REVIEW

Nutrigenomics and personalized nutrition: science and concept

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Diet and genomes interact. Nutrition has the most important life-long environmental impact on human health. While nutrigenetics addresses how an individual's genetic makeup predisposes for dietary susceptibility, nutrigenomics asks how nutrition influences the expression of the genome. Nutrigenomics builds on the three omics disciplines transcriptomics, proteomics and metabolomics. They are a prerequisite for nutritional systems biology, the understanding of the interaction between food components and diet with cells, organs and the whole body. Personalized nutrition is a conceptual analog to personalized medicine. While there are food products available that address requirements or preferences of specific consumer groups, these products are based on empirical consumer science rather than on nutrigenomics and nutrigenetics. The latter two build the science foundation for understanding human variability in preferences, requirements and responses to diet, and may become the future tools for consumer assessment motivated by personalized nutritional counseling for health maintenance and disease prevention.

Traditionally, nutrition research has dealt with providing nutrients to nourish populations. Nowadays, it focuses on improving the health of individuals through diet. Modern molecular nutritional research is aiming at health promotion and disease prevention and at performance improvement [1]. Personalized nutrition is the concept of adapting food to individual needs. While it has become apparent that consumers respond differently to diet, depending on their genetic makeup, lifestyle and environment, the related knowledge and understanding remain fragmented [2]. However, there is an increasing consumer awareness of understanding and assessing individual health status and nutritional needs. Responding to this changing consumer landscape, the nutrition business is developing products according to needs and desired benefits of specific consumer groups, be they healthy, at risk or diseased, such as sportive, elderly, diabetic, obese or allergic individuals [3].

The challenge in bringing personalized nutrition to the market lies in developing diagnostic, nutritional and service solutions. We have to identify consumer demands, define biomarkers of bioavailability, bioefficacy and disposition, assess measuring technologies, and translate research into business models. For example, measuring technologies are being evaluated in terms of their maturity and consumer accessibility. All these activities are currently ongoing in parallel in the private and public sector [3].

Nutrition has traditionally been considered an integral part of health maintenance and disease prevention (for example in ancient cultures such as China), but based on epidemiological surveys. The task is now to take personalized nutrition to the scientific level: in model studies, gene, protein and metabolite profiles of individuals in different health and nutritional conditions are analyzed. It is expected to find early signs (biomarkers) for deviations from healthy metabolism, and targets for possibly correcting these deviations by nutritional means [4]. The goal is to reveal human body reactions towards different diets at gene, protein and metabolite level in order to demonstrate nutritional efficacy [5]. Discovery technologies applied at gene, protein and metabolite level in the context of nutrition and health have the potential to deliver biomarkers for health and digestive comfort, reveal early indicators for disease disposition, differentiate dietary responders from nonresponders, and discover bioactive, beneficial food components [6]. The vision of developing personalized nutrition for health promotion and disease prevention requires the construction of a sound scientific basis for this concept.

Nutrigenomics & nutri(epi)genetics

Our diet interacts with our genes. Nutrigenomics asks how dietary components influence gene expression, while nutrigenetics asks how our genetic makeup makes us respond or not to dietary intervention [7]. Nutrigenomics

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assesses dietary influence at gene and protein expression and metabolite level and derives omics profiles typical for a nutritional intervention or status. Nutrigenetics typically characterizes SNPs with regards to their frequency in a given population and to their relevance for metabolic health or disorders [7]. For example, G-protein-located SNPs have been shown to predispose people in certain populations to metabolic syndrome, atherosclerosis or functional dyspepsia [8]. Furthermore, not only single-base mutations but also varying copy numbers for a given gene account for interindividual variability at genome level [9]. However these so-called copy-number polymorphisms or copy-number variants have not yet, to our knowledge, been put in a nutritional perspective.

Nutrigenomics stands for the dynamically evolving field of diet–gene interactions [10]. It is advancing thanks to technological progress at all three omics levels and profits from increasing correlation and integration of transcript, protein and metabolite data [6]. However, the latter requires understanding of the timing of the events of gene transcription, protein expression and metabolite generation, as well as the further maturation of informatic tools for integrative data analysis [11].

An impressive example of nutrigenomics applied to the improvement of human health at the population level is the European 'Diet, Obesity and Genes' (DiOGenes) project [101], the acronym standing for. The overall objective is to reduce the widespread health problems of overweight, obesity and related comorbidities among European consumers. In order to adequately address this challenging goal, DiOGenes investigates how key genomic and dietary lifestyle factors combine in different people to precipitate weight gain, weight regain and its associated comorbidities. In particular, the consortium deploys an integrated scientific approach to identify key psychological, lifestyle and genetic factors, as well as biomarkers, that will provide a scientific basis for predicting whether a subject will maintain a healthy weight or not. Six research, technology and development lines integrate nutrigenomics, nutrigenetics, population studies, food technology and consumer behavior. The final deliverable of the project is to increase wellbeing among European consumers by exploiting the new knowledge generated to promote safe, high-quality diets, minimizing risks of overweight and obesity.

Nutrigenomics, with its potential to deliver dynamic biomarkers for nutrition and health status as well as ingredient activity and efficacy, is increasingly being linked to nutri(epi)genetics, which can furnish long-term or static biomarkers for individual disposition towards diet and nutritional imprinting. Nutrigenetics will certainly contribute to improved study cohort definition. The standardization initiatives launched in the omics community will increasingly be complemented by equally indispensable efforts of harmonizing dietary interventions in terms of, for example, standardized diets with defined micro- and macronutrient content and origin. An international consortium is beginning to address the annotation of the human genome according to nutritional criteria [12].

Epigenetics does not look at DNA sequence variation but at post-translational modifications of DNA-binding proteins (e.g., histones and chromatin) [13,14] and of DNA itself (methylation) [15]. These biochemical alterations of the genome and the 'packaging' molecules influence DNA accessibility and, thereby, transcription. These effects can last for a long period in life and can even be transmitted from one generation to another [16]. Furthermore, heritable, environmentally induced epigenetic modifications have been shown to underlie reversible transgenerational alterations in phenotype [17].

While monozygous twins have the same genotype, most monozygotic twin pairs are not identical, but are phenotypically discordant. One possible explanation for this finding is the existence of epigenetic differences. Fraga *et al.* examined global and locus-specific differences in DNA methylation and histone acetylation of a large cohort of monozygotic twins [18]. They discovered that twins are epigenetically indistinguishable during the early years of life, but older monozygous twins exhibited differences in content and genomic distribution of 5-methylcytosine DNA and histone acetylation, the latter affecting their gene-expression pattern.

Whereas many of the earlier studies had assumed that SNPs were the main source of human genetic variability, an increasing body of evidence now suggests the importance of additional layers of variability, including copy-number polymorphisms and epigenetic regulation, such as DNA methylation. Many complex diseases, such as inflammatory bowel disease (Crohn's disease and ulcerative colitis), have been shown to be related to SNPs on particular chromosomal regions, but are also associated with

copy-number variation of certain other genes [19]. Such discoveries suggest that a detailed description of the genetic background of complex diseases is a challenging but necessary objective in order to better prevent pathological development by, for example, adapted diets.

Epigenetics is just beginning to reveal its possible implications in nutrition. One aspect in this regard is the astonishing imprinting effect that nutrition can exert on a genome [20]: DNA methylation appears to provide a format for long-term dietary (re-)programming of the genome [21], suggesting that nutritional supplementation may have unexpected adverse consequences on gene regulation in humans, and that well-adapted diets already applied at pre- and post-natal stage may exert a fundamental and long-lasting positive impact. Some evidence shows that chronic diseases/conditions in adulthood are due to persistent perturbations/influences during early-life nutrition [22].

Even cognitive development seems to be amenable to genetically counseled nutritional intervention. Studies have shown that nutrients, such as n-3 long-chain polyunsaturated fatty acids, can affect brain development and, therefore, cognitive function. A recent publication showed that the association between breastfeeding and IQ is moderated by a genetic variant in a gene involved in the control of fatty acid pathways [23].

As diet is the most prominent life-long environmental impact on human health and as, with prolonging lifespan and changing lifestyle in developed countries, chronic diseases become more prevalent, nutrigenomics and nutrigenetics are key scientific platforms to promote health and prevent disease through nutrition that better meets the requirements and constraints of consumer groups with specific health conditions, particular lifestyles and in certain stages of life. Eventually, the nutrigenomics-rooted concept of personalized nutrition may translate into the development of new food products that target, if not individuals, at least groups of people with similar metabolic phenotypes and genetic risks. Current nutritional and genetic epidemiological methods yield 'risk factors' derived from population studies. These risk factors are statistical estimates of the percentage reduction in disease in the population, if the risk were to be avoided or the gene variant was absent. Developing individual risk factors considering the genetic diversity of human populations, the complexity of foods, cultures and lifestyles, and the variety of metabolic processes poses enormous challenges for personalizing dietary advice.

Humans are different

Humans span a remarkable range of phenotypes. Healthy human adults largely vary in their physical appearance, physical and cognitive performance, and in their food preference and requirements. Humans are most alike at birth, but as they progress through various life stages, they diversify into numerous lifestyles.

The 20th century witnessed a large scientific investment to elucidate the basic biological processes of humans, detailing biochemistry from genetics to physiology. However, most of that research focused on the common motifs and features of these processes across all humans. More recently, scientists have started to catalogue and understand the molecular basis behind the variation across humans.

Humans differ at the level of a wide range of basic biological variables. These variables are, in some cases, genetically determined chromosomal differences, for example, male and female, or allelic polymorphisms in structural or regulatory regions of specific genes. Differences are also due to the age and particular life stage of an individual (e.g., pregnancy, lactation, infancy, puberty, pre- and post-menopause and elderly). Other differences are derived from environmental influences that are either exogenous and random (e.g., exposure to sunlight, toxins and allergens), or endogenous and linked to a chosen lifestyle (e.g., excess or balanced caloric intake, meal frequency, exercise or sedentary behavior, regular sleep cycle or frequent change between time zones or shift work). Furthermore, each of these variables may exert effects on (epi)genetic or nongenetic elements, thereby conferring persistence of a particular phenotype through some of that individual's subsequent life and altering that individual's response to dietary components.

Nutritional needs vary with life stage, lifestyle & situation

Life stage

The nutritional requirements of humans depend on an individual's stage in life. Early in life, growth and development are primary biological objectives and change rapidly, as do the related dietary needs and responses [24]. Puberty and the transition to reproductive fertility cause a significant change in hormonal status, with physiological and metabolic consequences,

many of which alter dietary needs and responses [25]. The reproductive cycle itself (estrus, pregnancy, lactation and involution) represents all distinct physiological states for which varying nutritional implications apply beyond classical guidelines [26,27].

Thanks to modern disease prevention and therapy, human life expectancy has increased dramatically. One result of this success has been the emergence of 'elderly' as a sustained and distinct life stage. With greater numbers of elderly humans, their unique physiological, metabolic and even microbial states are being recognized, and so are their unique nutritional needs [28,29]. Disease, injury or pathology affects virtually every individual at some point in life. Clinical nutrition addresses the unique metabolic demands of disease states, and nutritional solutions are being designed to accelerate recovery and minimize long-term consequences from these periods.

Environment

The term 'environment' encompasses, in this context, all exogenous inputs to a phenotype, such as acute and chronic, random and volitional, as well as chemical, physical and behavioral impacts. The nature of these inputs can be attributed to their source (e.g., solar UV irradiation) or to their effects (e.g., vitamin D formation) [30]. These inputs can be either random and unavoidable (e.g., urban pollution) or volitional (e.g., smoking). They may also be generalized to a larger population (e.g., exposure to fluoridated drinking water) or may be unique to specific individuals (e.g., chronic consumption of sweetened beverages) [31].

Lifestyle

A critical aspect affecting an individual's environment and nutritional phenotype is the available food choices. While many consumers have access to increasingly diverse diets throughout the year, for others, choice does not necessarily afford diversity [32]. One of the luxuries of modern humans is the freedom to pursue preferred lifestyles. Faced with a highly diverse food supply, consumers can take advantage of a wide variety of dietary intakes of micro- and macronutrients and caloric contents. These intakes may come in diverse forms that may range from a single large meal per day to a dozen snack-like eating occasions.

Environment × genotype = imprinting

Environment at one stage in life can exert persistent effects on the nutritional phenotype later in life. These environmental impacts can manifest as imprinting, programming, memorization or colonization. As mentioned in the previous section, the explicit covalent modifications of DNA that persist through cell divisions are increasingly well described in the field of epigenetics [33].

In addition, the development of olfactory preferences persists through much of an individual's life, guiding their lifelong food choices [34]. Our sense of taste provides the final analysis of food prior to ingestion and uptake: once in the mouth, the gustatory sense tells us to spit or to swallow. We are attracted or repelled by visual and olfactory signals of food. In addition, olfactory and gustatory inputs are integrated with visual, visceral, mechanical and even auditory stimuli in the brain to generate complex flavor profiles. Each profile is classified with hedonic values of liking or disliking. This integration of sensory inputs into long-term food preferences is the major basis of an individual's food choice. As food choice determines the quality of diets, the quality of diets and their consequences for health are linked to the processes of taste. Taste and health are therefore tightly coupled.

Finally, an environmental factor that exerts persistent effects on nutritional phenotype is the composition and genetic diversity of the various microorganisms living in each individual's intestine, that is, the gut microbiota. Indeed, the basal metabolic state and indigenous bacteria play a crucial role in an individual's health. All mammals have symbiotic relationships with their gut microbiome, which consists of a diverse and metabolically active consortium of species exhibiting a spatially heterogeneous micro-ecology [35]. Evidence suggests that gut microbial metabolism and species variation within the microbiome of the mammal is of considerable importance in determining calorific bioavailability to the host [36].

Imprinting during prenatal development has been shown to cause methylation differences across entire regions of a fetal genome and can result from various nutrient imbalances and deficiencies of the mother [37]. As technologies for measuring epigenetic DNA modifications have emerged, studies in animal models exposed to various nutrients and environmental and lifestyle factors have shown the influence of these environmental parameters on the DNA methylation state [38]. Such studies suggest that

these nutritional factors are also relevant to humans, and similar persistent effects through epigenetic changes in the human genome could be predicted.

The remodeling of cells and tissues as a form of imprinting has been well documented, although not yet fully understood. Adipocyte hyperplasia early in development is proposed as one of the factors that could account for the high predisposition to adult obesity in children who are overweight [39]. These animal studies have documented that specific dietary factors early in life – of animals at least – stimulate or inhibit the proliferation of adipocytes. This effect, in itself, could account for a persistent and altered response to diets later in life. For example, the dietary factors omega-6 and -3 polyunsaturated fatty acid are apparently effective at altering cellular development within the range of normal human diets. Moreover, muscle mass is also responsive to the combination of conditioning and protein content of the diet [40]. The persistence of muscle mass, its influence on whole-body energy metabolism, its metabolic contributions post-training, and a larger store of amino acids as muscle proteins are expected to alter an individual's reaction to environmental conditions such as diet [41].

The imprinting of sensory preference is perhaps the least understood but most influential in the conditioning of modern humans to their habitual diets. Humans apparently do not rely on nutrient cues to guide their food choices; instead, they rely on a system of acquired food preferences. The remarkable property of olfactory preference is the process by which liking and disliking of particular flavors are acquired as a series of contextual memories early in life [42]. This system of acquired flavor preferences underlies much of the cultural variation in foods and cuisines around the world. This also means that flavor preferences for foods with poor nutrient quality, if acquired early in life, may guide a person's life-long habit of poor food choices, partly due to the fact that the sensations will continue to be positively perceived. These olfactory-based food preference patterns can be developed very early in life; for example, the flavor preferences of lambs for grazing is acquired from maternal feeding patterns established prior to weaning [43].

A final means by which early dietary exposure can program a person's response to later diet is the influence on an individual's gut microbiome. Such dietary influences can be achieved both through direct inoculation of particular microorganisms present in foods [44] or via the selective manipulation of subsets of microorganisms by food components that can only be fermented/utilized by certain bacterial populations [45]. Until recently, the role of an individual's microflora was considered to be relatively minor in terms of their overall health. Stimulated by the astonishing discoveries by Gordon *et al.* on the influence of specific bacteria on energy metabolism and predisposition to obesity [36,46], the microflora is being increasingly viewed as a pivotal factor in human metabolism, immunity, sensation, disease resistance, inflammation and comfort.

Food variables related to human diversity

The discoveries of the essential nutrients led to a major public health breakthrough by ensuring essential nutrient supply, thereby avoiding nutrient deficiencies and preventing related diseases, all at a population level. Although most of the population in developed countries and growing population segments in developing countries are adequately nourished, even from the perspective of essential nutrients, individuals within the population may profit from improved health through more specific recommendations. Moreover, in developed countries, caloric over-nutrition increasingly coincides with micronutrient deficiencies due to a unilateral diet and these two trends contribute to the rapidly growing epidemic of obesity and diabetes.

Food diversity is proving to be most important to individual health, especially beyond the scope of essential nutrients. Macronutrients, from simple sugars via lipids to high-quality protein, influence a person's health depending on makeup and condition. For example, foods rich in simple carbohydrates and starches harm individuals with insulin resistance, while they can improve the muscle status of elite endurance athletes, who typically exhibit high insulin sensitivity [47]. Diets high in protein are suggested to exert an unfavorable metabolic programming of early infants [48], yet they may be supportive for muscle mass conservation in the elderly [49].

The field of nutrition has increasingly investigated how bioactive food molecules may mitigate the risk and progression of chronic and degenerative diseases [5]. While some principles have emerged, the variation in response among individuals to those bioactives may be the most important conclusion and may set the stage for future personalized diet and health [2].

Personalized nutrition

Food personalization, as such, is not a new concept, but has been practised for centuries. However, the emerging scientific basis and industrialization of personalized nutrition and food are new phenomena. Human food choices have always been rooted in personal preferences and individual experiences, including sensory acuity, cultural habits and the personal economic situation. The nutrition community has recognized that different physiological events require significant adaptations to diet. For example, pregnant women, active athletes and elderly people have specific nutrient requirements, and those needs should guide dietary recommendations.

Today, the foods in the marketplace allow a substantial personalization of diets according to consumer knowledge and product marketing. This segmentation inevitably means a shrinking target consumer group. What are the criteria underlying the personal choices of consumers in a world of virtually unlimited options?

Taste

The most immediate and easily accessed criteria for food personalization are taste and flavor preferences. Although personal taste preferences have determined food choices for thousands of years, the genetic diversity of taste and olfactory sensation in humans is now recognized to be part of the diversity of food preferences [50,51]. In addition to genetic variation, olfactory preferences are principally a learned response to prior diet; for example, learned olfactory preferences to particular foods and flavors vary even among honey bees [52].

Cultural mores

A considerable diversity of food choices relates to core beliefs of their suitability to a particular religious or philosophical value system. While the origins and perpetuation of these choices (halal or kosher foods, vegetarian diets, religious fasting and so on) are not necessarily based on personal nutritional criteria, they do produce nutritional consequences, whether desirable or not [53,54].

Life stage

Mankind's experience over centuries has resulted in food personalization influenced by the specific physiological needs of the stages of human life, such as pregnancy, lactation, weaning, infancy, aging and recovery from illness. Innovative research points towards the importance of diets consumed during life-stage transitions (e.g., weaning and lactation) for long-term health effects [55].

Lifestyle

Many aspects of personalization of diets are linked to lifestyle choices. Although scientific evidence is accumulating around the nutritional relevance of such choices and their physiological impacts, historical observations and anecdotes remain the basis for an assumed value of specific food stuff. Foods within this category include, for example, products for athletes before, during and after exercise and training [56].

Lifestyle diseases

These conditions develop in a subset of the population and provide another opportunity for adapting nutritional solutions to consumers who are at risk of, or are already experiencing, health problems. Modern diagnostics are being developed with sensitive methods of identifying people with elevated disease risks. A variety of therapeutically oriented products are marketed to those at risk or diseased as a direct result of chronic lifestyle choices. Products with adapted nutrient composition are of potential value, whether targeted either to the symptoms of the problem (e.g., excess body weight and intestinal discomfort) or the lifestyle choices themselves, such as smoking, sedentary behavior or high-fat diets [57,58].

Inherited diseases

Humans have recognized the relevance of family history to health, and foods have been an integral part of related solutions. From predispositions such as allergies and intolerances [59] to inherited errors of inborn metabolism [60], diet is well known to contribute to the prevention and management of these aberrations. The importance of diet for inborn errors of metabolism has led to the worldwide adoption of blood-spot analyses at birth. It is now routine for most of the children born today to be tested for up to ten metabolic diseases, notably not by genotyping but by accurate concentration measures of metabolites whose inordinate abundance in blood are a diagnostic signature of the condition [61]. For example, phenylketonurea is well managed by metabolite-based diagnostics for personalization of low phenylalanine foods. The dramatic risk to the health of the affected individuals justifies measuring all infants at birth, even though the vast majority are uninvolved [62].

Genetic predispositions

A final level of personalization bases food choices on genetic variations. This approach refers to personalizing food according to genotyping and would be particularly suited where no other discernible phenotypic aspect can provide equivalent information. Scientifically, assessing metabolically relevant genes for sequence variants is most meaningful for further deepening our understanding of genetically imprinted predisposition towards diets and nutrients [8]. From a consumer application perspective, the development and implementation of such measures should adhere to the following principles: first, one should only genotype a consumer if there is a nutritional solution available that can be adapted to the genetic variants that are measured, second, the prevalence of the genotype of interest in a given target population should be measured in order to assess the economic feasibility to deliver adapted food solutions.

Conclusion & future perspective

Nutrition and health research and its implementation into food products will become increasingly personalized as the ability of scientific tools to distinguish important physiological differences merges with the industrial means to deliver individual solutions. This process is not a revolution of food, but rather reflects the continued diversification of foods that has been ongoing for centuries. Practical solutions for most consumers will benefit by focusing food personalization on validated nutritional solutions to established subsets of the population. Infants, pregnant and lactating women, active or sedentary adults, athletes, frail elderly and consumers who suffer from inherited or acquired diseases all represent large consumer groups with food requirements that both address their nutritional issues and ensure compliance by considering personal preferences in taste, texture and appearance. Developing nutritional foods to help diseased people recover should accompany the parallel approaches in personalized medicine.

The genomics sciences have delivered proof of the principle that humans are different with respect to optimal diets. As nutrigenomics and nutrigenetics build the scientific foundation for this, and as genotyping technologies become readily accessible, consumers may gain value through information on their personal genetic code. However, only those genetic variations should be assessed that can be adequately addressed by appropriate diets.

However, humans are not only genetically different. This highlights the necessary synergies between the genotyping and the holistic investigations of the metabolism deploying transcriptomics, proteomics and metabolomics, the latter three providing insights into how diet and health alter the expression or 'manifestation' of our genomes.

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Executive summary

- Nutrigenomics and nutrigenetics are the sciences; personalized nutrition is the resulting concept and application.
- Personalized nutrition already exists at different levels (e.g., cultural and sensorial preferences, life stage and lifestyle) but is not yet based on nutrigenetics and nutrigenomics. Today's power of nutrigenomics and nutrigenetics lies in improving our understanding of diet–gene interactions. Tomorrow, these tools may become applicable to consumer assessment and advice.
- Personalized nutrition requires diagnostics, prognostics and, most importantly, solutions for the consumer. Functional foods with proven benefits exist but they are not yet based on nutrigenomic or nutrigenetic efficacy and safety demonstration.
- Genomics (i.e., transcriptomics, proteomics and metabolomics), genetics (gene analysis at DNA sequence level) and epigenetics (analysis of nonsequence modifications of DNA and DNA-binding proteins) ideally need to be integrated to understand the complex interplay between food, diets and nutrients on the one hand, and the genes of the consumer on the other hand.
- Genomics and genetics are discovery tools to reveal candidate markers and explain mechanisms. They need to be followed up by validation, that is, minimally invasive biomarker assays in large, well-stratified human cohorts.
- In contrast to many genetic and genomic candidate markers published, only a few have made it, so far, into clinically established assays. This is owing to several reasons, some of which are of scientific and some of managerial or economic nature: discovery may be 'more appealing' than validation; candidate markers may not reflect the condition in question (e.g., immune disorders) but more general, underlying phenomena (e.g., inflammation); biomarker application requires diagnostics, for which the economic payoff has, so far, been small; candidate markers have to be integrated and managed in R&D pipelines.

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