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Nutrigenomics and Malnutrition: Advances in Prevention and Therapeutic Strategies

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ABSTRACT

Malnutrition, in all of its forms, including undernutrition, micronutrient deficiency, and nutritional imbalance caused by obesity, is one of the world's most serious health issues. Even after many years of interventions by public health professionals, conventional dietary guidelines have not been very effective because they do not account for the vast differences in genetics and epigenetics that influence nutrient metabolism and responses in individuals. Nutrigenomics is an area of study that investigates the interactions between diet and genes, providing a completely different perspective on malnutrition. This narrative overview summarizes the molecular mechanisms by which nutrients regulate gene expression. How genetic polymorphisms influence food requirements and metabolism, and how epigenetic changes relate dietary intake to long-term phenotypic impacts. Nutrigenomics is specifically studied in regard to protein-energy malnutrition, micronutrient deficiencies (iron, zinc, vitamin D, and folate), and the growing global prevalence of malnutrition-related metabolic disorders. The review also investigates how machine learning, multi-omics technologies, and gut microbiome-gene interactions have advanced precision feeding strategies. According to current research, single nucleotide polymorphisms in genes such as MTHFR, FADS1/FADS2, FTO, TCF7L2, VDR, and GC have a considerable impact on both the risk of malnutrition and the therapeutic efficiency of dietary therapy. Epigenetic programming provides actionable preventive targets during critical developmental windows, particularly via methyl-donor pathways. Personalized dietary recommendations, microbiome-integrated nutritional algorithms, and genotype-guided supplements are examples of translational techniques with high clinical potential. According to the article, the next logical step in combating malnutrition is to incorporate nutrigenomic ideas into global nutrition policy, clinical practice, and therapeutic design. This will necessitate interdisciplinary collaboration, equitable access to genomic tools, and robust ethical frameworks to ensure benefit for various groups.

INTRODUCTION

Malnutrition is one of the most serious and long-term threats to human health in the world. The World Health Organization estimates that 2.3 billion people are malnourished in some way, whether it is sarcopenic obesity in aging populations of high-income countries, kwashiorkor in low-income settings, iron-deficiency anemia in reproductive-age women, or stunted growth in children. People living in places with poverty, food insecurity, infectious disease, and inadequate healthcare face the brunt of this burden. However, malnutrition, which manifests as nutritional imbalance, micronutrient deficiencies, and metabolic dysfunction brought on by highly processed meals, continues to occur even in places with abundant food (1).

Over the majority of the twentieth century, efforts to address hunger focused on the distribution of standardized nutritional supplements, agricultural improvement, and macroeconomic development. These actions saved millions of lives. They have, however, encountered a recurring limitation: population-level dietary recommendations cannot account for the significant variances in how different persons react to the same nutrients. While a sibling on the same dose of iron supplements may remain anemic, a youngster taking the supplement may thrive. The weight loss outcomes of persons following identical low-calorie diets vary dramatically. This heterogeneity has substantial genetic foundations, as well as behavioral and environmental variables (2).

Nutrigenomics is the scientific study of the reciprocal relationship between the genome and dietary components. This field is made up of two complementary domains: nutrigenomics, which investigates how nutrients and bioactive food compounds control gene expression at the transcriptional, translational, and epigenetic levels, and nutrigenetics, which examines how inherited genetic variation shapes individual responses to nutrients. The empirical basis of nutrigenomics has increased dramatically since the decoding of the human genome and the subsequent development of high-throughput genotyping technology, providing insights that are beginning to impact clinical nutrition practice (3).

This narrative review draws on evidence from a variety of sources, including clinical trials, genome-wide association studies, epigenomic analyses, microbiome research, and multi-omics integration studies, to provide a comprehensive account of what nutrigenomics has revealed about malnutrition and what it promises for prevention and treatment. The scope purposely includes the full gamut of nutritional diseases, from overnutrition and metabolic malnutrition caused by obesity on one end of the spectrum to protein-energy malnutrition and micronutrient deficiencies on the other. By doing so, the review hopes to illustrate that nutrigenomics is a foundational field with urgent implications for global nutrition justice, rather than a luxury science solely for wealthier societies seeking optimal wellness.

HISTORICAL BACKGROUND OF NUTRIGENOMICS

It is not a recent discovery that food and genetics interact to influence health outcomes. Ancient medical systems, including Ayurveda and Hippocratic medicine, noticed that genetic constitutions influenced dietary demands and that people's food tolerance differed. However, the molecular basis for these observations did not become clear until the twentieth century. Archibald Garrod's landmark discovery in 1902 of alkaptonuria, a disorder in which the body cannot properly metabolize particular amino acids due to an enzyme failure, established the idea that inborn metabolic mistakes might result in disease in the context of regular dietary consumption. Garrod's concept of "chemical individuality" was foresighted because it proposed that genetic variation resulted in distinct nutritional requirements. This concept would not be fully implemented until the molecular period (4).

Perhaps the most notable early example of nutrigenomics in action was the discovery of phenylketonuria (PKU) in the mid-twentieth century. If left untreated, infants born with loss-of-function mutations in the PAH gene, which genes for phenylalanine hydroxylase, accumulate toxic levels of phenylalanine from dietary protein, resulting in severe intellectual impairment. It was revolutionary to discover that a simple dietary intervention, restricting phenylalanine consumption, may prevent neurological tragedy. One of the first uses of genotype-guided dietary therapy was newborn PKU screening, which was employed in the 1960s and continues to be a standard for the field (5). Following the completion of the Human Genome Project in 2003, the formal concept of nutrigenomics as a discipline gained traction in the early 2000s. The availability of comprehensive genomic data enabled the development of the necessary technical infrastructure to demonstrate correlations between food exposures and gene expression on a genome-wide scale. The Rotterdam Study, the Nurses' Health Study, and early genome-wide association studies all contributed to a systems-level knowledge of diet-genome interaction by identifying associations between common polymorphisms and dietary phenotypes (6).

Over the last decade, advances in next-generation sequencing, single-cell transcriptomics, methylome profiling, and gut microbiome characterization have propelled the discipline forward. Nutrigenomics now addresses the polygenic, multi-system complexity of common nutritional diseases such as obesity, type 2 diabetes, cardiovascular disease, and the full range of malnutrition-related disorders that affect populations across the income spectrum, rather than just single-gene disorders.

MOLECULAR FOUNDATIONS: GENE-NUTRIENT INTERACTIONS

How Nutrients Regulate Gene Expression

Nutrients are both potent regulators of gene transcription and substrates for metabolic activities. A number of dietary components interact directly with nuclear receptors, transcription factors, and chromatin-modifying enzymes, changing the expression of hundreds of genes at the same time. Because of this regulating power, dietary changes can produce rapid, widespread changes in cellular physiology. This finding has substantial implications for understanding how nutrition causes or prevents disease (3). Fatty acids are an example that has been thoroughly studied. Long-chain polyunsaturated fatty acids (LC-PUFAs), particularly omega-3 fatty acids such as eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA), activate peroxisome proliferator-activated receptors (PPARs), nuclear receptors that control the transcription of genes regulating lipid oxidation, inflammation, insulin sensitivity, and adipogenesis. When EPA/DHA activates PPAR-alpha in hepatocytes, fatty acid oxidation genes (ACOX1, CPT1A) are upregulated, whereas lipogenic genes (FASN, SREBP1c) are downregulated. Saturated fat-rich diets, on the other hand, activate the NF-kB pathway and decrease PPAR-alpha activity, which increases inflammatory gene programs (7). Carbohydrates primarily alter gene expression via glycemic-mediated insulin signaling. Rapid rises in blood sugar induce insulin to be produced, which begins the PI3K/Akt/mTOR signaling cascade and drives anabolic gene programs like cell division, protein synthesis, and lipogenesis (8). Carbohydrate-responsive element-binding protein, or ChREBP, is a direct glucose sensor that moves to the nucleus and induces the expression of lipogenic and glycolytic genes. Chronic overconsumption leads to constitutive ChREBP activation, resulting in hepatic steatosis and metabolic syndrome. Amino acids regulate gene expression using a variety of mechanisms. For example, leucine directly activates mTORC1 (mechanistic target of rapamycin complex 1), a master regulator of cellular growth and protein synthesis. A molecular mechanism behind the muscle atrophy found in kwashiorkor is the reduction of mTORC1 activity in

dietary conditions defined by protein restriction, resulting in downregulation of ribosome biogenesis genes and reduced muscle protein synthesis (9). Micronutrients are widely used as cofactors for enzymes that affect genes. For example, zinc is required for the action of around 300 enzymes and is a structural component of zinc-finger transcription factors. Zinc deficiency impairs immune gene expression, growth factor signaling, and inflammatory regulation by lowering the capacity of zinc-finger proteins like WT1, SP1, and GATA family members to bind DNA. Similarly, after being converted to its active form 1,25-dihydroxyvitamin D3, vitamin D interacts to the vitamin D receptor (VDR) and forms a heterodimer with the retinoid X receptor (RXR). This directly modulates the transcription of several hundred genes involved in immune response, calcium homeostasis, cell cycle regulation, and insulin secretion (10).

Genetic Polymorphisms Affecting Nutrient Metabolism

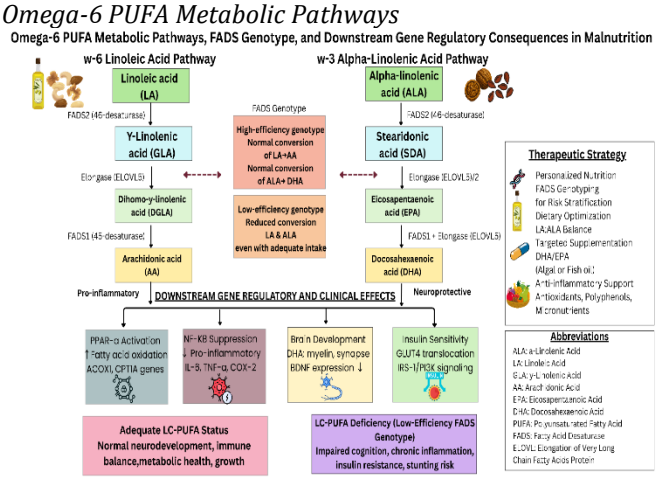
SNPs, or single base-pair alterations in the DNA sequence, are the most common type of genetic variation and the primary driver of inter-individual heterogeneity in food metabolism. The bulk of the estimated 10 million SNPs with minor allele frequencies larger than 1% in the human population are functionally neutral, although a considerable fraction are found in the coding or regulatory domains of genes that are critical for metabolism (2). MTHFR (methylenetetrahydrofolate reductase) is one of the most extensively studied genes in nutritional genomics. The common C677T polymorphism (rs1801133) inhibits the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary circulating form of folate and an important methyl donor for DNA methylation and nucleotide synthesis, lowering enzyme thermostability and activity. To maintain adequate methyl-donor capacity, homozygous carriers of the TT genotype require much more dietary folate and have MTHFR activity that is approximately 70% lower than that of CC homozygotes. MTHFR-TT children that live in low-folate environments are more vulnerable to malnutrition. Inadequate dietary intake and delayed metabolic processing result in severe folate deficiency, which has ramifications for neural tube development, hematopoiesis, and immunological function (11).

The FADS1 and FADS2 genes encode the enzymes that convert short-chain polyunsaturated fatty acids (linoleic acid and alpha-linolenic acid) into longer-chain derivatives (arachidonic acid, EPA, and DHA). Common polymorphisms in these genes considerably modify desaturase efficiency: loss-of-function variations diminish LC-PUFA synthesis, resulting in a functional shortage of DHA and arachidonic acid, which is notably deleterious to the brain development of newborns and young children (12). This genetic component explains why neurodevelopmental outcomes from LC-PUFA supplementation trials in neonates differ so dramatically; children with low-FADS activity genotypes may benefit significantly more than those with high baseline desaturase activity. Numerous frequent variants of the FTO (fat mass and obesity-associated) gene alter appetite regulation, leptin sensitivity, and adipose tissue gene expression, all of which influence energy balance. The risk which affects the ghrelin/leptin axis, is associated with increased BMI, fat mass, and dysregulated energy intake. The FTO risk genotype interacts with dietary composition in an important way for preventing malnutrition: high-protein diets appear to lower the risk allele's weight-promoting effect, whereas high-glycemic-index foods boost it. This is an obvious nutrient-gene interaction with therapeutic implications (13).

VDR (vitamin D receptor) polymorphisms alter the transcriptional response to vitamin D in its target tissues, particularly at the BsmI, ApaI, TaqI, and FokI loci. These SNPs also influence the receptor's affinity for 1,25-Dihydroxyvitamin D3. A higher vitamin D level is required for persons with low-affinity VDR mutations to have equivalent biological effects on insulin generation, calcium absorption, bone mineralization, and immune regulation. VDR polymorphisms provide a genetic layer of sensitivity that may not be adequately addressed by typical supplementation guidelines in populations where poor dietary consumption and limited sunlight exposure already impair vitamin D adequacy (14).

Figure 1

Omega-6 PUFA Metabolic Pathways



MALNUTRITION: GLOBAL BURDEN AND CLASSIFICATION

Malnutrition encompasses a wide range of ailments caused by insufficient, excessive, or imbalanced food intake in proportion to physiological requirements. The WHO classification system recognizes three broad domains: overweight and obesity, diet-related noncommunicable diseases (NCDs), and undernutrition (which includes stunting, wasting, underweight, and micronutrient deficiency) (1). In 2023, there were more than 149 million stunted children under the age of five worldwide, with South Asia and Sub-Saharan Africa bearing the brunt of the burden. In the same year, 45 million children experienced wasting, a severe nutritional shortage associated with a significantly increased risk of death. During the same period, more than 2.1 billion adults were overweight or obese. This number represents not only excess calories but also usually severe micronutrient shortages disguised behind a facade of sufficient or excessive energy intake; this phenomenon is known as

"hidden hunger" or "the double burden of malnutrition" (15).

The dual load poses a significant challenge to nutrigenomic science. Numerous genetic and epigenetic variables that enhance the risk of undernutrition in resource-constrained situations also raise the risk of metabolic disease during dietary alterations and nutritional transitions. The thrifty genotype theory, which was first proposed by Neel in 1962 and later refined by epigenetic developmental programming frameworks, states that metabolic phenotypes that are poorly adapted to caloric abundance are the product of genetic and epigenetic adaptations to food deprivation (16). Understanding this hereditary continuum is crucial for designing nutritional interventions that address malnutrition across the board. Over 2 billion people suffer from micronutrient malnutrition, which is defined by a deficiency of vitamins and minerals despite seemingly adequate calorie intake and has been associated to a variety of clinical effects. Iron deficiency is the most frequent micronutrient shortfall in the world, affecting approximately 1.6 billion people and impairing immune system performance, cognitive development, and reproductive outcomes. The most common preventable cause of childhood blindness remains vitamin A deficiency. Iodine, zinc, and B vitamin deficiencies, such as folate, vitamin B12, and thiamine, are linked to high morbidity rates. Nutrigenomics demonstrates that the genomic background has a substantial impact on both the therapeutic response to supplements and the chance of developing these deficiencies (17).

NUTRIGENOMICS IN PROTEIN-ENERGY UNDERNUTRITION

Genetic Determinants of Growth and Stunting

Stunting is the most common symptom of chronic undernutrition in children, defined as height-for-age more than two standard deviations below the WHO growth reference median. It shows a cumulative failure of linear development caused by insufficient protein and calorie intake. Genetic variety contributes significantly to individual susceptibility in equally impoverished settings, although environmental and socioeconomic factors are the primary predictors at the group level. Polymorphisms in the growth hormone-insulin-like growth factor axis have been found as major modulators of stunting risk using genome-wide association studies and candidate gene analysis. Common polymorphisms in the GH1 and IGF1 genes have an effect on growth hormone production and IGF-1 bioavailability. Children homozygous for low-activity GH1 mutations exhibit lower growth velocity responses to protein repletion, suggesting that genetic background may play a role in the dietary intervention ceiling. Similarly, polymorphisms in IGFBP3, which codes for insulin-like growth factor binding protein 3 and governs IGF-1 bioavailability, affect the growth response to nutritional rehabilitation (18).

The role of mTORC1 in translating nutritional status into somatic growth is an important mechanistic result from nutrigenomic research on stunting. In protein-sufficient circumstances, amino acids, particularly the branched-chain amino acids leucine, isoleucine, and valine, activate mTORC1 via the Regulator-Rag GTPase complex, promoting ribosome biogenesis, protein synthesis, and chondrocyte proliferation at growth plates. In protein-deficient conditions, growth-plate chondrocyte activity decreases, autophagy occurs, and mTORC1 levels fall. Thus, vulnerability to stunting in settings of low protein consumption may be controlled by genetic differences that modify mTORC1's sensitivity to amino acid availability, an area of active research (9).

Wasting, Kwashiorkor and Inflammatory Gene Networks

Acute malnutrition, which manifests as wasting and kwashiorkor, is the most severe end of the protein-energy undernutrition range, with mortality rates ranging from 10% to 30% even with therapy. Clinicians have long struggled to distinguish between marasmus (severe wasting without oedema) and kwashiorkor (edematous malnutrition), as both illnesses can occur in populations with similar levels of dietary deprivation. Nutrigenomics has begun to reveal the genetic and epigenomic variations underpinning these clinical characteristics (19). Baye and colleagues' GWAS found substantial relationships between SNPs in immune-regulatory loci, specifically IL6 (interleukin-6) and TNF (tumor necrosis factor alpha), and wasting risk in East African children. This is physically consistent: inflammatory cytokines reduce hunger, limit nutritional absorption, divert metabolic resources from growth to immune activation, and promote muscle catabolism via ubiquitin-proteasome pathway activation. Genetic polymorphisms that constitutively increase pro-inflammatory cytokine production may enhance these responses under dietary stress (5).

Kwashiorkor has been linked to oxidative stress and reduced antioxidant defense, which may have a genetic basis. Variants in GPX1 (glutathione peroxidase 1) and SOD2 (superoxide dismutase 2) that reduce antioxidant enzyme activity may predispose to the edematous phenotype under the combined assault of protein deficiency and high-aflatoxin dietary exposure, a hypothesis supported by metabolomic studies of serum oxidative stress markers in children with edematous versus non-edematous malnutrition in Sub-Saharan Africa (20). Gut microbiome dysbiosis is now recognized as a crucial characteristic of severe acute malnutrition (SAM) with unique genetic dimensions. Children with SAM had a significantly reduced number of Bifidobacterium, Lactobacillus, and Faecalibacterium prausnitzii, bacteria that produce short-chain fatty acids (SCFAs), which are essential for intestinal barrier integrity and immunological modulation. Host genetic variations in pattern recognition receptors (TLR2, TLR4, NOD2) that modulate mucosal immune responses to commensal bacteria affect the degree of gut dysbiosis under nutritional stress and the pace of microbiome recovery after nutritional rehabilitation (21).

NUTRIGENOMICS IN OVERNUTRITION AND OBESITY-RELATED MALNUTRITION

Polygenic Architecture of Obesity and Dietary Response

When calorie intake consistently surpasses energy

expenditure, obesity is a type of malnutrition that results in pathological adipose tissue buildup and consequent nutritional deficiencies. While environmental factors, food system design, physical activity patterns, socioeconomic determinants, explain population-level trends in obesity prevalence, genetic factors account for 40-70% of BMI variability between individuals, based on twin and adoption studies (13). Common obesity has a highly polygenic genetic architecture. Due to the limitations of common-variant GWAS methodology in capturing rare variant and gene-environment interaction effects, the largest genome-wide association meta-analyses have now identified over 900 genetic loci associated with BMI, collectively explaining approximately 6% of population variance in BMI. However, this figure underestimates true genomic contribution. The most robust associations cluster around genes involved in hypothalamic appetite regulation (MC4R, PCSK1, BDNF), adipogenesis (PPARG, ADRB3), energy sensing (FTO, TMEM18), and circadian rhythm (CLOCK, ARNTL) (20).

A number of sophisticated investigations have mechanistically clarified the FTO locus, which has the strongest and most consistent common-variant correlation for BMI. The risk variations at this locus act as long-range regulatory elements that affect the expression of IRX3 and IRX5, transcription factors involved in the thermogenic programming of adipocytes, rather than via the FTO protein itself, an RNA demethylase. In comparison to those with protective genotypes, risk allele carriers have lower PRDM16 expression, impaired brown/beige adipocyte thermogenesis, and greater white-to-beige adipocyte conversion ratios, indicating that their adipose tissue is physiologically "cooler" and stores more energy as fat (13). There is immediate therapeutic significance to these mechanistic discoveries. Dietary approaches that support mitochondrial uncoupling and thermogenesis, such as high-protein diets (which have strong thermic effects), dietary capsaicin, and exposure to cold, may be especially beneficial for people with high-FTO-risk genotypes, whereas high-glycemic carbohydrate diets may be disproportionately harmful to this genotype group. The transition from average dietary recommendations to genotype-stratified recommendations that take individual metabolic architecture into consideration is a prime example of the fundamental promise of nutrigenomics.

Micronutrient Deficiency in the Context of Obesity

Micronutrient deficiency is a crucial and often overlooked aspect of obesity-related malnutrition. Iron, vitamin D, zinc, vitamin B12, and folate deficiencies are common in obese people despite their excess calories. This paradox can be explained by a combination of poor dietary quality, increased micronutrient requirements from expanded adipose tissue mass, inflammation-mediated sequestration, and impaired micronutrient bioavailability (22). About 35–50% of extremely obese people had circulating 25-hydroxyvitamin D3 levels below the sufficiency threshold of 50 nmol/L, indicating that vitamin D insufficiency is especially common in obese populations. Because adipose tissue is lipophilic, it effectively removes vitamin D from circulation by sequestering it. The vitamin D axis is double-compromised in obese people with low-affinity VDR polymorphisms: tissue responsiveness is muted and circulating availability is decreased. Therefore, nutrigenomic profiling of VDR status may be especially helpful in directing the dosage of supplements in this population (14).

Hepcidin, the liver-derived peptide hormone that serves as the master regulator of iron homeostasis, is at the center of a unique nutrigenomic mechanism that underlies iron deficit in obesity. Chronic low-grade inflammation caused by obesity is typified by increased IL-6, which increases the production of hepcidin in the liver through the STAT3 signaling pathway. Despite normal or higher body iron reserves, excessive hepcidin prevents ferroprotein-mediated iron export from enterocytes and macrophages, resulting in a functional iron-sequestration condition that presents as chronic disease-related anemia. Genetic variations in TMPRSS6, which codes for matriptase-2, a hepcidin repressor, and HAMP, which codes for hepcidin, alter baseline hepcidin levels and affect an obese person's vulnerability to this type of iron deficiency (23).

EPIGENETIC MECHANISMS LINKING DIET AND MALNUTRITION

DNA Methylation and Nutritional Programming

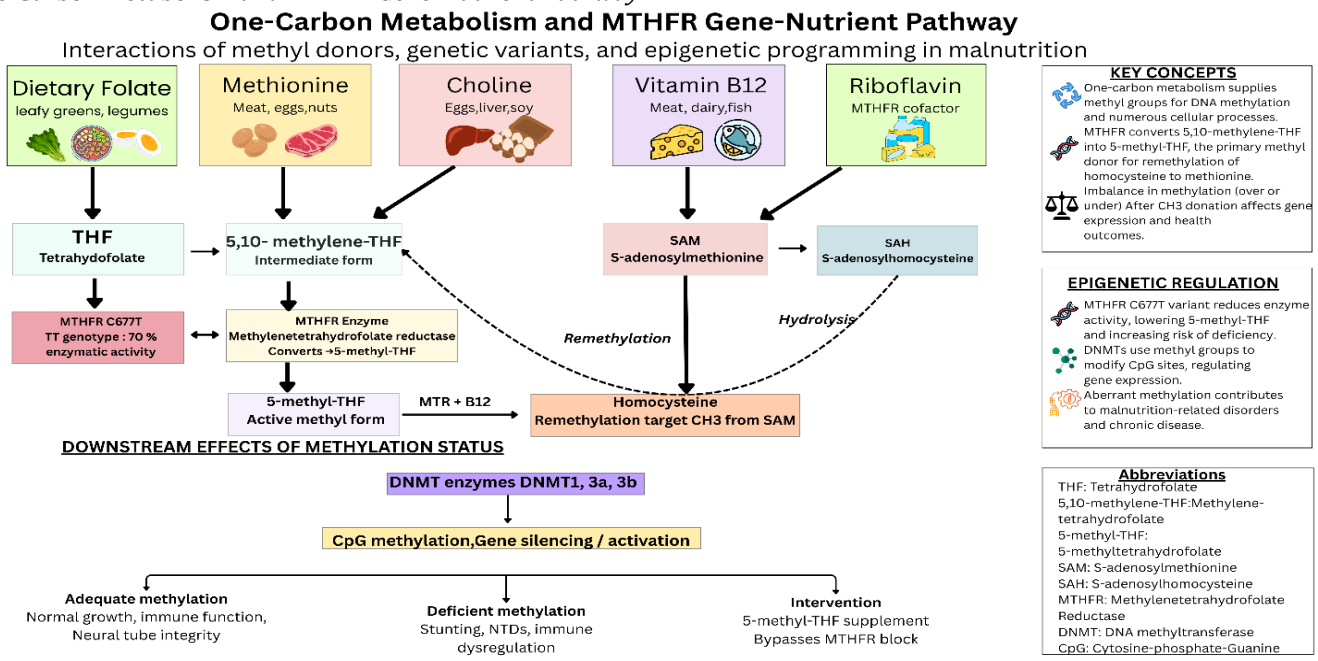
The most significant biological link between dietary intake and long-lasting phenotypic change is epigenetic alterations, which are heritable changes in gene expression that do not modify the underlying DNA sequence. DNA methylation is the most well-studied epigenetic process. DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b) use S-adenosylmethionine (SAM) as the methyl-group donor to catalyze cytosine methylation at CpG dinucleotides. The methylation landscape of the genome is directly affected by nutritional status because SAM is produced from dietary methionine via the one-carbon metabolic cycle, which requires sufficient intakes of folate, vitamin B12, choline, and riboflavin (24). The groundbreaking research on metastable epialleles in mice, specifically the agouti viable yellow (Avy) locus, clearly showed that a mother's dietary methyl-donor intake during pregnancy could change the offspring's DNA methylation pattern at particular genomic loci, changing their coat color, body weight, and adult disease risk. The human equivalent of this concept has been explored in the Gambian birth cohort studies by Dominguez-Salas and colleagues, who found that the season of conception, which determines periconceptional methyl-donor nutrient availability through agricultural production cycles, was associated with systematic differences in DNA methylation at metastable epialleles in infant blood (25).

In the context of malnutrition, periconceptional folate deficiency produces genome-wide hypomethylation that has been associated with neural tube defects, intrauterine growth restriction, and altered programming of metabolic and immune gene networks in the offspring. Conversely, excessive methyl-donor supplementation in specific genomic contexts can produce epigenetic silencing of tumor suppressor genes, illustrating that the relationship between nutritional status and epigenetic change is dose-dependent and context-specific, rather than simply 'more is better' (24). Developmental plasticity, the period during

which epigenetic patterns are most responsive to nutritional input, is concentrated in the periconceptional window, embryogenesis, and the first 1,000 days of postnatal life. Offspring epigenomes are programmed toward energy conservation traits, such as decreased metabolic rate, higher fat deposition efficiency, and increased hunger, when mothers are undernourished during these windows. The "thrifty phenotype" theory and the epidemiological finding that low birth weight is linked to an increased risk of adult metabolic disease are both supported by these adaptations, which may be life-saving in an environment of ongoing food scarcity but become maladaptive when the child moves to an obesogenic food environment (16).

Figure 2

One-Carbon Metabolism and MTHFR Gene-Nutrient Pathway



Histone Modifications and Chromatin Remodeling

In addition to DNA methylation, post-translational changes of histone proteins, the scaffold proteins around which DNA is wound to create chromatin, are another way that nutrition and dietary bioactive chemicals affect gene expression. Acetylation, methylation, phosphorylation, and ubiquitination are examples of histone modifications that collectively control chromatin accessibility, which in turn controls transcription factor binding and gene expression (26). Histone deacetylases (HDACs) compress chromatin and frequently inhibit transcription by eliminating acetyl groups from histone lysine residues. Food-based HDAC inhibitors, such as sulforaphane (found in cruciferous vegetables), butyrate (produced by colonic fermentation of dietary fiber), and resveratrol (found in diets high in polyphenols), maintain chromatin in a more open, transcriptionally permissive configuration. Because severely malnourished people's diets consistently lack dietary fiber and polyphenols, which contribute to the epigenetically driven regulation of immune and antioxidant gene networks, HDAC inhibitor exposure is minimal in starving circumstances (27).

The patterns of histone methylation also rely on nutrients. One-carbon food availability and chromatin status are directly linked when methyltransferases that require SAM as a cofactor catalyze the methylation of histone H3 at lysine 4 (H3K4me3), a signal linked to transcriptional activity. On the other hand, during protein deprivation, the repressive mark H3K27me3, which is deposited by the Polycomb Repressive Complex 2, builds up at growth-promoting gene loci and contributes to the epigenetically imposed growth arrest seen in stunted children (26).

Non-Coding RNAs in Nutritional Regulation

Non-coding RNAs, especially long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), are increasingly implicated as important mediators of nutrient-gene interactions. Target mRNAs' 3' untranslated regions are bound by microRNAs, which are tiny (~22 nucleotides) RNA molecules that cause translational repression or mRNA destruction. Numerous miRNAs are sensitive to nutritional status; it has been demonstrated that dietary fatty acids, glucose, amino acids, and micronutrients control miRNA expression, with subsequent impacts on gene networks related to metabolism, inflammation, and development (28). The insulin resistance observed in kwashiorkor is a result of the upregulation of miR-21 and miR-223 in malnourished children, which target genes involved in insulin signaling (PTEN, FOXO3A). Hepatic steatosis and dyslipidemia are caused by the dysregulation of miR-122, a liver-specific miRNA that is highly responsive to dietary carbohydrate and fat content and controls gene networks involved in cholesterol and fatty acid metabolism (29).

MICRONUTRIENT DEFICIENCIES: GENOMIC PERSPECTIVES

Iron Deficiency and the Genomics of Iron Homeostasis

Iron deficiency continues to be the most common micronutrient deficiency in the world and a significant factor in the burden of diseases linked to malnutrition. A

network of genes, including HFE, TFR2, HJV, HAMP (hepcidin), SLC40A1 (ferroprotein), DMT1 (SLC11A2), and TMPRSS6, are involved in the molecular regulation of iron homeostasis, which is now well recognized. This gene network's polymorphisms significantly change the efficiency of iron absorption, storage capacity, and vulnerability to excess or deficiency (23). When dietary iron intake is sufficient or excessive, the haemochromatosis gene's C282Y mutation significantly inhibits the sensing of transferrin-bound iron and decreases hepcidin synthesis, resulting in pathological iron overload. On the other hand, in population studies, common gain-of-function variations in TMPRSS6 (especially rs855791) are linked to increased iron absorption and a decreased incidence of iron-deficiency anemia. These variants also more effectively inhibit hepcidin. These results imply that alternative dosages and formulations may be needed for iron supplementation programs aimed at communities with high TMPRSS6 gain-of-function variation prevalence than those aimed at populations with hepcidin-activating variant backgrounds (23).

A particularly significant nutrient-gene interaction has been identified by Georgieff and colleagues' research on brain iron: early iron deficiency during crucial periods of brain development modifies the expression of myelin basic protein (MBP), BDNF (brain-derived neurotrophic factor), and the iron transporter SLC11A2 in hippocampal tissue. Some of these alterations in gene expression continue even after iron supplementation, indicating that the epigenetic effects of early iron shortage lead to long-lasting neurodevelopmental damage that cannot be entirely reversed by supplementation later on (30).

Zinc and the SLC30/SLC39 Transporter Family

The immune system, DNA synthesis, wound healing, growth, and the control of more than 300 enzyme systems all depend on zinc, an important trace metal. An estimated 2 billion people worldwide suffer from zinc insufficiency, which is more common in populations that rely on diets high in phytate-based cereals since phytate chelates zinc and lowers its bioavailability. Individual zinc homeostasis is significantly influenced by the ZIP/ZnT transporter family, according to nutrigenomic research. Common variants of the SLC30A8 gene, which codes for ZnT8, a zinc transporter that sequesters zinc into pancreatic beta-cell secretory granules, have conflicting effects: common high-zinc-binding variants are linked to better beta-cell function, while a rare loss-of-function variant (W325X) paradoxically lowers the risk of type 2 diabetes. This surprising discovery has prompted extensive investigation into the relationship between zinc transporter genotype and dietary zinc availability in determining insulin secretory capability and diabetes risk (10). During times of food insufficiency, zinc homeostasis depends on the ZIP4 transporter (SLC39A4), which mediates intestinal zinc absorption. Acrodermatitis enteropathica, a severe inherited zinc malabsorption illness that results in severe growth failure, immunological dysfunction, and skin lesions, is caused by loss-of-function mutations in ZIP4. Further nutrigenomic research is required in this area since subclinical decreases in ZIP4 expression brought on by common promoter variations may contribute to marginal zinc status in persons with questionable food consumption (31).

Folate, Vitamin B12, and One-Carbon Metabolism

In one-carbon metabolism, the metabolic network that transfers single-carbon units for nucleotide biosynthesis, DNA methylation, and amino acid interconversion, folate and vitamin B12 are essential nutrients. Megaloblastic anemia, neurological dysfunction, and neural tube abnormalities in offspring during the periconceptional phase are among the overlapping clinical signs caused by deficiencies in either nutrient. This pathway's genetics are extremely important for preventing malnutrition. Beyond MTHFR, polymorphisms in MTRR (methionine synthase reductase), MTR (methionine synthase), MTHFD1 (methylenetetrahydrofolate dehydrogenase), and SLC19A1 (folate transporter 1) influence the efficiency of folate metabolism and methylation. Individual folate requirements can be predicted more accurately by combining studies of several one-carbon pathway gene polymorphisms than by using MTHFR C677T alone. In a low-folate dietary setting, a child with compound heterozygous mutations in MTHFR and MTRR is far more likely to experience severe folate insufficiency than would be expected based just on dietary intake statistics (11).

Gastric intrinsic factor (encoded by GIF), the cubam receptor complex (CUBN and AMN) in the ileal enterocyte, and the transcobalamin II transporter (TCN2) in blood are all involved in the multi-step process of vitamin B12 absorption. TCN2 polymorphisms, especially rs1801198, change transcobalamin II's affinity for cobalamin, which lowers cellular B12 delivery even at sufficient serum B12 levels. This essentially results in a "functional B12 deficiency" at the tissue level when normal circulating quantities are present. In impoverished populations, where traditional biomarker thresholds may overlook genotype-specific insufficiency states, nutrigenomic analysis of vitamin B12 pathway genes may enhance the sensitivity of B12 deficient diagnosis (32).

Vitamin D: The Sunlight-Genome Interface

Vitamin D deficiency is unique among micronutrient deficiencies in that it arises from the intersection of three factors: dietary intake (from fortified foods and oily fish), cutaneous synthesis (requiring ultraviolet B radiation), and genetic variation across the vitamin D metabolic pathway. The latter involves at least four gene families: DHCR7 (7-dehydrocholesterol reductase, which controls availability of the photosynthetic substrate), CYP2R1 (25-hydroxylase, the primary hepatic activating enzyme), CYP27B1 (1-alpha-hydroxylase, the renal activating enzyme), and GC (vitamin D-binding protein, which determines circulating availability) .The work of Prentice and colleagues in African and South Asian populations demonstrated that genetic variants across GC, CYP2R1, and DHCR7 loci explained approximately 30% of population variability in circulating 25-hydroxyvitamin D3 concentrations, a genetic contribution comparable to that of sunlight exposure in tropical settings. Individuals carrying low-efficiency variants at multiple loci in these genes have profoundly impaired vitamin D synthesis even under adequate sun exposure and dietary intake, creating

a genotype-dependent supplementation requirement that standard clinical guidelines do not currently capture (33). The clinical consequences extend well beyond bone health. Vitamin D signaling regulates the expression of antimicrobial peptides (cathelicidin, defensin-beta2), T-regulatory cell development, and insulin-secretory gene programs in pancreatic beta-cells. The combination of dietary deficiency and low-efficiency genotype results in a severely compromised vitamin D axis in malnourished children living in low-sunlight, high-latitude, or highly air-polluted environments. This has implications for susceptibility to respiratory infections, tuberculosis, and autoimmune dysregulation (14).

GUT MICROBIOME, NUTRIGENOMICS, AND MALNUTRITION

Microbial Mediation of Nutrient-Gene Interactions

The about 38 trillion microbial cells that live in the human digestive tract are known as the gut microbiome. They serve as a metabolically active organ that significantly influences the connection between host gene expression and dietary intake. The microbiome converts bile acids and polyphenols into bioactive metabolites, ferments indigestible dietary fibers to produce SCFAs (acetate, propionate, and butyrate), synthesizes vitamins K2, B12, and biotin, and continuously interacts with host pattern recognition receptors to control mucosal immune gene programming (34). Butyrate is the main energy substrate for colonocytes and a strong HDAC inhibitor. It is mainly generated by Roseburia intestinalis and Faecalibacterium prausnitzii through the fermentation of resistant starch and non-starch polysaccharides. Butyrate maintains barrier integrity and decreases pathogen translocation by upregulating the expression of tight junction proteins (claudin-1, occludin, and ZO-1) in intestinal epithelial cells through its HDAC-inhibitory activity. Butyrate-producing bacteria are systematically reduced in malnourished children who eat diets low in dietary fiber. This results in increased intestinal permeability, epigenetically mediated downregulation of barrier genes, and chronic endotoxemia, which causes systemic inflammation and nutrient malabsorption (21).

Through its impacts on intestinal motility, bile acid metabolism, and enterohepatic circulation, the gut microbiome also controls the availability of nutrients throughout the body. Bile salt hydrolases, which are expressed by Bacteroides species, deconjugate primary bile acids to create secondary bile acids, which are powerful signaling molecules that activate the farnesoid X receptor (FXR) in hepatocytes and intestinal epithelium. FXR activation controls hepatic glucose and lipid metabolism gene programs, decreases hepatic bile acid synthesis (CYP7A1), and produces FGF19, which modifies energy expenditure. Therefore, the decrease of bile acid diversity linked to dysbiosis in malnourished persons has metabolic ramifications that go well beyond simple malabsorption (35).

Host Genetics, Microbiome Composition and Malnutrition Risk

The composition of the gut microbiome is shaped by a combination of environmental factors (diet, antibiotic exposure, mode of delivery at birth, breastfeeding) and host genetics. Twin studies have estimated that genetic heritability of microbiome composition ranges from 20-40% for specific taxa, with the strongest heritable associations observed for Bifidobacterium abundance (influenced by LCT genotype through lactase persistence), Methanobrevibacter smithii abundance, and the Firmicutes-to-Bacteroidetes ratio (36). The lactase persistence polymorphism (LCT-13910C>T) provides a clear example of host genetics shaping microbiome composition with nutritional consequences. Individuals carrying the ancestral lactase non-persistence allele (CC) cease producing intestinal lactase after weaning; in lactose-containing food environments, undigested lactose reaches the colon where it is fermented by colonic bacteria, enriching Bifidobacterium and Lactobacillus species with beneficial effects on microbiome diversity, but also causing diarrhea that can exacerbate malnutrition in vulnerable children. Conversely, in environments where fermented dairy products are the primary calcium source, lactase non-persistence genotypes confer calcium malabsorption risk that intersects with genetic vitamin D axis polymorphisms to multiply bone health vulnerability (37).

The FUT2 (fucosyltransferase 2) gene determines secretor status, the ability to express ABO blood group antigens on the intestinal mucosa, with profound effects on microbiome composition. Non-secreter individuals (homozygous for FUT2 loss-of-function variants; approximately 20% of Europeans and Africans) show significantly reduced Bifidobacterium abundance and altered microbiome diversity compared to secretors. Since Bifidobacterium species play critical roles in folate synthesis, carbohydrate fermentation, and intestinal immune homeostasis, FUT2 non-secretors may be at elevated micronutrient malnutrition risk in environments of marginal dietary folate intake, a nutrient-gene-microbiome interaction of practical clinical importance (36).

ADVANCES IN NUTRIGENOMICS TECHNOLOGIES

Genome-Wide Association Studies and Polygenic Risk Scores

Genome-wide association studies (GWAS) have been transformative in identifying common genetic variants associated with nutritional phenotypes and malnutrition-related outcomes. By simultaneously testing millions of SNPs across the genome for association with a phenotype of interest, GWAS bypasses the need for a priori hypotheses about causal genes and has revealed unexpected biological pathways linking diet, genetics, and disease. In nutrition research, GWAS have identified genetic loci for BMI, waist-hip ratio, blood lipid concentrations, fasting glucose, vitamin D status, iron status, and numerous dietary preference phenotypes including coffee consumption, alcohol metabolism, and bitter taste sensitivity (38).

Compared to single-SNP methods, polygenic risk scores (PRS) have the ability to more accurately forecast an individual's risk of malnutrition by combining the tiny effects of hundreds or thousands of common variants throughout the genome into a single summary score. A PRS

for vitamin D insufficiency risk that takes into account variations in DHCR7, CYP2R1, GC, and VDR may be able to pinpoint those who need individualized supplementation recommendations that go above typical population limits. Similarly, for high-risk infants diagnosed at birth, PRS for stunting risk including GH1, IGF1, and immune-regulatory gene variations could guide focused dietary supplementation (39). However, the ongoing Eurocentric bias of current GWAS databases limits the usefulness of GWAS-derived PRS for preventing malnutrition in low-income country settings. When applied to African, South Asian, or Indigenous populations, the groups most affected by malnutrition, PRS developed from these data significantly decreased predictive accuracy because the vast majority of GWAS participants were of European ancestry. For egalitarian nutrigenomics research, closing this gap by funding population-diverse genetic cohorts is a top objective. (40).

Transcriptomics, Proteomics, and Metabolomics

Beyond genomics, multi-omics techniques that combine dietary data with transcriptomics, proteomics, and metabolomics provide previously unheard-of clarity in describing how nutritional status alters cellular function. Beyond what can be deduced from static genotype data, RNA sequencing (RNA-seq) enables genome-wide assessment of gene expression responses to dietary changes in particular tissues, offering mechanistic insight. Thousands of proteins can be simultaneously quantified utilizing proteomics platforms that use data-independent acquisition mass spectrometry, revealing changes in protein modification and post-transcriptional regulation brought on by dietary status. A functional readout of the metabolic effects of both dietary consumption and genetic diversity is provided by metabolomics, which is the thorough profiling of small-molecule metabolites in blood, urine, or feces. Malnutrition is characterized by intricate network-level reorganizations involving cross-talk between energy metabolism, immune activation, growth signaling, and epigenetic maintenance rather than straightforward reductions in particular metabolic pathways, according to the integration of these data streams within a systems biology framework. By combining four omics layers with dietary data, Karczewski and Snyder's work revealed 112 new diet-gene-metabolite relationships and identified mTOR and AMPK signaling as the main nutrient-sensitive hubs in wasting adults. These discoveries have obvious implications for therapeutic treatment (41).

Epigenome-Wide Association Studies (EWAS)

Using the Illumina Infinium methylation arrays, which profile 450,000 or 850,000 CpG sites throughout the genome, epigenome-wide association studies (EWAS) have identified diet-associated methylation patterns at loci implicated in lipid metabolism, immune function, appetite regulation, and insulin signaling. EWAS apply the logic of GWAS to the epigenome, methodically identifying CpG sites whose methylation status is linked to nutritional exposures or malnutrition phenotypes (25). Finding epigenetic clocks, methylation-based biomarkers of biological age that are responsive to dietary status, is a crucial use of EWAS in malnutrition research. Research has demonstrated that children who suffer from acute malnutrition experience an acceleration of epigenetic aging; however, this acceleration can be partially reversed with dietary improvement and nutritional rehabilitation. After six months of dietary intervention, the Ramos-Lopez et al. study of the Mediterranean diet in obese individuals reported a mean 3.1-year reduction in epigenetic age. This is a startling indication that epigenetic ageing is dynamically responsive to food quality and can be used as a biomarker for therapeutic success (42).

Machine Learning and Artificial Intelligence in Precision Nutrition

The intricacy of nutrient-gene interactions, which involve hundreds of dietary components, thousands of genes, and their dynamic interplay over the life course, makes data integration more difficult than traditional statistical methods can handle. In order to find non-linear interactions and create prediction models of individual dietary response, machine learning (ML) algorithms such as random forests, gradient boosting machines, and deep neural networks are being used more and more on nutrigenomic datasets. By combining gut microbiome data, SNP genotyping, dietary records, and continuous glucose monitoring in a cohort of 800 people, Zeevi and colleagues' seminal study at the Weizmann Institute showed the potential of machine learning in customized nutrition. Their method significantly outperformed traditional carbohydrate content alone by predicting postprandial glycemic response to particular foods with 78% accuracy. Dietary modifications based on individualized predictions decreased postprandial glucose spikes by 43%. The multi-omics individualized nutrition paradigm was demonstrated by this work, which has sparked a surge of replication and extension research in a variety of demographics (43).

PRECISION NUTRITION: THERAPEUTIC STRATEGIES BASED ON NUTRIGENOMICS

Genotype-Guided Supplementation

Customizing micronutrient supplementation to each person's genotype is the most immediately practical clinical application of nutrigenomics in malnutrition. Nutrigenomic profiling allows the identification of individuals who require either higher doses or alternative forms of specific micronutrients, as opposed to applying uniform supplementation doses based on population reference intakes, which by definition are designed to meet the requirements of the majority of individuals but not those with genetically elevated needs (44). For MTHFR C677T TT homozygotes, supplementation with 5-methyltetrahydrofolate (the biologically active form of folate that does not require MTHFR enzyme conversion) is more effective than standard folic acid supplementation at raising circulating folate and reducing plasma homocysteine, a marker of inadequate one-carbon metabolism. This distinction has been demonstrated in multiple RCTs and is of particular importance during the periconceptional period, when folate-responsive neural tube defects occur in the first weeks of fetal development, often before pregnancy is recognized (11).

For FADS1/FADS2 low-efficiency genotypes, direct

supplementation with preformed LC-PUFAs (DHA, EPA, arachidonic acid) is more effective than supplementation with their precursors (alpha-linolenic acid, linoleic acid), since these individuals cannot efficiently interconvert them. The EU-funded multi-center trial by Koletzko and colleagues demonstrated that preterm infants with low-FADS genotypes showed significantly improved head circumference and neurodevelopmental scores when supplemented with DHA matched to their genotype-specific requirements, compared to standard supplementation protocols (45). For VDR and GC polymorphism carriers requiring higher vitamin D status, dose-adjustment strategies based on genotype have been proposed and are beginning to enter clinical practice in countries with advanced genomic medicine infrastructure. The challenge remains in establishing genotype-specific target serum 25-hydroxyvitamin D3 thresholds and implementing cost-effective genotyping at population scale, a feasibility challenge that differs markedly between high-income and low-income settings (33).

Personalized Dietary Prescriptions

Beyond supplementation, nutrigenomics supports the development of personalized dietary prescriptions, structured dietary plans that account for an individual's genomic, epigenomic, and microbiome profile to optimize nutritional outcomes. The clinical trial by Ordovas and colleagues is among the most rigorous to date in this domain: participants receiving nutrigenomic-guided dietary recommendations showed significantly greater reductions in waist circumference and triglyceride levels after 12 months compared to those receiving standard dietary guidelines, demonstrating that individualized genomic information adds clinically meaningful value beyond conventional advice (46). For malnutrition prevention in high-risk populations, personalized prescriptions might translate to community nutrition workers equipped with point-of-care genotyping to identify children most likely to benefit from specific therapeutic food formulations (e.g., high-FADS children prioritized for DHA-fortified ready-to-use therapeutic food; MTHFR-TT children prioritized for methyl folate-enriched foods), alongside monitoring of epigenetic biomarkers to track the efficacy of intervention in real time (44).

Epigenetic Reprogramming Through Diet

Perhaps the most ambitious frontier in nutrigenomic therapy is the deliberate use of dietary interventions to reprogram the epigenome in individuals whose malnutrition has left epigenetic scars. This strategy is grounded in the recognition that epigenetic marks, DNA sequence, are reversible in principle, and that dietary components capable of modifying the activity of epigenetic enzymes (HATs, HDACs, DNMTs, histone methyltransferases) can alter methylation and chromatin state at specific loci (27). Methyl-donor supplementation techniques have demonstrated promise in lowering global hypomethylation and reestablishing the silence of transposable elements and oncogene loci in folate-depleted people. Dietary methyl-donor replacement restored methylation at important CpG sites and decreased circulating inflammatory markers in methyl-depleted people, with specific benefits at loci controlling insulin signaling and adipogenesis, according to the Waterland and Garza EWAS (47).

Multiple epigenetic enzymes are simultaneously modulated by dietary polyphenols such as curcumin (found in turmeric), epigallocatechin gallate (found in green tea), quercetin (found in onions and apples), and resveratrol (found in red grapes). Curcumin inhibits DNMT activity, reduces H3K9 methylation (a repressive chromatin mark), and activates Nrf2 target gene expression (including antioxidant enzymes). In the context of malnutrition-associated oxidative stress and inflammatory gene overactivation, dietary polyphenol supplementation represents a practically accessible epigenetic therapeutic strategy that does not require genomic profiling to implement, though its efficacy may be modified by the individual's baseline epigenetic state and gut microbiome composition (27).

Ready-to-Use Therapeutic Foods and Nutrigenomics

Ready-to-use therapeutic foods (RUTF), lipid-based nutrient supplements formulated to treat severe acute malnutrition, have been transformative in community-based SAM management. Standard RUTF formulations based on peanut paste, dried skimmed milk, sugar, and a vitamin-mineral complex achieve recovery rates of 70-80% in uncomplicated SAM. However, 20-30% of children show slow or non-response to standard RUTF, a proportion that nutrigenomic research is beginning to illuminate. Non-response to RUTF has been associated with specific gut microbiome compositions (in particular, low abundance of Clostridial species and Bifidobacterium), which in turn correlate with host genetic variants in innate immune and mucosal immunity genes. Throughout nutritional rehabilitation, children with certain TLR4 polymorphisms that lower mucosal immune reactivity to commensal bacteria may sustain dysbiosis, hindering the microbiome regeneration required for complete nutrient absorption and metabolic restoration. Future RUTF formulations that are customized to the genetic and microbiome profiles of non-responders and include particular prebiotics (to encourage beneficial microbiome recovery) or probiotics (to directly restore important taxa) represent an intriguing future in precision nutrition (19).

NUTRIGENOMIC APPROACHES IN VULNERABLE POPULATIONS

Pregnant Women and the Periconceptional Window

The most important window for dietary epigenetic programming of offspring health is the periconceptional phase, which runs from three months before to conception through the first trimester. The growing embryo's genomic methylation patterns are methodically deleted and reestablished throughout this window, resulting in a time of maximum sensitivity to the availability of methyl-donor nutrients. The composition of the gut microbiota, genetic variations in one-carbon metabolism genes, and maternal nutritional condition all influence the epigenetic program that is passed on to the developing fetus (24).

Optimizing folate, vitamin B12, choline, and zinc status prior to conception is the first step in nutrigenomic

approaches to maternal nutrition, ideally guided by knowledge of the mother's one-carbon pathway genotype. During the periconceptional period, women with MTHFR C677T TT genotypes should ideally supplement with methylated forms of folate. Higher-dose or hydroxocobalamin-form supplements may be beneficial for women with vitamin B12 insufficiency risk genotypes (TCN2 polymorphisms). The hepcidin-pathway genotype should be taken into consideration when ensuring dietary iron adequacy, and supplemental iron dosages should be modified to account for predicted absorption efficiency. One type of metabolic deficiency that occurs during pregnancy and has significant epigenetic effects on the fetus is gestational diabetes. In the placenta and fetal tissues, maternal hyperglycemia during fetal development modifies DNA methylation at imprinted loci and non-imprinted metabolic genes, training offspring toward increased obesity, decreased insulin sensitivity, and an increased risk of type 2 diabetes. To reduce the transfer of transgenerational epigenetic risk, women with high-risk FTO, TCF7L2, and KCNJ11 genotypes may benefit from nutrigenomic-guided dietary carbohydrate reduction during pregnancy and periconceptional glycemic management (25).

Infants and Young Children: The First 1,000 Days

It has been shown that the "first 1,000 days," or the time between conception and 24 months of postnatal age, is the window of greatest potential for nutrition-based intervention to prevent stunting, cognitive impairment, and later metabolic disease. The gut flora develops, the immune system matures, the brain grows at its fastest rate, and epigenetic patterns controlling metabolism and stress reactions are set during this time. The developmental trajectories attainable by nutritional intervention within this window are significantly altered by genetic diversity (18). The classic early-life nutrigenomic intervention is breastfeeding. Hundreds of bioactive substances found in breast milk, including oligosaccharides, immunoglobulins, cytokines, hormones, exosomal miRNAs, and human milk oligosaccharides, interact with the infant's gut epithelium, microbiota, and immune gene networks in ways that formula milk is unable to fully mimic. Crucially, the human milk oligosaccharide (HMO) composition of breast milk is genetically determined by the mother's FUT2 secretor status. Secretors produce a richer and more varied HMO profile that specifically encourages Bifidobacterium colonization in the infant's gut, with subsequent advantages for immune programming and micronutrient synthesis (37).

Elderly Populations and Sarcopenic Malnutrition

Sarcopenia, a progressive loss of skeletal muscle mass and function associated with micronutrient deficiencies, is the most common manifestation of malnutrition in older people. This condition is frequently accompanied with insufficient dietary protein intake, decreased physical activity, and compromised anabolic hormone signaling. Polymorphisms in the androgen receptor (AR), vitamin D receptor (VDR), angiotensin-converting enzyme (ACE), myostatin (MSTN), and insulin-like growth factor pathway genes are the nutrigenomic basis of sarcopenic starvation. A widespread nonsense polymorphism (R577X) in ACTN3 (alpha-actinin-3), which codes for a structural protein in fast-twitch muscle fibers, is homozygous in about 18% of the population. ACTN3-XX people have altered muscle fiber type composition, decreased explosive power, and increased susceptibility to sarcopenic deterioration during aging and in circumstances of protein shortage. They also lack functional alpha-actinin-3 in their skeletal muscle. Leucine-rich protein intake that is adequate to maximally stimulate mTORC1-dependent muscle protein synthesis, along with resistance training that encourages fast-to-slow fiber type transitions compatible with their genotype, should be the main focus of nutrigenomic strategies for preventing sarcopenia in ACTN3-XX individuals (48).

Because VDR is present in skeletal muscle fibers and controls the transcription of genes involved in calcium management (ATP2A2, CASQ1), myogenic differentiation (MyoD, myogenin), and muscle fiber type specificity, vitamin D-VDR signaling is especially crucial for muscle health. In order to attain the same muscle-preserving effects of VDR activation, elderly people with low-affinity VDR polymorphisms may need higher vitamin D status targets than currently advised for standard populations. They also exhibit rapid muscle mass loss and more severe sarcopenia (14).

CHALLENGES, ETHICAL CONSIDERATIONS, AND FUTURE DIRECTIONS

Translational Challenges

Nutrigenomics has made tremendous conceptual and empirical strides, but there are still many obstacles in the way of turning this research into useful nutritional therapies, especially in low- and middle-income nations where malnutrition is most prevalent. The expense and infrastructure needed for genetic profiling is the greatest direct translational obstacle. While the cost of whole-genome sequencing has fallen from approximately USD 3 billion in 2003 to under USD 500 by 2024, it remains prohibitive for routine clinical or public health application in resource-constrained settings. Point-of-care genotyping platforms for clinically actionable variants, analogous to rapid diagnostic tests for infectious diseases, represent a more accessible near-term solution, but require validation across diverse population genetic backgrounds (49).

A second translational challenge is the complexity of genotype-phenotype relationships in nutritional science. Most nutritional traits are highly polygenic and modified by environmental, behavioral, and microbiome factors that interact non-linearly with genetic variants. This complexity means that genotyping a small number of actionable SNPs, while clinically useful, captures only a fraction of the genomic determinants of nutritional status. As PRS and multi-omics models mature and become more computationally accessible, this limitation will diminish, but the pace of progress depends on investment in population-diverse genomic cohorts that are currently underrepresented in global research databases (40). Another significant challenge is the nutritional assessment issue. Accurately characterizing dietary intake is necessary for nutrigenomics research, but dietary assessment is infamously challenging and depends on self-reported food frequency questionnaires, 24-hour meal

recalls, or weighed food records, all of which are prone to systematic measurement error. When developed, objective biomarkers of food intake, signatures that represent certain dietary patterns apart from self-report, will significantly increase the accuracy of nutrigenomics research (41).

Ethical Considerations

Nutrigenomics' clinical and public health applications present significant ethical issues that need to be addressed in tandem with the field's scientific advancement. The most significant of them is the possibility of genetic determinism, which is the false belief that genetic variations give set, unalterable dietary fates that cannot be significantly altered by behavioral or environmental intervention. In the setting of malnutrition, where structural factors like poverty, unfair food systems, and political marginalization are the main culprits, this danger is very severe. Genetic explanation must not displace structural intervention or shift responsibility for nutritional inadequacy from societies to individuals. Privacy and data governance concerns are substantial in nutrigenomics research. Genomic data are inherently identifying, even anonymized genomic datasets can potentially be re-identified through cross-referencing with other databases. In population-level nutrigenomics studies in low-income countries, where regulatory frameworks for genomic data protection are less developed, ensuring community-level consent, equitable benefit sharing, and data sovereignty requires explicit, participatory ethical governance structures that go beyond standard individual informed consent models (50).

The commercialization of nutrigenomics through direct-to-consumer (DTC) genetic testing services, which offer personalized dietary recommendations based on SNP panels, raises concerns about the quality, accuracy, and clinical validity of the interpretations provided. Several systematic assessments of DTC nutrigenomics services have found significant inconsistencies in dietary recommendations for the same genetic variants across different companies, and a general lack of rigorous clinical validation of the genotype-phenotype associations being commercialized. Regulatory oversight of DTC nutrigenomics services must be strengthened to protect consumers, particularly in vulnerable populations where marketing of personalized nutrition products may exploit health anxieties or displace evidence-based interventions (49).

Future Directions

Several scientific frontiers hold particular promise for advancing the nutrigenomic approach to malnutrition prevention and treatment. Single-cell multi-omics, which enables simultaneous profiling of genome, transcriptome, epigenome, and chromatin accessibility within individual cells, will reveal the heterogeneity of cellular responses to nutritional status within tissues and allow mapping of cell-type-specific gene-nutrient interactions at unprecedented resolution. This technology is particularly relevant for understanding the differential effects of malnutrition on gut epithelial cell populations, hepatocytes, pancreatic beta-cells, and immune cell subsets. Spatial transcriptomics, which maps gene expression patterns while preserving tissue architecture, will reveal how nutritional status alters gene expression gradients along the small intestinal crypt-villus axis and within adipose tissue stromal depots, providing mechanistic insight into malnutrition-associated intestinal dysfunction and adipose tissue remodeling that is invisible in bulk tissue transcriptomic analyses (51).

Long-read sequencing technologies (PacBio, Oxford Nanopore) are enabling the characterization of structural genomic variation, including copy number variations, tandem repeats, and large insertions/deletions, that was largely invisible to short-read sequencing platforms. Structural variants in metabolic gene loci may explain a significant fraction of the 'missing heritability' of nutritional phenotypes not captured by common-variant GWAS, and their characterization in diverse global populations is an important next step (52). Finally, the integration of nutrigenomics with digital health platforms, wearable continuous glucose monitors, dietary tracking apps, microbiome testing, and telemedicine, creates the possibility of closed-loop precision nutrition systems in which real-time dietary data, metabolic monitoring, and genomic information are synthesized by ML algorithms to generate dynamic, adaptive dietary recommendations. While currently available primarily in high-income health technology markets, the falling cost of these tools and the expanding penetration of mobile health platforms in low-income settings create a plausible pathway to broader implementation of precision nutrition in global health contexts within the next decade (43).

CONCLUSION

Malnutrition, in all its forms, is not a uniform condition that yields to uniform solutions. The evidence reviewed in this article makes clear that genetic variation shapes every dimension of nutritional health, the efficiency with which nutrients are absorbed and metabolized, the thresholds at which deficiency produces harm, the epigenetic programs through which dietary exposure in early life imprints long-term metabolic trajectories, and the degree to which therapeutic dietary interventions achieve their intended effects. By methodically shedding light on these aspects at the molecular level, nutrigenomics provides a fresh theoretical and practical basis for the study of malnutrition. This is a particularly fortunate time for the field due to the convergence of multiple technical currents. Access to genomic data is becoming more accessible due to declining sequencing prices. The simultaneous analysis of a research participant's genome, epigenome, transcriptome, microbiome, and metabolome is made possible by multi-omics integration platforms. From the complexity these datasets produce, machine learning algorithms are deriving predictions that have therapeutic significance. Additionally, there is a growing institutional interest for nutrigenomic techniques as global health organizations realize that individual-level precision strategies must be used in addition to population-level interventions. However, one must be aware of the hazards and limitations of nutrigenomics in order to fully grasp its potential. The polygenic complexity of nutritional phenotypes means that genotype-guided guidance based

on a small number of SNPs will remain an approximation for the foreseeable future, and many gene-nutrient interactions found in high-income populations need to be validated across a variety of genetic backgrounds. It is important to prevent structural nutrition policy from being replaced by genetic reductionism. Additionally, there is an urgent need to improve the ethical frameworks governing the gathering, privacy, and commercial use of genetic data in communities that are nutritionally susceptible. Microbiome-integrated dietary intervention design informed by host genetic background and genotype-guided micronutrient supplementation, especially for MTHFR, FADS, VDR, and iron homeostasis pathway variants, are likely to be the most significant short-term contributions of nutrigenomics to malnutrition prevention and treatment. Longer term, AI-assisted precision nutrition systems that combine multi-omics with real-time dietary monitoring and epigenomic treatment approaches that target the developmental programming legacies of early malnutrition have the potential to be revolutionary. Nutrigenomics does not take the place of the necessity to guarantee food security, eradicate poverty, and create fair health systems in order to bridge the molecular to the global. Instead, it deepens our comprehension of the biological significance of these imperatives and provides us with more accurate means of meeting them. The final test of nutrigenomics will be whether it equally reaches the stunted children in the Sahel, the iron-deficient pregnant women in South Asia, and the elderly withering in high-income countries' nursing homes.

REFERENCES

1. UNICEF. The state of food security and nutrition in the world 2023. 2023. https://doi.org/10.4060/cc3017en
2. Corella D, Ordovas JM. Nutrigenomics in cardiovascular medicine. Circulation: Cardiovascular Genetics. 2009;2(6):637-51. https://doi.org/10.1161/circgenetics.109.891366
3. Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French T-AC, Tai ES, et al. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. Lifestyle Genomics. 2011;4(2):69-89. https://doi.org/10.1159/000327772
4. Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. Molecular Medicine. 1996;2(3):274-82. https://doi.org/10.1007/bf03401625
5. Zhang Z, Zhang G, Zhang S, Zhao J. Fructooligosaccharide reduces weanling pig diarrhea in conjunction with improving intestinal antioxidase activity and tight junction protein expression. Nutrients. 2022;14(3):512. https://doi.org/10.3390/nu14030512
6. Kaput J, Rodriguez RL. Nutritional genomics: the next frontier in the postgenomic era. Physiological genomics. 2004;16(2):166-77. https://doi.org/10.1152/physiolgenomics.00107.2003
7. Jump DB, Botolin D, Wang Y, Xu J, Christian B, Demeure O. Fatty acid regulation of hepatic gene transcription. The Journal of nutrition. 2005;135(11):2503-6. https://doi.org/10.1093/jn/135.11.2503
8. Hanhineva K, Törrönen R, Bondia-Pons I, Pekkinen J, Kolehmainen M, Mykkänen H, et al. Impact of dietary polyphenols on carbohydrate metabolism. International journal of molecular sciences. 2010;11(4):1365-402. https://doi.org/10.3390/ijms11041365
9. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. Cell. 2017;168(6):960-76. https://doi.org/10.1016/j.cell.2017.02.004
10. Hara T, Takeda T-a, Takagishi T, Fukue K, Kambe T, Fukada T. Physiological roles of zinc transporters: molecular and genetic importance in zinc homeostasis. The journal of physiological sciences. 2017;67(2):283-301. https://doi.org/10.1007/s12576-017-0521-4
11. Hsu S, Prince DK, Williams K, Allen NB, Burke GL, Hoofnagle AN, et al. Clinical and biomarker modifiers of vitamin D treatment response: the multi-ethnic study of atherosclerosis. The American Journal of Clinical Nutrition. 2022;115(3):914-24. https://doi.org/10.1093/ajcn/nqab390
12. Koletzko B, Lattka E, Zeilinger S, Illig T, Steer C. Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. The American journal of clinical nutrition. 2011;93(1):211-9. https://doi.org/10.3945/ajcn.110.006189
13. Claussnitzer M, Dankel SN, Kim K-H, Quon G, Meuleman W, Haugen C, et al. FTO obesity variant circuitry and adipocyte browning in humans. New England Journal of Medicine. 2015;373(10):895-907.
14. Prentice A, Schoenmakers I, Laskey MA, De Bono S, Ginty F, Goldberg GR. Symposium on 'Nutrition and health in children and adolescents' Session 1: Nutrition in growth and development Nutrition and bone growth and development: A meeting of the Nutrition Society hosted by the Irish Section was held on 14–16 June 2006 at University College Cork, Cork, Republic of Ireland. Proceedings of the Nutrition Society. 2006;65(4):348-60. https://doi.org/10.1079/pns2006519
15. Shrimpton R, Rokx C. The double burden of malnutrition. A review of global evidence Washington, DC: World Bank. 2012.
16. Hales CN, Barker DJ. The thrifty phenotype hypothesis: Type 2 diabetes. British medical bulletin. 2001;60(1):5-20.
17. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, De Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. The lancet. 2013;382(9890):427-51. https://doi.org/10.1016/s0140-6736(13)60937-x
18. Agnihotri N, Rudjord Hillesund E, Bere E, Wills AK, Brantsæter AL, Øverby NC. Development and description of New Nordic Diet scores across infancy and childhood in the Norwegian Mother, Father and Child Cohort Study (MoBa). Maternal & Child Nutrition. 2021;17(3):e13150.
19. Isanaka S, Langendorf C, Berthé F, Gnegne S, Li N, Ousmane N, et al. Routine amoxicillin for uncomplicated severe acute malnutrition in children. New England Journal of Medicine. 2016;374(5):444-53. https://doi.org/10.1056/nejmoa1507024
20. Singhi P, Saini AG, Malhi P. Child maltreatment in India. Paediatrics and international child health. 2013;33(4):292-300.
21. Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, Alam MA, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature. 2014;510(7505):417-21. https://doi.org/10.1038/nature13421
22. Damms-Machado A, Weser G, Bischoff SC. Micronutrient deficiency in obese subjects undergoing low calorie diet.

Nutrition journal. 2012;11(1):34.
23. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood. 2003;102(3):783-8. https://doi.org/10.1182/blood-2003-03-0672
24. Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. Molecular and cellular biology. 2003;23(15):5293-300.
25. Dominguez-Salas P, Moore SE, Baker MS, Bergen AW, Cox SE, Dyer RA, et al. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. Nature communications. 2014;5(1):3746. https://doi.org/10.1038/ncomms4746
26. Berger SL. The complex language of chromatin regulation during transcription. Nature. 2007;447(7143):407-12.
27. Milagro F, Mansego M, De Miguel C, Martínez J. Dietary factors, epigenetic modifications and obesity outcomes: progresses and perspectives. Molecular aspects of medicine. 2013;34(4):782-812. https://doi.org/10.1016/j.mam.2012.06.010
28. Mentzel CMJ, Anthon C, Jacobsen MJ, Karlskov-Mortensen P, Bruun CS, Jørgensen CB, et al. Gender and obesity specific microRNA expression in adipose tissue from lean and obese pigs. PloS one. 2015;10(7):e0131650.
29. Jansson-Knodell CL, Rubio-Tapia A. The fashionable gluten-free diet—wear with caution. Oxford University Press; 2021. p. 491-2.
30. Georgieff MK, Brunette KE, Tran PV. Early life nutrition and neural plasticity. Development and psychopathology. 2015;27(2):411-23. https://doi.org/10.1017/s0954579415000061
31. Hambidge KM, Krebs NF. Zinc deficiency: a special challenge. The Journal of nutrition. 2007;137(4):1101-5.
32. Rosenblatt DS. Inherited disorders of folate and cobalamin. Homocysteine Metabolism: From Basic Science to Clinical Medicine: Springer; 1997. p. 61-8.
33. Prentice A, Goldberg GR, Schoenmakers I. Vitamin D across the lifecycle: physiology and biomarkers. The American journal of clinical nutrition. 2008;88(2):500S-6S. https://doi.org/10.1093/ajcn/88.2.500s
34. Sonnenburg JL, Bäckhed F. Diet–microbiota interactions as moderators of human metabolism. Nature. 2016;535(7610):56-64.
35. Claus SP, Ellero SL, Berger B, Krause L, Bruttin A, Molina J, et al. Colonization-induced host-gut microbial metabolic interaction. MBio. 2011;2(2):10.1128/mbio. 00271-10. https://doi.org/10.1128/mbio.00271-10
36. Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, et al. Human genetics shape the gut microbiome. Cell. 2014;159(4):789-99.
37. Lewis ZT, Totten SM, Smilowitz JT, Popovic M, Parker E, Lemay DG, et al. Maternal fucosyltransferase 2 status affects the gut bifidobacterial communities of breastfed infants. Microbiome. 2015;3(1):13. https://doi.org/10.1186/s40168-015-0071-z
38. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in~ 700000 individuals of European ancestry. Human molecular genetics. 2018;27(20):3641-9.
39. Choi SW, Mak TS-H, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. Nature protocols. 2020;15(9):2759-72. https://doi.org/10.1038/s41596-020-0353-1
40. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Current clinical use of polygenic scores will risk exacerbating health disparities. Nature genetics. 2019;51(4):584.
41. Karczewski KJ, Snyder MP. Integrative omics for health and disease. Nature Reviews Genetics. 2018;19(5):299-310. https://doi.org/10.1038/nrg.2018.4
42. Ramos-Lopez O, Milagro FI, Riezu-Boj JI, Martinez JA. Epigenetic signatures underlying inflammation: An interplay of nutrition, physical activity, metabolic diseases, and environmental factors for personalized nutrition. Inflammation Research. 2021;70(1):29-49.
43. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. Cell. 2015;163(5):1079-94. https://doi.org/10.1016/j.cell.2015.11.001
44. Grimaldi KA, Van Ommen B, Ordovas JM, Parnell LD, Mathers JC, Bendik I, et al. Proposed guidelines to evaluate scientific validity and evidence for genotype-based dietary advice. Genes & nutrition. 2017;12(1):35.
45. Koletzko B, Boey CC, Campoy C, Carlson SE, Chang N, Guillermo-Tuazon MA, et al. Current information and Asian perspectives on long-chain polyunsaturated fatty acids in pregnancy, lactation, and infancy: systematic review and practice recommendations from an early nutrition academy workshop. Annals of Nutrition and Metabolism. 2014;65(1):49-80. https://doi.org/10.1159/000365767
46. Ordovas JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. bmj. 2018;361.
47. Waterland RA, Garza C. Potential mechanisms of metabolic imprinting that lead to chronic disease. The American journal of clinical nutrition. 1999;69(2):179-97.
48. Scott D, de Courten B, Ebeling PR. Sarcopenia: a potential cause and consequence of type 2 diabetes in Australia's ageing population? Medical Journal of Australia. 2016;205(7):329-33. https://doi.org/10.5694/mja16.00446
49. Pavlidis C, Patrinos GP, Katsila T. Nutrigenomics: A controversy. Applied & translational genomics. 2015;4:50-3. https://doi.org/10.1016/j.atg.2015.02.003
50. Yaqoob P. Fatty acids and the immune system: from basic science to clinical applications. Proceedings of the Nutrition Society. 2004;63(1):89-105. https://doi.org/10.1079/pns2003328
51. Stuart T, Satija R. Integrative single-cell analysis. Nature reviews genetics. 2019;20(5):257-72.
52. Eichler EE, Flint J, Gibson G, Kong A, Leal SM, Moore JH, et al. Missing heritability and strategies for finding the underlying causes of complex disease. Nature reviews genetics. 2010;11(6):446-50. https://doi.org/10.1038/nrg2809