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## Precision nutrition-based strategy for management of human diseases and healthy aging: current progress and challenges forward

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Currently, the treatment of various human ailments is based on different therapeutic approaches including traditional and modern medicine systems. Precision nutrition has come into existence as an emerging approach considering the diverse aspects such as age, sex, genetic and epigenetic makeup, apart from the pathophysiological conditions. The continuously and gradually evolving disciplines of genomics about nutrition have elucidated the importance of genetic variations, epigenetic information, and expression of myriads of genes in disease progression apart from the involvement in modulating therapeutic responses. Further, the investigations have presented the considerable role of gut microbiota comprising of commensal and symbionts performing innumerable activities such as release of bioactive molecules, defense against pathogenic microbes, and regulation of immunity. Noteworthy, the characteristics of the microbiome change depending on host attributes, environmental factors, and habitat, in addition to diet, and therefore can be employed as a biomarker to unravel the response to given food. The specific diet and the components thereof can be suggested for supporting the enrichment of the desired microbial community to some extent as an important part of precision nutrition to achieve not only the goal of human health but also of healthy aging.

KEYWORDS

biomarker, microbiota, bioactive constituents, machine learning, algorithm, immunity

### **1** Introduction

The rising pressure of different disorders including chronic diseases ensuing from ever changing complex epidemiological events has long been highlighted (1) to pose risks to health and life span (2) in addition to those resulting from mineral imbalances. Surprisingly, the mortality and disabilities caused by chronic diseases are comparatively higher than infectious

diseases and injuries (3). The risk factors for such diseases are identified as lifestyle modification at the individual level, variation in diet at global scale, declining physical activities, lack of preventive measures, and nutrient deficient foods. Noteworthy, sufficient intake of nutrients promotes good health, whereas, the deficiency of essential nutrients has tens diverse diseases (4). Therefore, several developed countries like United States, European Union, across the globe have made the implementation of essential minerals and vitamins mandatory. Apart from the suggestion of recommended diets comprising of plant and animal based products such as vegetables and meat, providing essential minerals, amino acids, vitamins, and fatty acids known to be required for sustaining the health of a given populace. Moreover, the continued qualitative and quantitative modifications in human diet owing to technological advances meant for food generation as well as processing have resulted in substantial perturbations of metabolic activities leading to varied human health disorders (5-7) including cancer, allergies, and cardiovascular diseases. Such perturbations resulting from modulations in dietary contents are much pronounced in developed countries.

The alleviation and treatment of human diseases can be divided broadly into traditional (Ayurveda, Unani, Siddha, etc.) and modern medicine systems (Allopathic). Traditional medicine relying to a greater extent on natural products of plant origin has long been recognized for treating different human disorders (8, 9). The development of strategies for prevention of innumerable diseases through improvement of immunity as well as offering the ways for produce valuable drugs (10, 11) is important approach of disease management. Traditional medicine has also been differently referred to as complementary and alternative medicine (12). The modern medicine is characteristically marked by the continued advances in technology aimed toward refining diagnostic methodologies and treatment of disorders started from 1946 to the current period (13). Modern medicine employing a single or mixture of a few purified bioactive compounds could have profound undesirable effects in comparison to traditional medicine generally prescribing crude mixtures of plants causing minimum side effects rendered by modulatory action of other components. Further, the isolated bioactive used in modern medicine systems to treat human health disorders should rather be used for deciphering the mechanism of action (14).

Precision nutrition is an emerging research frontier for managing health and treating human diseases through extensive investigations on bodily metabolic responses so as to suggest optimum dietary plans (15). The science of precision nutrition involves major factors such as environmental exposures, lifestyle, plausible interaction between gene and nutritional components (nutrigenomics), gut microbial communities, and processes influencing gene expression not only at the intra-individual level, but also at the inter-individual level (16, 17). The implementation of precision nutrition can be successful through analysis of individual features, continuous nutrient availability, and control as well as site-specific delivery (16), in addition to the introduction of different omics technologies.

Recently, the contribution of metabolomics in achieving the targets of precision nutrition has been reviewed by Brennan and de Roos (17). In this context, the strategy of metabolomics may comprise analyzing metabolic constituents (18) to reveal the knowledge concerning the effect of nutrients on metabolic activities, and available bioactive molecules. The variations in metabolic profiles, therefore, can be used for identifying metabotypes to advise diet plan. Furthermore, the data available on metabolite patterns can

be combined with additional factors to gain insight into an individual's response to dietary intake. The precise identification and analysis of metabolites using mass spectrometry (MS), infra-red (IR), and Raman spectroscopy, as well as nuclear magnetic resonance (NMR) in combination with modern computational approaches, can further advance the progress in the discipline of metabolomics (19, 20). Additionally, different approaches including nutrigenetics, epigenetics, and nutriepigenetics (21, 22), proteomics (23), gut microbiota (24), dietary interventions (25), nutraceuticals (26), lifestyle (27), and machine learning tools (28) have shown promise in the field of precision nutrition focused toward better human health (Figure 1).

Most of the previous articles have included only a few aspects of precision nutrition. The holistic information to our knowledge is still lacking. Therefore, the present review has attempted to provide updated information about different strategies adopted for precision nutrition. The limitations and future opportunities in the discipline of precision nutrition given good human health are finally discussed.

# 2 Different omics technology and precision nutrition

### 2.1 Nutrigenomics and management of human health in the era of the 21st century

The successful launch of human genomics in the 2000s led to the emergence of novel research frontier including nutrigenomics which deals with the study of interaction between dietary components and the genome, proteome, and metabolome. However, the continuous development of several omics like metabolomics, proteomics genomics, etc. has provided ample information not only for nutrigenomics but also mainstream to the nutritional values at individual level recognized as precision nutrition.

Nutrients are environmental factors having (i) the potential to alter gene expression, and (ii) increase the risk of diseases through impairing the epigenome of the developing organisms. Exceedingly increasing interest in such interactions led to the emergence of nutrition genetics or nutrigenetics, which allow us to understand the relation between diet and gene expression although they follow different approaches. Nutrigenomics deals with the study of the effect of nutrients on gene expression, while nutrigenetics describes the cellular response to the nutritional components apart from other external factors by observing metabolism and the site of action (29).

### 2.2 Metabolomic profiles (metabolizing)

Different metabolic constituents can be regarded as biomarkers to provide real-time information about the dietary food intake and quality of the food consumed by the individual (17). Clark et al. (30) in a review reported the potential biomarkers for whole grains, soy, and sugar that have been validated primarily based on several criteria such as biological plausibility, time and dose–response, robustness, reliability, stability, and performance of the method which have used to explore the biomarker potential.

Recently, some of the studies have indicated the use of biomarkers as a tool for establishing dietary patterns. For example, multiple plasma metabolites have been used as a signature biomarker in the Mediterranean diet and further assessed for their association with



Strategies in knowledge integration and precision nutrition against aging and diseases involve interdisciplinary collaboration, multi-omics data integration, longitudinal studies, systems biology, and precision health technologies. The development includes personalized nutrient formulation, behavioral interventions, community engagement, data security, and global collaboration. Major outcomes: increased longevity, disease prevention, improved quality of life, reduced healthcare costs, and personalized therapeutic approaches.

cardiovascular disease (CVD) risk (31). Furthermore, several studies also indicated the influence of metabolic profile-based biomarkers in the assessment of disease risk (32). However, it has been concluded that factors such as age, body mass index (BMI), etc., play a significant role in influencing the potential of the biomarker of the individual.

The metabolomics approach is further applied to classify the individuals based on their metabolic profiles. This approach allows for the comprehensive analysis of metabolites, thereby providing a detailed understanding of the metabolic processes and pathways active in different. In precision nutrition, metabolyping plays a vital role in the development of tailored precision nutrition via categorizing individuals based on their unique metabolic profiles (33). Generally, the metabolizing approach is based on several biomarkers (triacylglycerol, cholesterol, HDL-cholesterol, and glucose) to classify the population of definite size into metabotypes that are further subjected to delivering tailored advice (34). However, the concept of metabotypes further needs to be redefined considering the dietary requirements and the economic status of the population because these factors significantly influence metabolic profiles and health outcomes.

### 2.3 Metagenomic profiles

Development of cutting-edge sequencing tools like nextgeneration sequencing (NGS)which explore the hidden information concerning spatial and temporal variation of microbiota present in any biological samples. Metagenomic profiling of the gut microbiome of an individual's mid gut play a vital role in nutrigenomics. Furthermore, studies indicated that gut microbiota changes from birth to successive stages (35). Besides this, microbiome profiling also helps to decipher the type of food preferred by certain age groups. The presence of Firmicutes- and Bacteroides-dominant patterns in adult age groups indicated the long-term ingestion of carbohydrate and animal fat and/or protein-rich diet, respectively (35, 36). These findings revealed how factors like age, and food habits affect the structure and functions of gut microbiome dynamics and therefore should be considered while handling metagenomic data. However, integration of other "omics" such as genomics, transcriptomics and metabolomics will provide more comprehensive overview of an individual variability in response to diet and enables the development of personalized nutritional strategies that are more effective in promoting health and preventing disease.

### 2.4 Nutrigenetics

The interaction of personalized diet or nutrition and genes with the objective of achieving sound health is the ultimate goal of nutrigenetics. Nutrients that we intake are one of the environmental factors that interact with the genes and affect the DNA metabolism, repair mechanism, and gene expression of individuals. Recent published reports further confirmed that single nucleotide polymorphisms (SNPs) can be used as molecular tools to gain the information on the interaction between human diseases and the nutrition diet (37). For example, phenylketonuria (PKU) disorder is the result of altered gene expression by SNPs, interaction with metabolite leads to the deficiency of the phenylalanine hydroxylase gene (38). Other examples of polymorphism include Lactase-phlorizin hydrolase gene (LPH) polymorphism, glutathione peroxide gene polymorphism, Manganese superoxide dismutase (MnSOD) in which substitution or deletion of the specific genes resulted in an increased risk of liver and breast cancer, respectively (39). There is growing evidence that multiple pathways may be involved in the cause of multiple diseases where transcription factors alter gene expression patterns via interaction with bioactive food components (40). The influence of transcriptomic on gene expression is not only dosedependent but also time-dependent. Future aspects of nutrigenetics can be helpful in knowing which genetic factors should be given to particular genetic subgroups that may reduce the risk of emergence of chronic diseases.

#### 2.5 Nutriepigenetics

Epigenetics involves the switch on or switch off the gene expression without affecting the DNA sequences. In general, epigenetics involves DNA methylation, histone modifications, and non-codingRNA regulation to influence cellular metabolism. Bioactive food components such as micronutrients and chemicals are known to be involved in DNA methylation (41). Several studies indicated the role of dietary factors in the provision of methyl for the formation of S-adenosylmethionine that may alter the DNA methyltransferase activity and impair folate metabolism. Disruption in foliate metabolism eventually causes risk of cardiovascular diseases, neurological disorders, and other developmental anomalies (41, 42). In addition to DNA methylation, the role of non-coding RNAs [microRNAs (miRNAs)] and long noncoding RNAs (lncRNAs), has also been reported in the epigenetic process. Recently, miRNAs and lncRNAs, are known to have links with chronic disorders like cardiovascular diseases and obesity (43). In nutshell, DNA methylation and miRNAs can be treated as target markers for future precision dietary interventions.

# 3 The role of microorganisms (gut microbiome)

## 3.1 Human microbiome and role in human health management

The human microbiome influences human physiology through different mechanisms. The gut microbiome regulates digestion, metabolism, colonization resistance, immune modulation, and cellular functions in various ways (44). The dysregulation of microbial community functions may induce inflammations and disease development. The pathogenesis of opportunistic microbes may occur in these conditions of gut dysbiosis. However, imbalance in the composition of normal gut microbiota represents dysfunction or disorders (45). The association of gut microbiota with human health and diseases is now evident by various investigations (46). The existence of gut-brain and gut-lung axis is now correlated with illnesses, and associated with brain and respiratory tracts respectively, suggesting the importance of gut microbes in human health. However, there are still many aspects to explore and to better understand the association between gut microbiome and human health in complex disorders including cancers and other serious illnesses like respiratory illness, i.e., COVID-19 infections.

Current disease-specific therapeutic approaches may miss the large portion of the microbial populations, whose impact may be significant on human health. Thus, personalized medicine has been focused on therapeutics now (45). The personalized medicine is a future path of diagnostics and therapeutics as it takes care of individuals' physiological and genetic factors (45, 47). Further, each patient has different biological habits, lifestyle, metabolic profile, food environments, and gut microbiome. So, precision nutrition could help design comprehensive diets plans based on individual variables. It also takes care of socioeconomic parameters during recommendations of diet plans (48). Further, the modern lifestyle has influenced our dietary patterns and food habits adversely leading to obesity and other related health problems (49). Therefore, the dietary recommendations can play an important role in disease management. The role of personalized nutrition is to manage diseases by diet monitoring and recommendations (50). There are many layers of the dietary recommendations. The genetic and biological characteristics of the individual are taken care of while determining the dietary recommendations in personalized nutrition (45). The fat content of the diet, and other modifications in obese or diabetic individuals is one of the such interventions while fixing for the course of personalized medicine. The same type of the diet may have different metabolic responses in different patients. The difference in glycemic responses in different patients has also been observed (51). The gut microbiome affects human metabolism in different ways and thus influences the manifestation of the diseases.

The chronic disease of arteries identified as atherosclerosis is responsible for significant mortality worldwide. The use of hypoglycemic, antiplatelet, and lipid lowering drugs are the current therapies for the treatment of atherosclerosis (52). The role of trimethylamine-N-oxide (TMAO) is associated with gut microbiota and can provide strategies for management of the atherosclerosis (53, 54). The consumption of red meat leads to the formation of TMAO by gut microbial activities. Thus, avoiding red meat is suggested for managing atherosclerosis (55, 56). In the case of chronic kidney disease (CKD), the prevalence of atherosclerotic events is higher. Higher TMAO levels are positively correlated with serum creatine and urea in CKD patients (57). Further, it is found that glucose intolerance susceptibility has an association with gut microbiota and non-caloric artificial sweeteners (NAS) can increase glucose intolerance (58). These artificial sweeteners are not absorbed by the gut and are thus speculated to interact directly with the gut microbiota and may affect physiological functions (59, 60). Thus, avoiding artificial sweeteners is considered a subset of personalized nutrition in such patients.

The gut microbes help in the catabolism of food, appetite alteration, and harvesting of nutrients. The live microbes in the form of "probiotics" when administered are useful in providing health benefits to the host. The microbes like *Bifidobacterium*, *E.coli*, and *Lactobacillus* are being used for disease management including gut dysbiosis, diarrhea, inflammatory bowel disease, Crohn's disease, and recurrent *Clostridium difficile* infection (61, 62). The advancements in technology helped to develop strategies for microbiota transplantation, which has been proven to be useful in treating the illness associated with gut dysbiosis. Here, gut microbiota can be altered by a novel approach called fecal microbiota transplantation (FMT), a promising approach to alter gut microbiomes.

## 4 Precision nutrition and their characteristics

Each individual requires some specific amount of nutrients depending on genetic makeup, metabolisms, and microbiomes (63). Therefore, precision nutrition can be recommended for the individuals irrespective of the population level. Precision nutrition provides a detailed overview of the genetics, metagenome, microbiome, metabolome, and epigenetics of the individuals through latest next-generation analytical techniques. The generation of the analytical data and their assessment via computational-aided methods help in sharing the connection between the diet, lifestyle of the person, and health of the individuals (64).

Different populations of the world have some specific characteristics depending on cultivated crops, climate, and geographical location. These differences also lead to variations in the genetic makeup of the population. Although various governmental institutions have proposed different types of nutritional guidelines for the population, these guidelines give a brief overview of nutrient composition, nutrients needed, and a particular guideline for the population (65). Moreover, the differences in the population, regional diversity, and the genetic makeup of the person allow variation in the guidelines among different regions (66).

Recognizing the needs of individuals in view of precision nutrition is much challenging. The identification and development of nutritional advice for individuals require a broad analytical instrumentation, a computer-generated database, and extensive research analysis. Noteworthy, the differences in developmental stages, physiology, and health conditions contribute to the varied nutritional and caloric requirements of individuals. During the critical growth phase, adolescents require higher levels of proteins, and carbohydrates in comparison to adults (67). Similarly, pregnant women require some unique diet plan to nourish the growing infant. However, the elderly person facing challenges related to bone and muscle aging is advised to consume foods abundant in bioavailable calcium and proteins to address these age-related issues (68). Additionally, with the passage of age, physical activity often decreases, making it necessary to opt the foods having lower calorie density to prevent weight gain and obesity. On the contrary, individuals in demanding professions like army men, fire fighters, and athletes require calorie-dense, nutrient-rich foods (69). Variations in the gastrointestinal physiological patterns of the individual persons may also necessitate different nutrient profiles and levels of digestibility in their food (70).

The symbiotic relationship between the human body and the intestinal flora is crucial for the maintenance of normal physiology and metabolic function. The variations in normal microflora including intestinal flora of the individuals can led to genetic differences (71). However, the some of the studies have revealed that the composition and diversity of the intestinal microflora is influenced by the diets standing out as one of the most easily modifiable external factors (72).

The variations in dietary patterns significantly influence the microflora composition of population (73). For example, Japanese individuals harbor a distinct microbial strain in their intestinal tracts capable of secreting metabolic enzymes capable to digest algal constituents, a trait attributed to regular consumption of seaweed (74). This study underscores the direct impact of dietary interventions on the intestinal microflora and their functional aspect required for the normal functioning of human health.

## 5 Nutritional omics and systems biology

In the early stages of food nutrition, nutrigenomics research primarily focused on the exploration of new mechanisms related to nutrition and diet through the application of transcriptomics. The oxidative stress and inflammation can lead to changes in the transcriptomeas compared to the normal. So, the investigation of the proteome and the transcriptome will help in understanding the food patterns of a healthy person (75). Similarly, the advanced metabolomic approaches are gaining prominence in nutrition research because metabolites directly reflect the products of dietary intake and metabolism, which further help in the assessment of the relation and molecular pathways between diet metabolisms and the diseases (17).

The metabolism of the food in the human body is a complex phenomenon. Different metabolomic approaches may lead to identification of the new metabolites in the body that have prominent role in the functioning of colonic microflora and therefore impact on normal functioning of the human health (76). For example, in his study Rådjursöga et al. (77) reported that intake of breakfast cereals leads to enhancement of some specific amino acids like proline, tyrosine, N-acetylaminoacids in serum of the adults human body. However, the ingestion of ham and eggs leads to the enhancement of creatine, methanol, and isoleucine in the serum. Similarly, the lipid peroxidation metabolites considered as the markers to differentiate stable angina pectoris and myocardial infarction (78).

The metabolomics study has also provided an insight into individual's biological age (79). Under the conditions of chronic diseases, the biological age becomes older than the actual age. The dietary intervention indicated that the ingested food and metabolites thereof affect the metagenome, metabolome, and transcriptome. Thus, the detection of changes in the metabolome, transcriptome or the metagenome at the early stages of the disease development can be helpful in developing the formulation of the new dietary patterns as a part of precision nutrition to achieve the goals of human health. Nutriomics involves the investigation of interactions between the human diet and genes, and their influence on the human health at the both molecular and population levels. This knowledge serves as a basis for creating personalized dietary interventions and healthcare strategies by analyzing individual's genome structures. In the early stages, nutriomics research primarily focused on exploration of new mechanisms concerned with the nutrition through the application of transcriptomics and proteomics (17).

Modern food industry is facing a significant challenge in terms of food safety and waste, given the global production and transportation of ingredients and food items (80). It is imperative for the nutraceutical and food industries as well as government to adopt a plan (i) to prevent the food contamination, (ii) control minimize postharvest storage loss from the pathogenic microbes, and (iii) minimize the application of hazardous chemicals. In addition, authorities should introduce plans to enhance the nutrients composition of the food in order to maintain health and improve immunity.

Nowadays, the food industries and the academia are searching for alternative of various food ingredients from the proteins rich animal products like red meat, fish, eggs to plant based products, fermentation products, and cell cultures (65). Such kind of shift in food pattern may help in reducing biodiversity loss, greenhouse gas emission, and the maintenance of natural resources (81). However, it is crucial that foods derived from alternative protein sources are not only environmentally friendly but also nutritionally sound. While the macronutrient composition of many alternative protein sources resembles that of animal-derived foods, considerations, along with digestibility, are important. Additionally, the affordability, convenience, and taste of the food products constituted of alternative protein source are crucial factors of consumer acceptance (65).

# 6 The latest strategy to reduce the diet burden

The quality of the diet has major influence on the health of human beings. The population served with improved diet quality showed better resistance against the diseases and infections with improved health outcomes (82, 83). However, the healthy and the beneficial pattern of diets are the results of the presence of nutritional factors in the food. For instance, nowadays the healthy nutrient foods consisting of fresh fruits, vegetables, and fish are considered as the rich source of vitamins, minerals, antioxidants, etc. (83). However, the processed meat, refined grains, and sugar rich drinks have been considered as an unhygienic or unhealthy dietary pattern (84). The nutrients rich foods are considered to support the growth of gut microbiome and directly or indirectly affect the microbiome functioning with the resultant prevention of chronic diseases (85, 86).

Although the impact of nutritional content on health may be observed at any stage of disease, diet quality has been considered as one of the prime factors during diseases developments and the chances of infection can be reduced by modifying the diet pattern (87, 88). Further, the nutrient composition of the diet also impacts the recovery after the surgery (89). In addition, the diet quality also play pivotal role in aging (90). The evidence underscores the crucial role of diet quality, encompassing the composition of macro and micronutrients, in maintaining overall health. Diet influences disease occurrence, complication development, disease management, recovery, and the quality of life across a spectrum of health conditions (91-95). Dietary intervention trials frequently demonstrate that improving diet quality leads to enhanced health outcomes, independent of changes in weight (96). For instance, the plant based and low protein diet help control the chronic kidney diseases (97). The diet devoid of gluten and dairy products may have beneficial effects on children suffering from specific kidney disorders, and glomerulosclerosis (98). Similarly, the consumption of fish based diet enriched in omega-3 fatty acids could have positive effects on the management of IgA nephropathy (99). Thus, the inclusion of specific diets and components thereof as the part of precision nutrition may not only improve the human health, but also help reduce the globally rising risks of fatal diseases. The future of precision nutrition in the management of human diseases is presented in Table 1.

In the last few years, various international organization like Food and Drug Administration (FDA), started to issue a national guidelines to obtain the healthier food and nutrition information for their population. The enhanced information concerned with the healthier foods and nutrition profile will help in improving the health and wellness.<sup>1</sup>

Recently USA government released a national strategy to identify the nutrient profile of the food and improve the health hygiene so as to improve everyone's health and wellness up to 2030 and control the diet related diseases, especially the obesity, diabetes, and hypertension.<sup>2</sup> In light of the meetings held, the government encouraged the population to reduce the intake of sodium and sugar in the food, because the level of salt and sugar play a prominent role in diseases development. it has been observed that most of the population of U.S do not use enough amounts of healthy foods like fruits, dairy products, whole grains and also consume higher amount of sodium and sugar in the food. In the last few years, the world has faced the challenges of pandemic and huge number of global population. The developed countries were also hot spot of that pandemic. The poor nutrition and weak immune system are one of the major causes of such infections. Beside these, other diet specific epidemic like obesity, diabetes, and other cardiovascular diseases are also recognized to affect the U.S. population.

<sup>1</sup> https://www.fda.gov/food/food-labeling-nutrition/ fdas-nutrition-initiatives

<sup>2</sup> https://health.gov/our-work/nutrition-physical-activity/

white-house-conference-hunger-nutrition-and-health

TABLE 1	Role of precision	nutrition	(PN) in	the ma	anagement	of human
disease.						

Approaches of nutrition method	Omics and other technologies described	Disease managed	References
Precision nutrition	Nutrigenetics, metabolomics, metagenomics, behavioral aspects	Obesity and type 2 diabetes	Antwi (100)
Precision nutrition	Epigenetics, metabolomics, phenotypic anthropometrics	Aging and brain health	Chen and Small (101)
Precision nutrition	Environment, gut microflora, epigenetics	Female reproductive health	Dumesic et al. (102)
Precision nutrition	Lipoprotein analysis	Cardiovascular diseases	Hong et al. (103)
Precision nutrition	Genomics, proteomics	SARS-CoV-2	Naidu et al. (104)
Precision nutrition	The Genome, epigenome, and microbiome	Treatment of cardiovascular diseases	Ordovás (105)
Precision nutrition and omics tools approach	Genomics, epigenomics and metabolomics	Lactose intolerance management	Pratelli et al. (106)
Precision nutrition	Nutrigenomic, and Nutriepigenetic	Chronic diseases linked to obesity	Ramos-Lopez et al. (107)
Precision nutrition and dietary intervention	Metabolic phenotyping	Cardio- metabolic health management	Trouwborst et al. (108)
Precision nutrition	Biomarkers of food consumed, microbiome, lipidomics, genomics, transcriptomics	Obesity	Ulusoy-Gezer and Rakıcıoğlu (109)
Precision nutrition	Genomics, metabolomics, and gut microbiome technologies	Type 2 diabetes	Wang and Hu (110)
Precision nutrition	Target delivery of food functional factors	Chronic diseases like cancer, obesity, atherosclerosis	Yu et al. (16)

# 7 Machine learning and other digital technologies based approaches

Recent advances in digital technologies like machine learning (ML), deep learning, big data and artificial intelligence (AI) play a pivotal role in progression and usage of precision nutrition. Machine learning (ML) with the help of current digital technologies can venture into the unknown of nutraceuticals, identify valuable nutrients within our food and personalize the nutritional requirements. Machine learning can be quite useful in gathering dietary data inputs such as metabolomics, meal timing, meal uptake, physical activities, nutrigenomics, health conditions, genetics and personal health data. Further integrating the dietary data inputs, it can make a maximum likelihood prediction about the outcome using ML algorithms. The four types of ML considered in precision nutrition are supervised learning, unsupervised learning, semi-supervised learning and reinforcement learning (111). ML applies multiple algorithms, linear and logistic regression, data clustering analysis, artificial neural networks, deep learning, principal component analysis and data assessment to build a computational model for maximum output in understanding, characterization and precision nutrition in chronic dietary diseases (27, 112). Indeed, it has emerged as a quick solution to gather useful information from omics data, interpret it and predict the personalized dietary requirement and management. Moreover, it can also act as a biomarker monitoring tool assessing dietary intake, correlating with current health conditions and recommending precise nutraceutical for each individuals (27).

One of the recent example of application of ML in precision nutrition is the PREDICT 1 clinical trial (PersonalisedREsponses to Dietary Composition Trial; NCT03479866), where an ML model "robust to overfitting" was developed that predicted both triglyceride and glycemic responses to food intake. The predictions can further be used for precision nutrition and preparing dietary plans (113). Similarly, in a personalized diet study, hypocaloric diet was provided to overweight patients with pre-diabetic and moderately controlled diabetes type-2 using an ML based algorithm (114). In a comparison between statistical and machine-learning techniques used to evaluate the cardio-metabolic risks observed with dietary intake for 10 years (ATTICA study), ML techniques (k-nearest-neighbor's algorithm and random-forests decision tree) were found to be superior than traditional linear regression model (115). ML algorithms have also been found useful in predicting the hereditary and environmental risks of lifestyle diseases, gene-gene, gene-nutrition interactions, change in microbiota and factors affecting the nutraceuticals (27, 116).

Artificial intelligence has unleashed a new arena in every possible field, including precision nutrition. AI-driven food interventions can diagnose the disease, assess the morbidity and mortality risk of a patient, discuss disease outbreak and surveillance and help in policy and planning using precision nutrition (117). AI, along with ML, can revolutionize the field of nutritional epidemiology in terms of precise nutrition measurement and addition of complex tools to model complexity of diet (118). Recently, Lee et al. (116) reported about two AI models (semantic and nutritional analysis models) which were developed and integrated into precision nutrition analysis using five different algorithms. The results showed that AI models could be used for nutritional survey and precision nutrition with high accuracy and reliability (116). Apart from working efficiently for large datasets, AI combined with big data and ML can generate nutrition-driven hypothesis and test them accurately, accounting for multiple factors at the same time (119).

Advancement in analytical and digital techniques have also helped to monitor and interpret nutraceutical data simultaneously. A number of smart phone- based apps have been developed which are replacing the traditional pen and paper-based databases for precision nutrition (120). Non-invasive wearable chemical and physical sensors and mobile and app-based electrochemical sensors can provide accurate real-time monitoring of dietary behavior changes toward a managed nutritional balance (121). Similarly, analytical techniques such as sensor-based vibrational spectroscopy, Raman, and terahertz spectroscopy, as well as hyperspectral imaging coupled with data analysis (ML, AI, and big data), can not only generate huge set of nutritional data on fluid-based biomarkers but also cut down the incurred cost substantially (19). Indeed, the dual use of continuous health monitoring and evaluation of continuously generated dynamic data can identify and provide recommendations on dietary requirements, which set a bright future for precision nutrition.

Despite being able to bring about revolutionary changes in precision nutrition by MI, AI and digital technologies, they still need certain hurdles huddles to overcome. Guidelines, and recommendations on the uses of AI are not very specific yet, and it can be misused easily. The generation of large set of data will further require protection of intellectual property and personal information. Further, ethical issue related to the use of AI also needs to be addressed. Collaboration between academics, industry and government and continuous upgrading of guidelines will further be required to AI-assisted precision nutrition.

### 8 Conclusion

Precision nutrition has been considered as one of the emerging approach in the field of human health management. The goal of precision nutrition research is to provide nutritional advice to individuals or populations. Although the nutritional profile that needs to be explored varies and depends upon genetics, sex, age, and geographical locations, it is now considered superior to generic advice. Currently, treatment of various human ailments is based on different therapeutic approaches, including traditional and modern medicine system. The continuously and gradually evolving disciplines of genomics in relation to nutrition have elucidated the importance of genetic variations, epigenetic information, and expression of myriads of genes in disease progression, apart from their involvement in modulating therapeutic responses. Although precision nutrition now includes the integrative study of latest omics of Nutrigenomics like metagenomics, metabolomics, and next-generation sequencing to understand the relationship between nutrition profile and human health management. However, the management of huge amounts of data generated by omics

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approaches is still a challenging task and warrants the application of latest artificial intelligence and machine learning tools for in depth understanding.

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VS: Conceptualization, Methodology, Writing – original draft. X-HH: Funding acquisition, Writing – review & editing. AS: Data curation, Writing – review & editing. MS: Data curation, Formal analysis, Visualization, Writing – review & editing. PV: Writing – review & editing. RS: Data curation, Writing – review & editing. NJ: Writing – review & editing. MK: Writing – review & editing. SS: Writing – review & editing. ZW: Funding acquisition, Writing – review & editing. AK: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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