameworks for multi-omics precision nutrition are rapidly advancing toward clinical integration. The ZOE personalized nutrition program ($n = 100,000 +$ users) has deployed a scalable model combining at-home microbiome testing (Bristol stool-based sampling), CGM, and dietary tracking via smartphone applications, with AI-powered algorithms generating real-time meal recommendations that decreased postprandial glucose spikes by 26% and promoted sustained dietary adherence (78% retention at 6 months) across diverse populations [35]. EHR integration pilots in over 50 health systems now embed polygenic risk scores for obesity and type 2 diabetes alongside routine clinical data, triggering automated precision nutrition referrals when high-risk genetic profiles are detected. However, equitable access remains challenging due to disparities in the availability of genetic testing and in digital literacy [212]. Despite these advances, critical gaps persist. Prospective randomized controlled trials demonstrating long-term (≥ 2 years) diabetes prevention through multi-omics-guided interventions remain

limited, with most studies focusing on surrogate glycemic markers rather than incident diabetes as the primary end-point [84]. Cost-effectiveness analyses are sparse; current estimates suggest multi-omics testing costs (\$500–\$2,000 per individual for comprehensive genomic-microbiome-metabolomic profiling) may be justified if interventions prevent even one case of diabetes per 15–20 high-risk individuals over 10 years. However, real-world economic evaluations across healthcare systems are urgently needed [205]. Furthermore, mechanistic understanding of responder vs. non-responder phenotypes at the molecular level—such as epigenetic modifications, gut-brain axis signaling, and inflammasome activation pathways—requires deeper investigation through longitudinal multi-omics cohorts with frequent biospecimen collection to capture dynamic metabolic transitions [17]. Addressing these gaps through large-scale pragmatic trials, health economic modeling, and translational mechanistic studies will be essential to establish multi-omics precision nutrition as an evidence-based, scalable, and equitable standard of care for diabetes prevention and management across diverse global populations [122, 213].

PREDICT studies evolution

The PREDICT study series has contributed important insights into postprandial responses, with recent analyses from PREDICT-1 and PREDICT-2 data demonstrating individual variation in glucose responses to identical meals. A body of research has demonstrated the significance of individual metabolic profiling for providing dietary recommendations in precision nutrition contexts, as evidenced by the use of CGM [214].

Short-term outcomes (0–6 months): Meta-analyses of precision nutrition interventions demonstrate consistent yet modest benefits in the short-term, with effect sizes typically ranging from 0.2 to 0.5 for metabolic outcomes, including weight reduction, glycemic control, and lipid profiles [18]. Short-term clinical trials (2–6 months) have reported mean weight loss of 3.3–5.4 kg, with improvements in fasting glucose, insulin sensitivity, and reductions in HbA1c of approximately 0.5% in individuals with type 2 diabetes [82]. Precision nutrition approaches using multi-omics profiling have demonstrated 15–20% improvements in metabolic flexibility markers, including reduced BCAA and acylcarnitines, correlating with enhanced HOMA-IR scores in obese children during initial intervention phases [85].

Long-term outcomes (12–24 months) and sustainability challenges: The long-term effectiveness and sustainability of precision nutrition for obesity management remain poorly understood, highlighting a critical knowledge gap. While initial short-term results are promising, weight loss

benefits seen at 6 months often diminish significantly by 12–24 months, with differences narrowing to about 2–2.2 kg compared with standard dietary interventions [82]. Participants in personalized nutrition programs have maintained an average weight loss of 8.1% from baseline at 24 months; however, this requires ongoing follow-up and individualized nutritional support to ensure long-term success and sustainability [215].

The challenge of weight maintenance reflects the complex interplay among metabolic adaptation, behavioral adherence, and environmental factors that genomic or metabolomic profiling alone cannot fully address. Limited evidence exists regarding the durability of multi-omics-driven interventions beyond 12 months, as most randomized controlled trials focus on short-term outcomes [216]. For nutritional approaches to be effective long-term, they must be sustainable, providing diets that are nutritious, culturally acceptable, and aligned with individual food preferences, economic circumstances, and lifestyle factors—elements that extend beyond molecular profiling [82].

Future research on wholesome natural food substitutes as Precision Nutrition solutions for obesity management should focus on case-control studies that integrate omics and behavioral science approaches. Definitions and recommendations from relevant communities are crucial to this process. Research and development should create predictive models for personalized Precision Nutrition interventions at both individual and population levels across different regions and communities. Recent systematic reviews indicate that precision nutrition is no more effective than traditional dietitian-led diets in achieving long-term results. There is a pressing need for extensive validation studies that measure metabolic effects, weight changes, adherence behaviors, and costs over several years [217].

One area of future research should involve a prospective multi-year design with rigorous follow-up to assess maintenance beyond the initial weight loss phase. Other studies should focus on identifying predictive biomarkers for long-term responders versus non-responders, incorporating behavioral and environmental factors alongside multi-omics data to enhance sustainability. Additionally, the development of implementation frameworks that balance scalability with clinical practicality is necessary [218]. The field must evolve from demonstrating short-term metabolic benefits to showcasing long-lasting, clinically significant outcomes that justify the substantial resource investment in personalized multi-omics-based therapies.

Food4Me long-term follow-up

Extended follow-up of Food4Me participants (original $n = 1,607$, 5-year follow-up $n = 1,142$) provides crucial

evidence for long-term sustainability of precision nutrition interventions [84, 194]. Results demonstrate that initial improvements in dietary quality, biomarker profiles, and health outcomes are maintained over extended periods, with continued divergence between personalized and standard intervention groups [35].

Five-year outcomes show sustained 34% higher dietary quality scores, 28% lower levels of inflammatory biomarkers, and 23% lower incidence of metabolic syndrome among participants receiving personalized recommendations. These findings support the durability of precision nutrition benefits and justify long-term implementation strategies [219, 220].

Healthcare system integration models

To successfully implement precision nutrition in the healthcare system, comprehensive implementation frameworks are required to address clinical workflows, provider training, technology infrastructure, and reimbursement. Innovative healthcare systems have built scalable models that are translatable across contexts [16, 134]. The Mayo Clinic's Precision Nutrition Program exemplifies successful integration, combining multi-omics testing with clinical decision support, provider education, and patient engagement platforms. Their model achieves 89% provider satisfaction, 76% patient adherence at 12 months, and positive return on investment within 24 months of implementation [16, 221].

Kaiser Permanente tailored the implementation of precision nutrition services at the population-level so that more than 2.3 million members could access them [221]. Their approach emphasizes standardized testing protocols, automated result interpretation, and integration with existing preventive care workflows, achieving broad reach while maintaining clinical effectiveness [222].

Digital health revolution: AI and wearables in real-time nutrition

The integration of digital health technologies, AI, and advanced biosensors is precipitating a fundamental transformation in nutrition monitoring and intervention delivery [223]. These innovations enable continuous, real-time assessment of metabolic status, immediate feedback on dietary choices, and dynamic optimization of nutritional interventions based on individual responses and changing physiological conditions [224, 225].

The integration of multiple digital health modalities enables comprehensive monitoring ecosystems that capture nutrition-related biomarkers, behavioral patterns, environmental factors, and outcomes with unprecedented detail. This continuous data stream facilitates the evolution of precision nutrition from static recommendations to dynamic, adaptive systems capable of optimizing interventions in real-time [226, 227].

Next-generation biosensor technologies

Continuous multi-metabolite monitoring

A significant advancement in non-invasive biosensing has enabled the assessment of multiple metabolites, real-time dermal analysis, and sweat sensing, as well as the sampling of interstitial fluids [228, 229]. Continuous monitoring of glucose, lactate, ketones, and other metabolites is achieved through wearable electrochemical biosensors that utilize advanced sensing platforms [230, 231].

CGMs have evolved beyond their initial use in diabetes management and are now significant nutritional tools for healthy individuals [232]. Recent CGM systems have been developed to include trend assessment, meal-response prediction, and the configuration of glycemic targets based on personal metabolic patterns [227]. Research indicates that implementing dietary modifications with CGM yields a 67% improvement in metabolic flexibility compared to conventional practices [233, 234].

The imminent release of biosensors capable of measuring stress hormones, inflammation, and micronutrient levels is poised to expand real-time monitoring capabilities further [235, 236]. Wearable platforms that can non-invasively measure vitamin D status, B vitamins, and electrolytes are entering clinical validation for approval. Their adoption may signify a significant advancement in the evaluation of nutritional status [237, 238].

Smart contact lenses and implantable sensors

Advanced biosensing systems include smart contact lenses for glucose and intraocular pressure monitoring, subdermal implantable biosensors for continuous biomarker monitoring, and smart textiles with biosensing functions [239]. The study posits that these technologies have the potential to facilitate continuous health monitoring with minimal interference, thereby enabling personalized nutrition recommendations by leveraging precise physiological data [240]. Research on the accuracy and user acceptance of a range of advanced platforms is yielding results. The bright contact lens, which monitors glucose levels, has been shown to have 92% accuracy compared with the fingerstick test. In contrast, implantable sensors for lactate and pH monitoring have demonstrated less than 5% drift over 6 months [239, 241].

AI in nutrition applications

Large language models for nutrition

The integration of large language models with nutritional databases and personalized health data could enable AI assistants to offer contextualized, real-time dietary advice. This system can analyze intricate biosensor data, consider individual preferences and constraints, and provide comprehensible justifications for its recommendations [242, 243].

Large language models in nutrition have demonstrated high proficiency in tasks such as meal planning and addressing dietary concerns. These professionals can consider a comprehensive array of factors, including nutritional requirements, food allergies, cultural preferences, budget constraints, and ingredient availability. Moreover, they can substantiate their recommendations with scientific reasoning, thereby enhancing their credibility and relevance in the field. However, AI-generated reasoning often hallucinates, resulting in confident but factually incorrect or entirely fabricated outputs that lack grounding in validated and current clinical evidence [140, 154]. Studies show that these systems may produce seemingly plausible yet inaccurate nutritional advice, reference non-existent studies, and offer outdated recommendations that do not align with clinical guidelines. Therefore, all dietary advice generated by AI must be verified by qualified nutrition professionals, such as registered dietitians and clinical nutritionists, to ensure its accuracy, safety, and suitability for a patient's context [155, 244].

The clinical validation of the system indicated that 89% of users reported satisfaction and that 73% adhered to the AI-generated meal plans over 6 months [12]. Importantly, this adherence should be interpreted alongside mandatory clinical oversight protocols that verify the nutritional adequacy and safety of AI recommendations before patient implementation.

Computer vision for food recognition

State of the art computer vision systems can now identify foods, estimate portion sizes, and calculate nutritional content from smartphone photos with >90% accuracy for common foods and >85% accuracy for complex mixed dishes. These systems integrate with personal health profiles to provide immediate feedback on meal choices and suggestions for optimization based on individual nutritional needs and goals [245, 246]. While the accuracy figures seem respectable, they reflect performance on test data collected in a controlled setting and do not generalize to real-world situations involving the preparation of various types of food with regional variability or ambiguous visual presentations [247, 248]. Furthermore,

AI-driven nutritional recommendations derived from image recognition data must be validated to ensure they are evidence-based and tailored to each individual's health status [154]. Health care professionals should critically evaluate the nutritional analysis generated by the AI for errors in portion estimation, ingredient identification, and macronutrient calculation before using it for clinical decision-making or patient advice [249, 250]. Verification protocols that incorporate automated image analysis alongside professional dietary assessments are essential for the safe and effective implementation of clinical nutrition practices.

Predictive AI models

As demonstrated by Bhuiyan and Nahid (2025), foundation models trained on comprehensive health datasets exhibit remarkable prediction accuracy for individual responses to dietary interventions [13]. The NutriGPT foundation model was trained on 2.4 million simulations of dietary intervention decisions made by patients who had previously changed their diets. The model demonstrated 91% accuracy in predicting the metabolic response following a dietary change, 87% in predicting which patients were likely to have adherence failures, and 82% in predicting the best time to intervene [251]. The use of predictive models facilitates a proactive approach to nutritional interventions, rather than a reactive one, suggesting alterations before issues emerge. When predictive models are employed to determine the timing and intensity of healthcare interventions, failure rates can be reduced by 56% and goal achievement increased by 43% [252].

Comprehensive digital health ecosystems

Modern precision nutrition platforms integrate multiple data streams, including wearable devices, smartphone applications, EHR systems, laboratory results, and environmental sensors, to create comprehensive health monitoring ecosystems. These platforms use federated learning to continuously improve recommendations while maintaining data privacy and security [253, 254].

Clinical studies of integrated digital health platforms demonstrate superior outcomes compared to single-modality approaches Table 5. Participants using comprehensive platforms show 73% better adherence to nutritional recommendations, 45% greater improvements in biomarker profiles, and 67% higher satisfaction scores. The key success factor appears to be the seamless integration of monitoring, feedback, and support rather than any single technology component [255, 256].

Table 5 Digital platform integration benefits

User Engagement	Ref
• 73% improved adherence rates	[255, 256]
• 45% longer engagement duration	[255, 256]
• 67% higher satisfaction scores	[255–257]
• 52% better goal achievement	[255, 256]
Clinical Outcomes	
• 38% greater biomarker improvements	[255, 256, 258]
• 29% reduced healthcare utilization	[255, 256]
• 34% faster goal attainment	[255, 256]
• 56% lower intervention failure rates	[255, 256]

Privacy, security, and ethical considerations

The integration of AI and multi-omics data in precision nutrition requires strong regulatory frameworks to ensure patient safety, data protection, and equitable access. The EU AI Act, which took effect in August 2024, classifies AI-based medical devices—including precision nutrition tools—as high-risk systems that demand rigorous validation, transparency, human oversight, and risk mitigation protocols [259]. Complementing this, the European Health Data Space (EHDS) Regulation, effective in 2025, facilitates secure secondary use of health data for research while establishing standardized data governance frameworks essential for multi-omics integration [260].

Data privacy is regulated by the GDPR, which requires explicit consent, data minimization, and protection of sensitive health information, including genomic and metabolomic profiles [261]. In the United States, the FDA issued guidance in January 2025 on AI-enabled device software functions, emphasizing lifecycle management, algorithmic transparency, and real-world performance monitoring to ensure safety and effectiveness [262]. Key ethical challenges include algorithmic bias and disparities in health equity. AI models trained on non-representative datasets may perpetuate inequities across racial, ethnic, and socioeconomic groups, worsening health disparities in access to precision nutrition [151, 263]. Addressing these challenges requires interdisciplinary collaboration among policymakers, clinicians, and AI developers to establish sector-specific guidelines, ensure diverse training datasets, promote transparency in algorithmic decision-making, and guarantee equitable access to precision nutrition technologies across all populations [12, 264].

Challenges and implementation barriers

Despite remarkable advances in multi-omics technologies and precision nutrition science, significant challenges continue to hinder widespread clinical implementation and equitable access to personalized dietary interventions [22, 186]. These barriers span technical, economic, social, and regulatory domains, each requiring targeted solutions to realize the full potential of precision nutrition for population health improvement [16].

Understanding and systematically addressing these challenges is critical for the successful translation of precision nutrition from research settings to routine clinical care [122]. Solutions must balance scientific rigor with practical feasibility, ensuring that advances benefit diverse populations rather than exacerbating existing health disparities [153, 265].

Technical and data integration challenges

Multi-omics data standardization

The integration of disparate omics datasets poses significant challenges. It is important to note that each dataset has a distinct data format, quality control procedure, batch effect correction, and analytical platform. Despite advancements in standardization, precision nutrition continues to be hampered by variability across laboratories. Consequently, the reproducibility of these findings is limited, precluding the establishment of generalizable conclusions [80, 266]. Current efforts focus on developing universal data standards, reference materials, and quality control protocols that can be implemented across diverse research and clinical settings [267, 268].

The absence of data patterns in nature has been shown to influence the process of multi-omics integration, as the availability of different omics layers across patients may vary. To ensure clinical applicability, advanced imputation methods and robust analytic techniques are required to effectively manage incomplete datasets, given the potential unavailability or cost-unfeasibility of complete omics profiling [20, 129].

Computational infrastructure requirements

Multi-omics data analysis necessitates substantial computational resources and specialized expertise, which may not be readily available in all healthcare settings. Cloud-based solutions and software-as-a-service platforms are emerging to address these barriers. However, concerns about data security, regulatory compliance, and cost remain significant obstacles for many institutions [269, 270]. The development of user-friendly analytical tools that clinicians can operate without extensive bioinformatics training is crucial for widespread adoption [22]. Automated pipelines, standardized workflows, and intuitive interfaces have been shown to facilitate the translation of sophisticated analytical capabilities into user-friendly clinical applications [271, 272].

The widespread adoption of precision nutrition is frequently constrained by substantial costs, limited access to advanced medical diagnostics, and disparate regional health infrastructure [16]. However, the accessibility and practicality of multi-omics profiling and digital health tools are limited for many populations, thereby raising concerns regarding health equity [273, 274]. To address these challenges, the development of cost-effective solutions is imperative, along with enhancing healthcare providers' training and facilitating access to new technologies.

Economic barriers and healthcare access

Cost-effectiveness and reimbursement

The financial burden of current comprehensive multi-omics profiling ranges from \$500 to \$2,000 per individual

Table 6 Cost-effectiveness analysis framework for precision nutrition (Per-Patient Costs)

Direct Costs	Potential Savings	Break-Even Timeline
Multi-omics testing: \$500–2,000	Reduced complications: \$2,000–15,000	Low-risk individuals: 3–5 years
Analysis software: \$50–200	Fewer failed interventions: \$500–3,000	High-risk individuals: 1–2 years
Clinical consultation: \$150–400	Improved adherence: \$1,000–5,000	Chronic disease management: 6–18 months
Follow-up monitoring: \$100–300	Preventive effects: \$3,000–20,000	Population health: 5–10 years
Digital platform: \$20–50/month	Productivity gains: \$2,000–8,000	Healthcare system: 2–4 years

Note: All costs and savings are presented on a per-patient basis. Multi-omics testing costs include genomic (\$48–137), metabolomic (\$137–279), and microbiome profiling. Cost ranges reflect variations across healthcare settings, intervention intensity, and geographic regions [1–3]. Break-even timelines represent estimated periods for cumulative savings to offset initial investment costs per-patient, stratified by risk profile and implementation context

[275], posing a substantial obstacle to its widespread implementation. Despite rapid declines in costs driven by technological advancements and economies of scale, these expenses remain prohibitive for a significant proportion of patients and healthcare systems [186, 275]. Recent advancements in nanopore sequencing and microfluidic technologies have demonstrated the potential for cost reduction, with single-cell multi-omics testing costs reduced from \$5,200/sample to more affordable levels [276]. Economic analyses demonstrate favorable long-term cost-effectiveness, but high upfront costs and unclear reimbursement policies limit adoption (Table 6) [134, 277]. The extent to which insurance coverage for precision nutrition services is available varies considerably, with the majority of payers currently categorizing multi-omics testing as experimental or investigational [185]. The absence of established regulatory frameworks for evaluating precision nutrition solutions engenders further barriers to coverage decisions [134]. The implementation of these tests faces various barriers, including financial constraints, the absence of standardized multi-omics testing techniques, and limited clinical utility frameworks for comprehensive genomic profiling in nutrition contexts [278].

Healthcare infrastructure requirements

To implement precision nutrition, in-depth changes to healthcare infrastructure—including provider training and technology improvements—are necessary [134]. A considerable number of health organizations lack the capacity and capability to implement these changes, minimal practices, and safety-net providers serving vulnerable populations [153]. The geographic disparity in access to precision nutrition services is pronounced, with urban academic medical centers at the forefront of implementation. Rural and other underserved regions demonstrate significant disparities [279, 280]. According to experts in the field, although telemedicine and mobile health solutions have the potential to address these disparities, further investment in telecommunications infrastructure and provider training is necessary [280, 281].

Population diversity and representation gaps

Genetic ancestry and reference populations

Precision nutrition strategies should account for genetic variation across ancestry groups to avoid exacerbating health disparities. Genetic variants that influence nutrient processing vary in allele frequencies and effect sizes across different populations depending on ancestry [282, 283]. The LCT gene exemplifies ancestry-specific genetic metabolic variability. The C/T-13,910 polymorphism (rs4988235), associated with lactase persistence, is found in over 90% of Northern Europeans, whereas its frequency is less than 10% in East Asians [284, 285]. Notably, ancestral populations in Africa and the Middle East have developed lactase persistence through independent mutations. A 2023 study involving various ethnicities found that the rs4988235 genotype predicts lactose intolerance with 85% accuracy among individuals of European ancestry, but only 42% among individuals of African ancestry [286]. The metabolic consequences extend beyond lactose tolerance; lactase-persistent Northern Europeans on a high-dairy diet have a 15–20% lower risk of type 2 diabetes compared to their lactase non-persistent counterparts [287]. Conversely, East Asian populations that lack lactase may produce more SCFAs by fermenting undigested lactose. For the TCF7L2 rs7903146 variant, allele frequencies range from 25 to 30% in Europeans, 35–40% in Middle Eastern populations, and 15–20% in East Asians. These differences in frequency also lead to varying effect sizes, with odds ratios ranging from 1.30 to 1.58. As demonstrated by these examples, ancestry-adjusted PRS and population-specific genomic databases are essential to ensure that interventions are not “precise” solely for individuals of European ancestry [288, 289].

Cultural and social determinants

To provide culturally appropriate precision nutrition recommendations, it is essential to consider the social determinants of health, including factors such as food access, cultural food practices, economic limitations, and social support [290, 291]. This source is beneficial for augmenting the school’s knowledge base. Research has demonstrated that technically optimal recommendations can, in some cases, have unintended consequences if they are

perceived as inconsistent with cultural norms or deemed impractical within specific social contexts. The integration of community-engaged research methodologies, encompassing the involvement of diverse populations in the design, implementation, and interpretation of studies, is imperative for the development of culturally responsive precision nutrition interventions [292]. Although these methods may require additional temporal, energetic, or other forms of input, they are frequently indispensable for achieving equitable outcomes and averting undesirable byproducts.

Regulatory framework and ethical considerations

Regulatory landscape evolution

Regulatory frameworks for precision nutrition are evolving rapidly but remain inconsistent across jurisdictions and application domains [293]. International harmonization of regulatory standards is needed to facilitate global development and implementation of precision nutrition technologies [294]. Current differences in approval requirements, evidence standards, and post-market obligations create barriers to innovation and limit access to beneficial interventions [265].

Data privacy and consent

The extensive collection and analysis of personal health data for precision nutrition raises significant privacy concerns that must be balanced with the benefits of personalized interventions [134]. Robust consent processes, data governance frameworks, and technical privacy protections are essential for maintaining public trust and ensuring ethical implementation [295]. As precision nutrition applications continue to proliferate, dynamic consent models that empower individuals to control the use and dissemination of their data are rapidly gaining prominence. These models must be user-friendly while simultaneously providing meaningful choice and control over personal health information [16, 68].

Algorithmic bias and fairness

The utilization of algorithms has the potential to perpetuate existing health disparities or generate even more pronounced disparities, contingent upon their validation in diverse populations by researchers [296]. Algorithmic bias stems from the potential incorporation of training data bias, the misapplication of model assumptions, and related factors. To ensure the fairness and adequacy of AI systems, it is imperative to leverage diverse development teams and inclusive datasets. Furthermore, it is essential to proactively mitigate bias in bias detection and continuously monitor the performance of algorithmic systems across various demographic subgroups. Regulatory frameworks are becoming increasingly stringent,

mandating the demonstration of algorithmic fairness for the approval and deployment of these systems [297].

Future perspectives and emerging frontiers

The future of precision nutrition lies at the intersection of rapidly advancing technologies, expanding scientific knowledge, and evolving healthcare paradigms [298]. Emerging frontiers include integration with digital therapeutics, expansion into preventive medicine, application to special populations, and development of population-level precision approaches that balance individual optimization with public health goals [142, 299–301].

Success in realizing this vision requires coordinated efforts across multiple domains, including technology development, regulatory science, health economics, implementation science, and health equity research [82]. The next decade will likely see precision nutrition transform from a specialized research area into a fundamental component of healthcare delivery and disease prevention [302, 303].

Technological innovations and integration

Next-generation omics technologies

The advent of emerging omics technologies holds great promise for expanding the breadth and depth of molecular profiling capabilities while concomitantly reducing costs and turnaround times. Single-cell multi-omics approaches hold great promise for achieving unprecedented resolution in the study of cellular responses to dietary interventions. These approaches will facilitate the revelation of tissue-specific and cell-type-specific effects that are currently invisible in bulk analyses [304]. Spatial omics technologies will provide critical insights into how nutrients and metabolites are processed within specific tissue microenvironments [305]. These approaches will be particularly valuable for elucidating the mechanisms underlying gut physiology, liver metabolism, and adipose tissue responses to dietary interventions at subcellular resolution. Long-read sequencing technologies will facilitate comprehensive characterization of structural variants, repeat regions, and epigenetic modifications that are challenging to assess with current short-read approaches [306]. This comprehensive genomic characterization will improve precision nutrition predictions by capturing previously undetected genetic influences on dietary responses.

AI and machine learning advances

Specifically, foundation models designed for biological data are poised to transform the field of precision nutrition. These models enable more accurate predictions with smaller datasets and better generalization across populations [119, 142]. The aforementioned models will incorporate multimodal data, including omics, clinical,

behavioral, and environmental data, to provide comprehensive health assessments and recommendations.

The use of causal inference methods will facilitate a more nuanced understanding of the interventions that will prove most efficacious for particular individuals, thereby transcending the limitations of correlation-based predictions and enabling a mechanistic understanding of dietary responses [307]. These approaches are instrumental in developing personalized interventions, rather than the current practice of making personalized predictions. Federated learning approaches can facilitate collaborative model development across institutions while ensuring data privacy. This could result in the development of more robust and generalizable precision nutrition algorithms [308]. These approaches are particularly important for incorporating data from diverse populations and healthcare settings.

Digital therapeutics integration

Precision nutrition is increasingly integrated with digital therapeutic platforms that provide evidence-based interventions through software applications. These platforms integrate personalized nutrition counseling, behavioral coaching grounded in cognitive-behavioral therapy, and peer support to address the psychological and social dimensions of dietary behavioral modification [300]. Technologies related to virtual and augmented reality may offer new opportunities for nutrition education, meal planning, and behavioral modification. The aforementioned immersive technologies can simulate culinary processes, provide real-time nutritional data, and facilitate engaging educational experiences that enhance comprehension and adherence to dietary recommendations.

Expanding clinical applications

Precision nutrition in cancer care

Oncology represents one of the most promising frontiers for precision nutrition applications, with growing evidence that nutritional interventions can influence treatment responses, reduce side effects, and improve survival outcomes. Tumor-specific metabolic profiles and treatment-induced metabolic changes create opportunities for highly targeted nutritional support [309]. The integration of pharmacogenomic and nutritional genomic data facilitates the optimization of diet-drug interactions, thereby enhancing treatment efficacy while reducing toxicity. Precision nutrition approaches have the potential to address cancer cachexia, treatment-related complications, and long-term survivorship concerns through personalized interventions [310]. Immuno-nutrition is a particularly active area of research, with studies focusing on how specific nutrients and dietary patterns can optimize immune responses to immunotherapy [311]. Preliminary research indicates that dietary interventions guided by

the microbiome's composition may enhance the response to checkpoint inhibitors and other immunotherapies.

Mental health and cognitive function

The gut-brain axis represents a pivotal nexus for precision nutrition applications in mental health and cognitive function. Recent research suggests that dietary interventions guided by microbiome profiling and genetic variants affecting neurotransmitter metabolism may improve depression, anxiety, and cognitive performance [312, 313]. Personalized approaches to brain health nutrition consider individual differences in blood-brain barrier permeability, neuroinflammation susceptibility, and neurotransmitter metabolism. These approaches demonstrate potential for preventing cognitive decline, optimizing cognitive performance, and supporting mental health across the lifespan [314].

Aging and longevity

The process of “precision nutrition” aims to promote healthy aging by optimizing cellular repair, managing inflammation, and enhancing metabolic flexibility. Genetic variations associated with cellular aging processes, DNA repair, and stress responses are used to personalize interventions that promote longevity and health span [315]. The development of customized nutritional strategies, tailored to specific aging pathways such as mTOR signaling, autophagy, and mitochondrial function, has led to personalized approaches based on individual genetic and biomarker profiles. Researchers posit that these approaches may enhance the treatment of age-related diseases and reduce functional dependency [316, 317].

Pediatric and developmental applications

The nutritional needs of children vary with their developmental and growth requirements, laying the foundation for long-term health. Nutrient requirements, which are influenced by genetic factors, metabolic development, and growth variations, guide infant feeding, childhood nutrition, and adolescent dietary interventions [318]. Genomic and microbiome risk profiling for early-life nutrition has the potential to help prevent obesity, allergies, and metabolic diseases in later life. Achieving an equilibrium between optimization and safety is imperative, as adequate nutrition during development is paramount [319, 320].

Population health and public policy integration

Population-level precision approaches

In the future, precision nutrition must balance individual optimization and population health objectives. Scalable approaches can enhance health outcomes while preserving personalization most effectively. This necessitates the

development of sophisticated models that account for population heterogeneity and the strategic implementation of precision methods in regions with the most significant public health implications [16]. A combination of PRS and population stratification methods will facilitate the identification of subgroups that will benefit most from precision strategies, rather than those who will thrive with population-based recommendations [125]. This targeted strategy has the potential to optimize health benefits while concurrently managing the implementation costs and complexity.

Global health applications

Precision nutrition methods can be adapted for low-resource settings and implemented as affordable interventions targeting specific populations, focusing on genetic variants and dietary patterns. These strategies support cost-effective interventions that have a significant impact on and align with existing healthcare systems. As mobile health platforms and streamlined testing protocols gain popularity, precision nutrition approaches will become increasingly viable for global health [321]. These initiatives are designed to address micronutrient deficiencies, optimize the use of local foods, and prevent diet-related diseases in a manner tailored to the specific needs of the population.

Regulatory science and ethical framework development

Adaptive regulatory frameworks

The development of precision nutrition technologies is imperative for the future and must be prioritized with a focus on safety. To maintain a competitive advantage amid technological advances and regulatory changes, it is imperative to implement adaptive regulatory frameworks that promote continuous improvement and the generation of empirical evidence in real-world settings [322]. Achieving global regulatory consistency is expected to stimulate the development and adoption of precision nutrition technologies, thereby making beneficial solutions accessible to a large population. Recent collaborative regulatory science initiatives have begun to address these coordination challenges [323].

Ethical AI and algorithmic governance

As AI becomes increasingly central to precision nutrition, robust governance frameworks for algorithmic fairness, transparency, and accountability become critical. These frameworks must address bias prevention, explainability requirements, and ongoing monitoring of algorithm performance across diverse populations [151]. Participatory approaches to AI development that involve diverse stakeholders in design, validation, and deployment decisions will be essential for ensuring that precision nutrition technologies serve the interests of all

populations equitably. Community engagement and co-design approaches are emerging as best practices in this domain [142].

Education, training, workforce development, and the critical need for clinical practice guidelines

To implement precision nutrition, educational programs for health care providers, researchers, and the public are essential, as are much-needed clinical practice guidelines (CPGs) to facilitate evidence-based practice [16, 206]. The sector is currently facing significant deficiencies in guidelines, limiting clinical uptake. Despite the existence of ten guiding principles for personalized nutrition implementation established by the International Life Sciences Institute [324] and the first nutrigenetics CPGs for omega-3 fatty acids and plasma lipids using GRADE methodology [325], multi-omics applications still lack sufficient guidelines. The latest statement from the Red Iberoamericana de Nutrición Personalizada (RINN22) is beneficial for implementing precision nutrition [17]; however, substantial gaps remain in the standardization of genetic testing interpretation, multi-omics data integration, clinical decision-making algorithms, and ethical implementation [185, 326]. This absence hinders the establishment of credibility, verification of efficacy, and equitable access [327]. Surveys indicate that only 24% to 33% of registered dietitians feel prepared to integrate nutrigenomics into their practice, highlighting a disconnect between evidence-based applications and premature commercial uses [82, 325]. The author identifies key urgent priorities: developing evidence-based cancer prevention guidelines using GRADE or AGREE II for significant gene-diet interactions, extending beyond omega-3 and lipids, and creating standardized competency frameworks for health professionals [264]. Additionally, developing ethical implementation guidelines is crucial, addressing data privacy, ancestry-specific issues, and informed consent [328]. The final urgent priority is integrating precision nutrition concepts into medical, nursing, and nutrition curricula [206]. Without robust CPGs, precision nutrition may struggle to transition from research to practice for the benefit of the population [329].

Conclusion

The implementation of precision nutrition has the potential to shift the healthcare paradigm, particularly in the delivery of services. The platform utilizes customized methodologies that enhance health outcomes by leveraging multi-omics data, AI, and digital health tools. The integration of genomics, epigenomics, transcriptomics, metabolomics, proteomics, and microbiomics facilitates a comprehensive understanding of individual nutritional needs and responses to nutritional interventions [22, 67].

In the contemporary era, machine learning algorithms have demonstrated a remarkable capacity to predict the outcomes of therapeutic interventions with high accuracy. This technological advancement has also enabled the prediction of individualized dietary regimens that take into account genetic predispositions, metabolic processes, and environmental influences [28, 330]. In one-year longitudinal studies conducted in real-world clinical practice, precision nutrition interventions—defined as personalized dietary strategies integrating multi-omics-derived biomarkers (genomic variants, metabolomic profiles, and microbiome compositions) with continuous physiological monitoring into EHRs and clinical decision support systems—yielded notable improvements in the domains of glycemic control, lipid profile, and dietary adherence. The outcomes demonstrated a 42% improvement in glycemic control, a 38% improvement in lipid profile, and a 51% increase in dietary adherence compared with the standard of care [84, 113]. Consequently, the risks associated with chronic disease, healthcare utilization, and healthcare expenditures are significantly mitigated. These benefits provide an economic argument for continuing scaling up, despite the presence of front-end costs [191].

Digital health technologies and AI-driven applications facilitate real-time dietary monitoring and interventions by providing continuous biomarker feedback [331]. The proliferation of wearable devices, mobile applications, and integrated health platforms has created opportunities for responsive nutrition, enabling interventions to adapt to fluctuating physiological conditions and life circumstances [185]. However, significant challenges persist regarding data standardization, population diversity, cost-effectiveness, regulation, and equitable access [186, 331]. Addressing these issues necessitates collaboration among various stakeholders [17]. In the future, precision nutrition applications are poised to expand to include cancer care, mental health, aging, and pediatric populations [332].

Furthermore, forthcoming advancements in this field are poised to integrate population health frameworks with precision nutrition initiatives. Education and workforce development are of paramount importance, necessitating extensive training for healthcare providers and public education initiatives to enhance health literacy around precision nutrition [333]. The subsequent decade will determine whether precision nutrition fulfills its promises for health or whether implementation hurdles limit access to the privileged and specialized [334, 335].

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Author contributions

A.N. Writing – Original Draft, Data curation, Conceptualization, visualization, Y.V. Writing – Review & Editing, Supervision.

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