Perspective: The "Virtual Digital Twins" Concept in Precision Nutrition

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ABSTRACT

Nutritional and lifestyle changes remain at the core of healthy aging and disease prevention. Accumulating evidence underscores the impact of genetic, metabolic, and host gut microbial factors on individual responses to nutrients, paving the way for the stratification of nutritional guidelines. However, technological advances that incorporate biological, nutritional, lifestyle, and health data at an unprecedented scale and depth conceptualize a future where preventative dietary interventions will exceed stratification and will be highly individualized. We herein discuss how genetic information combined with longitudinal metabolomic, immune, behavioral, and gut microbial parameters, and bioclinical variables could define a digital replica of oneself, a "virtual digital twin," which could serve to guide nutrition in a personalized manner. Such a model may revolutionize the management of obesity and its comorbidities, and provide a pillar for healthy aging. *Adv Nutr* 2020;11:1405–1413.

Introduction

Precision medicine is transforming clinical practice. A record-high number of new precision drugs, pharmaco-genetic, and cancer risk-related genetic tests have been approved by the US FDA during the last 2 y, testimony to the practical benefits of extensive research on genetic and lifestyle factors impacting human health. The FDA approvals address the need to reshape health care by redefining drug target populations and provide patients with the most clinically effective, safe, and cost-effective personalized treatment options. The new era of data-driven medicine, vis-à-vis technological advances, provide the foundation for "the assessment and management of human health at an unprecedented level of resolution" (1), referred to as high-definition medicine. In a forward-thinking review article, Torkamani et al. (1), envisioned the future of high-definition technologies towards an "actual digital twin" health model in which deep phenotypic and molecular characteristics of a diseased person are most closely matched to thousands or millions of patients with the same disease and similar molecular profile, allowing better prediction of individualized treatment and health outcomes. Various computational, in vitro and in vivo "humanized" models align to this concept, particularly in oncology (2–4).

Several lines of evidence call for a major conceptual and practical shift in dietetics towards high-definition nutrition that would parallel progress in precision medicine. We herein discuss this evidence, emphasizing the need to combine genetic, immune, metabolic, behavioral, bioclinical, and meta-genomic data to guide nutrition in a truly personalized manner. Extending the "actual digital twin" health model (1), we conceptualize a future in which these health and biomolecular parameters will endow the definition of a digital replica of oneself, a "virtual digital twin" (**Figure 1**),
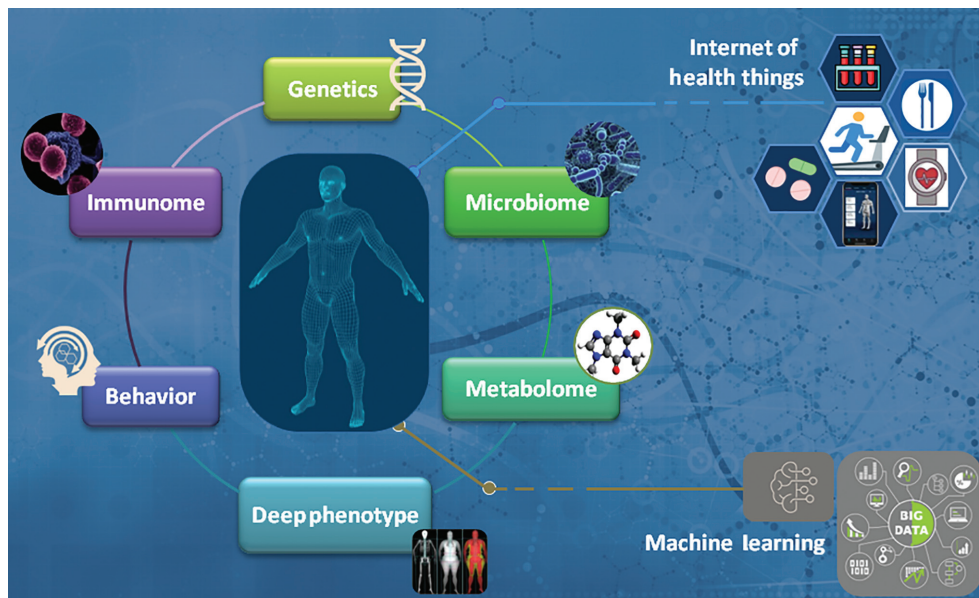
FIGURE 1 Genetic, epigenetic, immune, metabolic, microbial, and behavioral paths to nutrition interact, highlighting the need for a "holistic" approach to precision nutrition. A "virtual digital twin" could be constructed as a digital replica of oneself by combining longitudinal high-definition -omics data, bioclinical and phenotypic variables, and behavioral aspects (dietary habits, physical activity, sleeping patterns, etc.) of the same individual, collected through internet of things health care platforms and managed by machine learning algorithms to simulate specific dietary and lifestyle strategies in silico. Such a highly individualized platform may revolutionize the management of obesity and its comorbidities, and provide a pillar for healthy aging.

that could provide the most acceptable, adaptable, efficient, and cost-effective dietary and lifestyle recommendations.

Current Status of Knowledge

Genetic and epigenetic paths to precision nutrition

A plethora of twin and genome-wide association studies (GWAS) underscore a strong genetic influence on both human thinness (5) and obesity (6–8). Twin studies indicate that ∼40–70% of interindividual variability in BMI could be attributed to genetic factors (9), and >800 single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) have been associated with obesity (6–8). Many of these genetic variants impinge on key hypothalamic circuits that regulate appetite, emotional eating, and food intake (6), indicating that eating behavior—influenced by genetics—may significantly affect body mass. Other SNPs relate to energy metabolism and expenditure, insulin secretion and action, adipogenesis, and other key biological processes (6). As individual variants may have small or intermediate effects on BMI, genetic risk scores (GRSs) have been proposed as the most relevant source of identifying high-risk individuals who would benefit most from early lifestyle changes or preventative treatments (10). It should be noted, however, that an obesogenic environment is likely to preferentially uncover inherited susceptibility among those with highest genetic risk, in accord to the "missing heritability" reported in several obesity GWAS. Polygenic risk scores are emerging as the new frontier, by evaluating a large number of genetic

loci, not only those significantly associated with a defined phenotype or response (11).

There has been a long debate whether the macronutrient composition of dietary interventions impacts weight loss in individuals with obesity. In a seminal randomized clinical trial entailing 4 diets that differed in the percentages of essential macronutrients, the patterns of weight loss in overweight and obese were found similar for each diet (12). Notably, however, a considerable variation of weight loss was noted within each of the 4 dietary groups (12), indicating genetic influences in the response to dietary interventions. Beyond macronutrients, genetics may interplay with responses to micronutrients. For example, the association between vitamin D concentrations and cardiovascular disease risk varies among ethnic groups and likely reflects polymorphisms in genes involved in the biological activity of vitamin D (13).

Indeed, various clinical studies, including the POUNDS (Preventing Overweight Using Novel Dietary Strategies) Lost (12), the DioGenes (Diet, Obesity, and Genes) trial (14), PREDIMED (Prevención con Dieta Mediterránea) (15), Food4Me, and others, have uncovered genetic variants that may predict weight loss mostly in relation to specific macronutrients (16, 17). For example, obese individuals carrying the AA genotype of *FTO* rs1558902 respond to a high-protein diet with a significant reduction in BMI compared to those with a TT genotype (18). The AA genotype of *HNF1A* rs7957197 is associated with greater weight loss among individuals assigned to a low-fat diet

compared to those with TT alleles (19). Eating behavior has also been linked to specific variants. Thus, a high-protein diet significantly reduces the appetite of carriers of the A allele of rs9939609 at the *FTO* locus, whereas individuals with an A allele at *MC4R* rs7227255 display increased appetite when assigned a low-fat diet (20, 21). Variants at the *AMY1-AMY2* (amylase) locus (rs11185098) have been associated with weight loss irrespective of diet (22). Although association does not connote causation, several gene-diet associations have been experimentally validated in model systems [see, for example, (17, 23, 24)].

GRSs have also been explored in relation to responses to dietary components. For example, high coffee consumption has beneficial effects on weight loss only among those individuals with a high obesity GRS (25). A 32 SNP-based GRS can predict those individuals who are more susceptible to the adverse effects of sugar-sweetened beverages on obesity (26, 27) and a 13 risk allele GRS predicts reduction in blood triglycerides in individuals fed a diet supplemented with n–3 PUFAs (28). These are only a few examples of gene-diet interactions which, collectively, underscore the potential of genetically guided dietary recommendations for the management of obesity and for personalized healthy lifestyles (29). This area is rigorously explored by both the academic (30) and industrial sectors (31), including our teams.

Unlike the wealth of available information regarding the impact of genetic variants on BMI and nutritional responses, data on epigenetic effects is lagging behind. Whole genome DNA methylation profiles of adipose tissue and blood sampled from obese versus never obese individuals have identified a relatively small number of methylated genetic loci associated with BMI (32). Differential CpG methylation was predicted to affect genes involved in lipid and lipoprotein metabolism, substrate transport, and inflammatory pathways but appears to be predominantly the consequence rather than the cause of adiposity (32).

Nevertheless, there are several observations that underscore the need to continue exploring epigenetics in the context of precision nutrition. First, nutrition is a major environmental factor that may affect the epigenome, including DNA methylation. Second, the association of a subset of DNA methylation markers with BMI is stronger in certain populations (32). Third, the epigenetic heterogeneity observed at some of the differentially methylated loci among individuals, coupled with the graded relation between methylation and BMI, are indicative of epigenetic reprogramming, likely in adipocytes (32), which could be addressed by dietary and lifestyle interventions. This hypothesis aligns with the "epigenetic clock" model proposed by Steve Horvath in 2013 (33), which stipulates that "epigenetic age" is not only significantly related to biological age but is also both an indicator of overall health and subject to a healthy lifestyle (34). Along these lines, epigenetic reprogramming can ameliorate age-related hallmarks in vivo (35).

The immunome path to precision nutrition

Obesity is characterized by low-grade, subclinical systemic inflammation which affects several tissues and organs and impacts insulin sensitivity and secretion, and glucose homeostasis. As a result, obesity-associated inflammation is regarded as a driver of type 2 diabetes mellitus and a predisposing factor for the development of nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and several types of human malignancies (36).

Several studies have addressed changes in immune cell content in the peripheral blood in relation to BMI (37). The consensus drawn from the majority of these studies is that the immunophenotype of individuals with obesity differs from that of normal weight people, having increased numbers of white blood cells, neutrophils, intermediate $CD14^+CD16^+$ monocytes, and total $CD3^+$ and $CD4^+$ T cells, but reduced numbers of $CD8^+$ T cells and of regulatory T (T_{reg}) lymphocytes, a $CD4^+$ T cell subset which functions to counterbalance exaggerated inflammatory responses and maintain self-tolerance. Individuals with very low T_{reg} cell counts (<1.06%) have a 9.6-fold higher risk of developing an inflammatory obese phenotype (38). Elevated total lymphocyte counts, monocytes, and $CD4^+$ T cells are also found in the peripheral blood of overweight (39, 40). In contrast, effector memory $CD4^+$ T cells, which produce IFN-γ and TNF, are increased in obese but not in overweight individuals (40). We have recently reported experimental obesity-related changes in monocyte-macrophage responses to insulin characterized by increased glycolysis and a unique phenotype which may contribute to insulin resistance-associated inflammation (41). Several proinflammatory factors are also elevated in the plasma of individuals with obesity, including leptin, TNF, IL-6, and C-reactive protein (CRP) (42). CRP concentrations increase progressively with BMI (40) and decrease following weight loss (43). The aforementioned observations rationalized the development and use of inflammatory scores, which have uncovered associations with insulin resistance, BMI, waist circumference, and blood pressure (44).

Notably, systemic low-level inflammation is also a hallmark of aging. Dubbed "InflammAging" by Franceschi and colleagues (45), this aging-related inflammatory phenotype is typified by elevated serum concentrations of proinflammatory factors that include TNF, IL-6, and CRP, and are associated with frailty and increased morbidity and mortality in older adults (46). Elevated mortality risk in older people is also influenced by BMI (47). Effector memory $CD4^+$ T cells also increase with age (48), similar to the obese immunophenotype (40). Therefore, monitoring inflammatory markers could serve to mobilize dietary and lifestyle changes towards both healthy aging and obesity prevention.

Along these lines, dietary supplementation with n–3 PUFAs in healthy adults, and overweight and obese individuals has been correlated with reduced serum CRP, TNF, and IL-6 concentrations in several studies (49, 50). Notably, genetic variants have been found to interact with dietary fatty acids

to influence inflammatory responses (28, 51, 52). Micronutrients may also have significant effects on immune function; vitamin D3, for example, influences innate and adaptive immunity and confers anti-inflammatory properties, including positive effects on T_{reg} cell numbers (53). Several polymorphisms have been identified in vitamin D receptor and vitamin D metabolism-associated genes that affect organismal vitamin D status and health outcomes (54), further underscoring the need to combine genotypic, bioclinical, and nutritional data to achieve improved immunological outcomes.

The advent of novel technologies, such as single-cell profiling with mass cytometry (CyTOF), which enables >50 parameters to be assayed on single cells, is anticipated to provide high-definition immunophenotypic information and revolutionize our understanding of the interplay between nutrition and immunity. The "10,000 Immunomes Project" (55), which aspires to define all the genes and proteins that constitute the immune system, will also accelerate research towards this goal.

Microbiota: a novel path to precision nutrition

Advances in genomic technologies have dramatically expanded our appreciation of the extent of microbial colonization in different organs and tissues and its impact on both human physiology and disease (56, 57). These analyses so far suggest that the microbiota is an essential partner of various biological functions of the host, including development and training of the immune system, defense against pathogenic microorganisms, digestion of food components, and synthesis of certain micronutrients and bioactive compounds such as SCFAs and other metabolites [(56); see also next section].

In general, a low abundance of the phylum *Proteobacteria* and a high abundance of the genera *Bacteroides*, *Prevotella*, and *Ruminococcus* have been associated with a healthy adult intestinal microbiota (58). Compared with lean people, obese individuals have a different microbiota profile that is largely typified by a higher *Firmicutes*-to-*Bacteroidetes* ratio, reduced bacterial diversity, and altered representation of bacterial genes and metabolic pathways (59). Such microbial shifts are likely to pose a functional impact on obesity. Indeed, a 20% increase in *Firmicutes* phylum abundance translates to elevated energy harvest from food in humans (60). Similarly, the microbiota of leptin-deficient *ob/ob* mice enables higher energy extraction from nutrients in the absence of an increase in food consumption (61). These seminal observations raise important questions pertinent to the exploitation of microbiota composition in precision nutrition.

Currently, microbiome signatures are explored as prognostic markers. Thus, a low bacterial diversity is predictive of a propensity towards developing obesity (62) and cardiovascular diseases in relation to the consumption of certain nutrients (63, 64). Individuals with obesity bearing a low gene-count microbiome were also more refractory to improvement of inflammatory variables during weight loss interventions (65). Conversely, stratification according to the *Prevotella*-to-*Bacteroides* ratio improves the outcomes of nutritional interventions on weight loss (66). Dysbiosis and reduced abundance of SCFA-producing bacterial genera are observed in children with a high risk of developing type 1 diabetes mellitus even before the overt manifestations of the disease (67). Another example entails an algorithm that integrates microbiota and can accurately predict postprandial glycemic responses despite variations among individuals (68).

Due to the complexity and individuality of each person's microbiota, the extent to which modulation of microbiota composition can be realized in the context of precision nutrition and the management of obesity is currently unknown (69). Ideally, personalized intervention strategies could be developed to "normalize" a deregulated microbiota or further improve the response to a specific diet. Probiotics, prebiotics, synthetic stools, and stool transplantation have demonstrated efficacy towards weight reduction in experimental models of obesity which warrants further studies in humans. Along these lines, the obesity-associated reduction in T_{reg} cell numbers is reversed in mice administered probiotics (70), pertinent to the inverse correlation between T_{reg} and the inflammatory obese phenotype in humans (38).

However, the key determinant of human gut microbiota is diet (71, 72) which is also more amenable to intervention. Adherence to the Mediterranean diet, for example, leads to increases in the genera *Bacteroides*, *Prevotella*, and *Bifidobacteria* (73), and long-term consumption of fiber results in a high abundance of *Prevotella* genus (74), both of which are associated with a healthy intestinal microbiota. Although further clinical studies are required, the available evidence indicates that normalization of gut microbiota has the potential to contribute to metabolic health and weight loss (57). In the context of precision nutrition, it would be important to proceed beyond the compositional analysis of microbiota towards understanding its interaction with the host, including host genetics (57), and microbial metabolites that may serve as key mediators of the host-microbiota connection, as discussed in the next section.

Advances in metabolomics of nutrition

The metabolome entails the end-products of metabolic processes and it has thus attracted significant attention in nutrition sciences for the identification of biomarkers of dietary intake and obesity. Several conventional metabolites, such as nonesterified free fatty acids, triglycerides, and products of carbohydrate catabolism (e.g. pyruvate and lactate) are higher in the serum of obese subjects (42, 75). Additional metabolic alterations identified in obese compared with lean subjects included several branched-chain essential amino acids, the presence of which correlated with obesity-associated gut microbiota (42, 75). Functional studies showed that rats fed a high-fat diet supplemented with branched-chain amino acids rapidly developed insulin resistance (42), linking microbiota with circulating amino acids and obesity-related pathologies. This association was

further corroborated by the transcriptomic analysis of microflora from human twins discordant for obesity which uncovered induction of the de novo biosynthetic pathway for branched-chain amino acids in the microbiota of obese compared with lean twins (76). Remarkably, gut bacteria also produce metabolites capable of stimulating the central nervous system control of appetite, brain reward signaling, and emotional eating [reviewed in (77)]. These observations highlight the interplay between host genetic, metabolic, and microbial factors and further underscore the need for a holistic approach to nutritional interventions by combining several -omics outcomes.

Metabolomics has also been employed to identify biomarkers for differential responses to dietary interventions. Thus, weight loss in metabolically healthy obese women is accompanied by changes in plasma metabolites that include microbial products, lipids, and amino acids (78). For example, trimethylamine, an intermediate metabolite from the microbial metabolism of dietary carnitine and choline, is decreased after weight loss (78). Metabolomic studies in blood and urine from postmenopausal women with low bone density who received calcium and vitamin D supplements revealed different metabolic profiles which segregated with genotype and could partly predict nonresponders to treatment (79). Another study identified a metabolomic profile predictive of liver dysfunction in individuals fed a choline-depleted diet (80). Increased blood concentrations of acylcarnitines—intermediates of fatty acid and amino acid oxidation—are associated with cardiovascular diseases. Mediterranean diet interventions were found to diminish the risk of stroke associated with higher plasma concentrations of acylcarnitines before the intervention (81). These examples underscore the potential of exploring the human metabolome towards the identification of biomarkers that could predict responses to food components and dietary interventions in conjunction with additional -omics outcomes. Beyond obesity, metabolomics could be further explored to determine how food metabolites may influence food allergies or intolerances.

Behavioral aspects of nutrition
High-resolution monitoring of dietary behavior is an integral part of precision nutrition. A precise quantification of the type, amount, and frequency of food consumed by a person should ideally be accomplished by real-time monitoring rather than 24-h dietary recalls or short-term measurement of food consumption. Innovative technologies are being developed and will be increasingly utilized for the recording of dietary parameters. Table-embedded scales (82), automatic ingestion monitors that incorporate sensors for jaw motion with hand gestures and an accelerometer (83), smart-phone camera applications that calculate contents and calories through deep learning algorithms (84), and tooth-mounted sensors capable of recording a wide range of nutrients (85) are some examples of devices that aim to provide a more accurate means to log and adjust food consumption than dietary recalls. In addition to food quantity and quality, monitoring

of food timing is also important as it affects weight loss effectiveness in conjunction with circadian cycle-related gene variants (86, 87). Such technologies are often combined with wearable sensors that offer continuous or frequent recording of several health parameters, including heart rate, oxygen saturation, respiratory rate, and blood pressure.

Activity tracking devices may provide additional insight into physiological measurements, a convenient and indirect estimate of energy consumption, and an objective reference for the motivation of specific health-promoting behaviors. Activity tracking includes monitoring of sleep duration. Short sleeping behaviors have been associated with irregular eating, higher total energy intake, and lower quality diets (88). Therefore, improving sleeping patterns has been proposed as an integral part of health promotion strategies that extend to weight management (88).

New technological advances may also assist in the assessment of basic emotions which are relevant to eating behavior, including measurement of hunger and food reward (89). For example, voice and image analysis has been used to detect mood disturbances relevant to eating disorders (90). As emotional functions are influenced by social interactions (91), environmental monitoring at high resolution may further contribute to the modulation of physiological, cognitive, and emotional states in the context of precision nutrition.

Furthermore, recent evidence suggests that dietary habits and behavioral eating have a strong genetic influence (92, 93). For example, of 85 curated habits analyzed, 83 were found to be significantly heritable and to be associated with several SNPs (93). Collectively, current evidence suggests that behavioral aspects of nutrition should be considered through a combination of genetics and real-time monitoring of food intake, physical activity, and emotional states.

Future directions and challenges: towards a "virtual digital twin" model for human nutrition
The adoption of high-definition technologies is leading to the accumulation of a wealth of data regarding basic health units (e.g. whole genome SNP profiles, immunophenotypes, bioclinical data, etc.), behavioral information (e.g. physical activity tracking), and environmental monitoring (e.g. food consumption). The UK Biobank represents a prime example of these efforts that have also led to major discoveries in the context of gene-diet interactions. Entries from such sources could aid the identification of "actual digital twins," a set of people with similar characteristics at their most basic health units (1). The health outcomes of "actual digital twins" could be utilized to formulate basic prognostic models and actions that are predicted to be more relevant to the person in question and lead to improved outcomes compared with current practices.

A "virtual digital twin" could be constructed as a digital replica of oneself by high-definition data of the same individual, thereby extending the "actual digital twin" health model. To achieve a truly personalized platform in nutrition, the "virtual digital twin" should include a personal health baseline and enable the incorporation of health and lifestyle

data in young (disease-free) versus old (disease-prone) age, along the lines of the longitudinal holoʼome monitoring we have previously proposed for colon cancer (94). For example, the obesity GRS could serve as an early-life, albeit incomplete, virtual representation of a baseline risk of weight gain which could progressively be enriched by the incorporation of genomic, metagenomic, immune, behavioral, and deep phenotypic data to build a "virtual digital twin" (Figure 1). Integrative -omics technologies, wearable sensors, internet of things (IoT), and consumer internet behavior are available tools and potential sources of such data with increasing capabilities that could spearhead early preventive actions for health maintenance.

Deviations from health states, such as an increase in BMI, a reduction in gut bacterial diversity, changes in bioclinical parameters (e.g. CRP, serum lipid profile), or an elevated inflammatory score, should enable health professionals to simulate further specific dietary and lifestyle strategies in silico by using the patient's "virtual digital twin." In this manner, unwanted, unnecessary, or even harmful dietary or lifestyle choices could be eliminated and only the most promising interventions could be applied and monitored. A "virtual digital twin" may also serve as a powerful motivational tool that reinforces specific health care choices. Indeed, various public surveys have indicated that individuals are more likely to make nutritional choices and adhere to dietary recommendations if these are based on their molecular profile (95, 96).

The applicability of this model is underscored by a study by Price et al. (97) in which several metabolic, bioclinical, microbiome, and physical activity data were collected from 108 people 3 times over a 9-mo period and coupled to their genotype. Polygenic risk scores (PRS) and correlation networks were generated by integrating these data and identified clusters of analytes associated with physiology and disease which assisted in the implementation of behavioral coaching that helped individuals to improve health biomarkers. The results of this study represent an elegant example of high-definition health monitoring comprising a set of health and behavioral parameters that could serve as a pillar for the "digital twin" model of precision nutrition and healthy lifestyle.

Despite technological progress, several conceptual and practical barriers to the development and implementation of "digital twin" models need to be overcome. Personalized dietary advice is strongly determined by the way molecular, phenotypic, and bioclinical data are appreciated and utilized, calling for a change in the training that health professionals receive and a stronger interaction among relevant scientific disciplines. The former is highlighted by a recently published survey reporting that whereas 93.5% of dieticians perceived personalized nutrition as of high importance, only 9.5% of them had received some training on nutrigenetics (98). Although the cost of -omics technologies rapidly decreases and their performance increases, stronger computational tools and capabilities are likely to be required to accommodate and interrogate the large amount of data

generated. Mathematical models are being developed for both polygenic prediction of weight/obesity trajectories (7, 26) and in the context of genetically guided nutrition (99) but further development of machine learning algorithms will be required to fully realize the potential of big data exploration in precision nutrition (100). IoT health care platforms are rapidly emerging to support the networking of mobiles, wearables, and other physical devices but need to be extended to facilitate the assembly and integration of longitudinal biological, nutritional, lifestyle, and health data. The implementation of "digital twin" models will also require carefully defined technical means and safeguards to protect sensitive personal information along with a specialized, detailed legal framework. Important questions such as who processes these data, where and how it is stored, who/under what conditions has access to these data, how can maximum data access protection be achieved, as well as how safe and effective database interoperability is ensured, will need to be carefully addressed.

Conclusions

The rapid progress in the field of precision medicine paves the way for a major conceptual and practical shift in dietetics towards high-definition nutrition. It is now evident that the wealth of information extracted from the human genome, combined with longitudinal metabolomic, immune, behavioral, and gut microbial parameters and bioclinical variables could be explored towards improved dietary choices. A guide for the future will be to develop user-friendly, artificial intelligence-based "virtual digital twin" platforms (Figure 1) that will endow health professionals with fully informed decision-making capabilities, surpassing stratification and providing nutritional and lifestyle recommendations that are highly individualized. We propose that such a platform may revolutionize the management of obesity and its comorbidities, and provide a pillar for healthy aging.

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