ANNUAL REVIEWS

Annual Review of Food Science and Technology

Precision (Personalized) Nutrition: Understanding Metabolic Heterogeneity

Steven H. Zeisel

Nutrition Research Institute, Department of Nutrition, University of North Carolina, Kannapolis, North Carolina 28081, USA; email: steven_zeisel@unc.edu

Annu. Rev. Food Sci. Technol. 2020. 11:71–92

First published as a Review in Advance on January 13, 2020

The *Annual Review of Food Science and Technology* is online at food.annualreviews.org

https://doi.org/10.1146/annurev-food-032519-051736

Keywords

precision nutrition, personalized nutrigenetics, microbiome, epigenetics, environmental exposures

Abstract

People differ in their requirements for and responses to nutrients and bioactive molecules in the diet. Many inputs contribute to metabolic heterogeneity (including variations in genetics, epigenetics, microbiome, lifestyle, diet intake, and environmental exposure). Precision nutrition is not about developing unique prescriptions for individual people but rather about stratifying people into different subgroups of the population on the basis of biomarkers of the above-listed sources of metabolic variation and then using this stratification to better estimate the different subgroups' dietary requirements, thereby enabling better dietary recommendations and interventions. The hope is that we will be able to subcategorize people into ever-smaller groups that can be targeted in terms of recommendations, but we will never achieve this at the individual level, thus, the choice of precision nutrition rather than personalized nutrition to designate this new field. This review focuses mainly on genetically related sources of metabolic heterogeneity and identifies challenges that need to be overcome to achieve a full understanding of the complex interactions between the many sources of metabolic heterogeneity that make people differ from one another in their requirements for and responses to foods. It also discusses the commercial applications of precision nutrition.

INTRODUCTION

New science and better technology are changing how nutrition science is translated into more precise applications for improving the diets of both people and animals. Nutrients and food-derived bioactive molecules must be absorbed and metabolized before their final uses as sources of energy, catalysts for reactions, ligands for signaling receptors, or structural components of cells. Some metabolic pathways of interest are not mammalian but rather are pathways of metabolism in the symbiotic microbiota of the gastrointestinal tract. For many, if not all, steps of metabolism, there is considerable interindividual variation. This metabolic heterogeneity can result in differences in how people (or animals) respond to nutrients or bioactive molecules. If scientists could understand the sources of this nutrition-relevant metabolic heterogeneity, they could predict these variations, use this information to develop better estimates of an individual's dietary requirements, and develop better dietary recommendations and interventions. This is the basis for a new discipline called precision nutrition, sometimes referred to as personalized nutrition (de Toro-Martin et al. 2017). Large groups of people, usually of similar ancestry, share common underlying causes of metabolic heterogeneity (genetic, epigenetic, microbiota, and environmental differences). It is possible to stratify people so that policy and products can be targeted to reasonably sized subpopulations, making it economically viable to develop policy or food-based interventions that address metabolic inefficiencies present in large subgroups of people. For example, gluten-free foods are already available for people with genetic variants that result in gluten intolerance; lactose-free foods are available for people with deficient expression of lactase.

Precision nutrition methods could considerably reduce the unexplained variance in responses between people that so often plagues nutrition research. These noisy data can make it hard to conclude a nutrition intervention is effective. The lumping together of individuals who respond to treatment with those who do not respond generates underestimation of effect size and high variances. Precision nutrition enables scientists to better understand why there are responders and nonresponders to dietary interventions and to appropriately design studies powered to account for metabolic heterogeneity (**Figure 1**).

Precision nutrition is science based and is similar in concept to precision medicine/pharmacology, which is already widely implemented, for example, the US Food and Drug Administration requires labeling that recommends genetic testing to determine whether a person is a fast or slow metabolizer of the drug Warfarin (30–35% of patients carry *CYP2C9* gene variants and need a lower initial dose), and this genetic testing is reimbursable in the United States (Cent. Medicare Medicaid Serv. 2009, Ji et al. 2016, Shukla et al. 2018). The metabolic pathways for most drugs evolved not because people (or animals) used these drugs but because the pathways had to manage the metabolism of foods to which humans (animals) and their symbiotic microbiota were exposed.

We know enough to begin implementing precision nutrition, and current applications of precision nutrition have been successful, creating a foundation for the development of even better versions of precision nutrition when new tools, data, and understanding become available. Just as is true for precision medicine, there will be a process of continuous quality improvement that results eventually in the best understanding of the complex interactions that contribute to metabolic heterogeneity; thus, undoubtedly, precision nutrition will be continuously refined over time. Many inputs contribute to metabolic heterogeneity (including variations in genetics, epigenetics, symbiotic microbiota, lifestyle, diet intake, and environmental exposures). Not enough is known about their specific effects on dietary requirements and responses to diet. Also, there are evolving computational tools and mathematical models needed to integrate across the many sources of variance so that we can fully predict the effects of metabolic heterogeneity in an individual. The systems

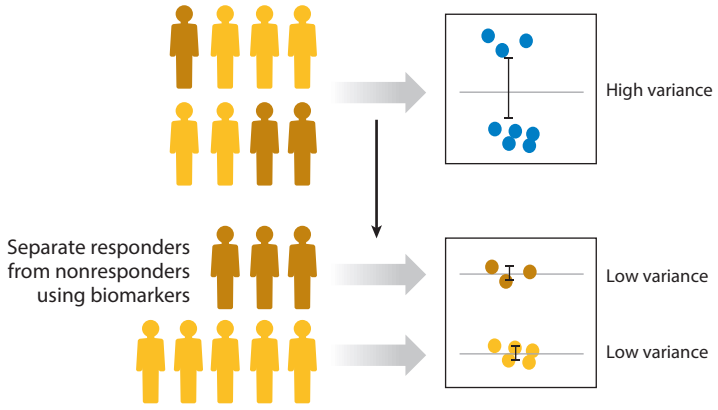

Figure 1

Precision nutrition enables scientists to better understand why there are responders and nonresponders to dietary interventions. Because of genetic, epigenetic, microbiota, and environmental differences, metabolic heterogeneity can result in differences in how people (or animals) respond to nutrients or bioactive molecules. When heterogeneous people are lumped together in studies of dietary interventions, large interindividual variance makes it difficult to detect significant effects. Large groups of people, usually of similar ancestry, share common underlying causes of metabolic heterogeneity. Using appropriate biomarkers, including genetic data, researchers can stratify people so that responders and nonresponders can be predicted for an intervention, and the resulting data analyzed separately, thereby reducing interindividual variability and enhancing the capacity to detect significant differences between groups.

biology model approach has been recently discussed in detail (Bauer & Thiele 2018, van Ommen et al. 2017). Methods for measuring all these inputs are not at the same stage of sophistication; therefore, inputs that can be easily measured tend to be prominent components of the first mathematical models developed for use in precision nutrition. Whereas scientists were recently reporting the effects of individual gene variants, they are now modeling the effects of complex patterns of gene variants and adding changes in microbial composition and microbial gene expression to these models (Bashiardes et al. 2018).

This review focuses mainly on genetically related sources of heterogeneity and identifies challenges that need to be overcome to achieve a full understanding of the complex interactions between the many sources of metabolic heterogeneity that make people differ from one another in their requirements for and responses to foods.

GENETIC VARIATION AS A SOURCE OF NUTRITION-RELEVANT METABOLIC HETEROGENEITY

Metabolic heterogeneity can derive from variants in genes that code for mRNA that is then translated into proteins as well as from variants in noncoding regions of genes. People have more than five million variations in their genetic code [any individual person has at least 50,000 of these single nucleotide polymorphisms (SNPs)] (Overbeek et al. 2005, Sabeti et al. 2007); they also have gene copy number variations (Reiter et al. 2016, Sharma et al. 2016) and tandem repeat (stretches of DNA that are highly variable in length) variations (Bilgin Sonay et al. 2015). These gene variants are inherited from ancient ancestors and therefore differ among people depending on their heritage (Overbeek et al. 2005, Sabeti et al. 2007). Animals have similar genetic variation (Kiddy 1979). These gene variants can perturb the expression and function of enzymes, transporters, or receptors and their ligands by changing the expression of the gene or the rate of translation of

mRNA into protein via modification of amino acid residues that affect the half-life of the protein(s) and/or alteration of the protein's structure, thereby changing how an enzyme binds to its substrate and products. These are called functional gene variants.

There are many examples of functional gene variants that affect the metabolism of dietary components. Cytochrome P450–1A2 is responsible for approximately 95% of caffeine metabolism (Rasmussen et al. 2002) and a functional SNP in the gene coding for this cytochrome (*CYP1A2* rs762551) decreases the amount of the cytochrome, resulting in slower caffeine metabolism (Sachse et al. 1999), which explains much of the interindividual variability in caffeine concentrations after the same caffeine dose. Similarly, functional SNPs in the gene coding for the aryl-hydrocarbon receptor for caffeine (*AHR* rs6968865 and rs4410790) can cause interindividual variability in the brain's response to caffeine ingestion (Josse et al. 2012).

There is a solid understanding of how functional SNPs alter the dietary requirements for the nutrient choline (Zeisel 2006). In the United States, intake of choline is significantly lower than recommended (Wallace & Fulgoni 2016), probably because the foods that are higher in choline (e.g., eggs, fatty meats) often are avoided due to dietary restriction of cholesterol intake (Zeisel et al. 2003). Choline can be derived from endogenous synthesis in the liver (see later discussion as to gender specificity) or from the diet. Choline is then transported by a carrier into cells, where it is either phosphorylated, acetylated, or oxidized. The phosphorylated forms of choline are used to make membrane phospholipids, the oxidized form (betaine) is used as a methyl donor, and acetylcholine is a neurotransmitter (Zeisel 2006). The methyl-donation function of choline intersects with the pathways for folate, vitamin B12, and vitamin B6 metabolism (Zeisel 2006) (**Figure 2**).

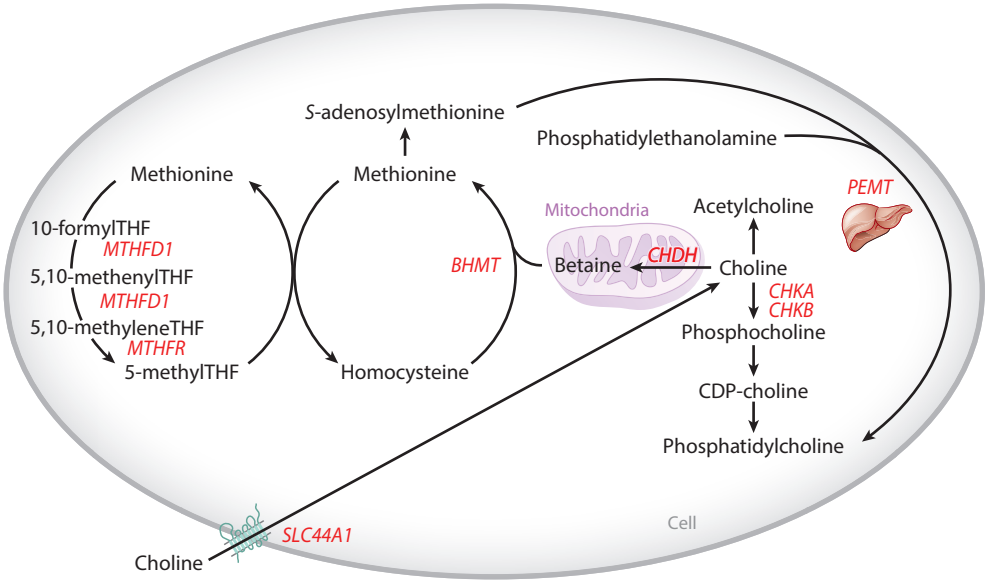

Figure 2

Polymorphic genes that influence choline requirements in people. Choline can be derived from endogenous synthesis in the liver by methylating phosphatidylethanolamine; it can also be obtained from the diet. Choline is then transported by a carrier into cells, where it is either phosphorylated, acetylated, or oxidized. The phosphorylated forms of choline are used to make membrane phospholipids, the oxidized form (betaine) is used as a methyl donor, and acetylcholine is a neurotransmitter. The methyl-donation function of choline intersects with the pathways for folate metabolism. Genes (*red*) with common polymorphisms influence how much choline a person needs to maintain optimal liver and muscle function.

Choline intake in the pregnant female is critical for normal fetal development (Boeke et al. 2013; Caudill et al. 2018; Shaw et al. 2004, 2006; Wang et al. 2016; Zeisel & Blusztajn 1994). Adults eating diets low in choline develop fatty liver and/or muscle breakdown that resolves when choline is restored to their diets (Fischer et al. 2007). Choline is an essential part of the diet for men and postmenopausal women, but many premenopausal women can make a source of choline (phosphatidylcholine) in their livers and for this reason need to eat less choline in their diet (Fischer et al. 2007). The capacity to make choline (in the form of phosphatidylcholine) is dependent on expression of the gene *PEMT*, and estrogen concentrations present in premenopausal and pregnant women are high enough that they can induce expression of this gene, with maximal induction achieved at estrogen concentrations obtained in the second trimester of pregnancy, when women have an increased demand for choline to build their baby (Resseguie et al. 2007). Men and postmenopausal women do not have enough estrogen to fully induce the gene's expression. A very common SNP in *PEMT* (rs12325817-C) reduces *PEMT*'s inducibility by estrogen, and women with this SNP have an increased dietary choline requirement; they are 25 times more likely to develop liver or muscle damage when eating a low-choline diet (Fischer et al. 2010, Resseguie et al. 2011). This polymorphism is much more common in women of European ancestry than in those of African ancestry (da Costa et al. 2006, Fischer et al. 2007, Silver et al. 2015). Other SNPs in genes related to one-carbon metabolism also alter the dietary requirement for choline in both men and women (da Costa et al. 2006, 2014; Ganz et al. 2017; Kohlmeier et al. 2005). For example, premenopausal women with the very common 5,10-methylenetetrahydrofolate dehydrogenase 1 polymorphism (*MTHFD1* rs2236225-A) were 15 times more likely than noncarriers to develop signs of choline deficiency when fed a low-choline diet (Kohlmeier et al. 2005). This is because this polymorphism decreases the availability of 5-methyltetrahydrofolate, an important methyl donor, thereby increasing the use of choline for methyl donation (Kohlmeier et al. 2005). Some common SNPs determine which organ fails first in people fed diets low in choline; people with polymorphisms in the gene encoding for the choline transporter, *SLC44A1* (rs7873937-G; rs2771040-G; rs6479313-G; rs16924529-A; rs3199966-C) as well as in the genes encoding for the kinases that phosphorylate choline once inside the cell, *CHKB* (rs1557502-A) and *CHKA* (rs2512612-T, rs6591331-T), were much more likely to develop muscle damage (da Costa et al. 2014). Men with polymorphisms in the gene that converts choline to betaine, *CHDH* (rs12676-A), have defective mitochondrial function in their sperm (Johnson et al. 2012).

Functional gene variants do not occur only in one-carbon metabolism; many SNPs exert readily apparent effects on metabolism. Vitamin D, like choline, can be derived from endogenous biosynthesis or from the diet (Miller 2017), and interacting and complex metabolic pathways are encoded by many genes involved in vitamin D metabolism (**Figure 3**). Vitamin D is formed from 7-deoxycholesterol in a reaction catalyzed by delta-7-sterol reductase (encoded by *DHCR7*) (Wang et al. 2010). Whether derived from food or endogenous synthesis, vitamin D needs to be activated by conversion to 25-hydroxy-vitamin D (25-OH-vitamin D) and then to 1,25-OH-vitamin D. The various forms of vitamin D are carried in the blood bound to vitamin D–binding protein (encoded by *GC*) and transported between the skin, liver, kidney, and other target organs. A P450 cytochrome C (*CYP2R1*; with some contributions from mitochondrial *CYP27B1* and *CYP27A1*) encodes the 25-hydrolyase activity (Miller 2017). The resulting 25-OH-vitamin D in the kidney filtrate must then combine with cubulin (encoded by *CUBN*) to allow it to be taken up into the renal tubule epithelia where another monooxygenase (encoded by *CYP27B1*) forms 1,25-OH_2-vitamin D. This activated vitamin D then binds to its receptor (encoded by *VDR*), a nuclear zinc finger protein. A complex containing a dimer of VDR-1,25-OH_2-vitamin D and retinoic acid receptor–retinoic vitamin D (the retinoic acid receptor is encoded by *RARA*) then binds to multiple binding elements on genes (including genes that regulate mineralization of bone

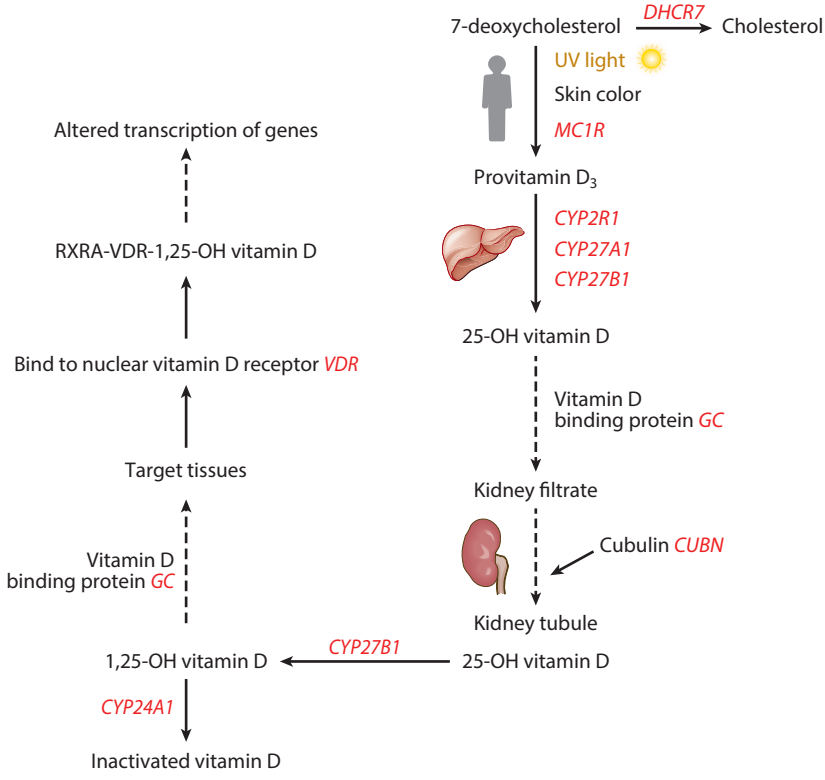

Figure 3

Polymorphic genes that influence vitamin D requirements in people. There are interacting and complex metabolic pathways encoded by many genes involved in vitamin D metabolism (*red*). Common polymorphisms in these genes modify the dietary requirements for vitamin D. Vitamin D is formed from 7-deoxycholesterol in the skin, which depends on UV light exposure; thus, genetic variation in skin color matters. Whether derived from food or endogenous synthesis, vitamin D needs to be activated by conversion to 25-hydroxy-vitamin D (25-OH-vitamin D) and then to 1,25-OH-vitamin D. The various forms of vitamin D are carried in the blood bound to vitamin D–binding protein and transported between the skin, liver, kidney, and other target organs. 25-OH-vitamin D must combine with cubulin to allow it to be taken up into the renal tubule epithelia where activated 1,25-OH_2-vitamin D is formed. This then binds to its receptor VDR. A complex containing a dimer of VDR-1,25-OH_2-vitamin D and retinoic acid receptor–retinoic vitamin D (the retinoic acid receptor is encoded by *RARA*) then binds to multiple binding elements on genes, affecting their expression. 1,25-OH_2-vitamin D is inactivated by 23- and 24-hydroxylation.

and calcium and phosphate metabolism, as well as 200 other genes), affecting their expression (Kohlmeier 2013). The major pathways by which vitamin D is inactivated are the vitamin's 23- and 24-hydroxylation by mitochondrial CYP24A1 (Miller 2017). People have genetic variants at several of these metabolic steps that affect their requirement for and responses to vitamin D.

We know that skin color has important effects on vitamin D synthesis in the skin (Kohlmeier 2013). Polymorphisms in the melanocortin 1 receptor (*MC1R*) gene modulate skin pigmentation; the low-function variants (*MC1R* rs1805007 and rs1805008) in European populations were likely inherited from Neanderthal ancestors. Multiple other variants result in light skin color (Liu et al. 2011). The concentration of the vitamin D precursor 7-deoxycholesterol is increased in the skin of people with a low-function variant of delta-7-sterol reductase (*DHCR7* rs7944926); this results in enhanced vitamin D synthesis (Wang et al. 2010). *CYP2R1* has a common genetic

variant (rs10741657) that lowers the formation of 25-OH-vitamin D (Elkum et al. 2014, Nissen et al. 2015, Wang et al. 2010). Polymorphisms near *CYP2R1* (rs2209314, rs2762939) also affect 25-OH-vitamin D concentrations (Barry et al. 2014). Polymorphisms in the gene encoding vitamin D–binding protein (*GC* rs7041, rs4588) increase 25-OH-vitamin D levels in blood after a vitamin D supplement (Ahn et al. 2010, Jolliffe et al. 2016), as do polymorphisms rs10766197 near *CYP2R1*, rs6013897 near *CYP24A1*, and rs7968585 near *VDR* (Barry et al. 2014, Wang et al. 2010). Common genetic variations alter the vitamin D receptor (VDR; *Apal* rs17879735, *Bsml* rs1544410, *Taql* rs731236, *FokI* rs2228570, and rs10735810). *Bsml* rs1544410 lowers risk of hip fractures; women with the *Bsm-I* CC genotype had greater improvement in bone mineral density after treatment with vitamin D3 than did those with the TT genotype (Palomba et al. 2005). *Fok-I* is a functional polymorphism that results in different translation initiation sites on VDR that lead to a less effective protein (Colin et al. 2000). People with the combination of *DHCR7* rs12785878, *CYP2R1* rs10741657, and *GC* rs2282679 have a more than twofold increased risk of vitamin D insufficiency (Elkum et al. 2014, Wang et al. 2010). The *CYP24A1* polymorphism (rs6013897), which alters the rate of inactivation of vitamin D, is associated with higher concentrations of vitamin D in the blood (Barry et al. 2014).

Lipid metabolism is also affected by genetic polymorphisms (**Figure 4**). People with the CC genotype of Apolipoprotein A2 (*APOA2* rs5082) have increased adiposity [body weight, body mass index (BMI), and waist circumference] and increased consumption of fatty foods compared to individuals who are homozygous normal or heterozygous for this gene variant (Corella et al. 2009, 2011). This SNP also perturbs dietary modulation of plasma ghrelin, a regulator of food intake (Smith et al. 2012). When an individual habitually consumes a diet low in saturated fat, the *APOA2* rs5082 SNP has no effect, but when a diet high in saturated fat is consumed, the people with the CC genotype for the SNP have higher BMI, whereas the people with TT and TC genotypes do not (Corella et al. 2011). In another example, increasing eicosapentaenoic acid (EPA) in the diet has a different effect on high-density lipoprotein (HDL) cholesterol depending on whether

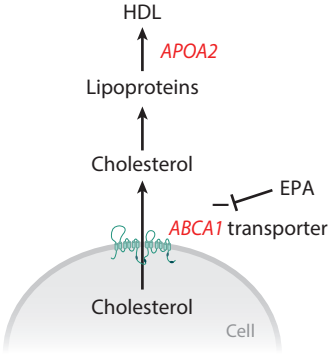

Figure 4

Polymorphic genes that influence lipid metabolism in people. Lipid metabolism is also affected by common genetic polymorphisms. People with common Apolipoprotein A2 (*APOA2*) variants have increased body weight, body mass index, and waist circumference and consume higher amounts of fatty foods. When a person eats a diet low in saturated fat, the *APOA2* polymorphism has no effect, but when a person eats a diet high in saturated fat, the effects on phenotype are revealed. Increasing eicosapentaenoic acid (EPA) in the diet has a different effect on high-density lipoprotein (HDL) cholesterol depending on whether individuals have a specific single nucleotide polymorphism in the ATP-binding cassette subfamily A member 1 (*ABCA1*). Plasma HDL cholesterol is higher in people with the CC genotype for *ABCA1* rs2246293 than in people with the GG genotype after EPA feeding.

individuals have a specific SNP in the ATP-binding cassette subfamily A member 1 (*ABCA1*) gene. This gene encodes for a cholesterol efflux transporter. The expression of *ABCA1* is decreased by DNA methylation at the site of *ABCA1* rs2246293. DNA methylation of the gene is decreased and plasma HDL cholesterol is higher in people with the CC genotype for *ABCA1* rs2246293 than in people with the GG genotype, in whom EPA can increase DNA methylation of *ABCA1*, suppressing this gene's expression and thereby lowering concentrations of HDL (Ma et al. 2016).

Data on genetic variation can be combined with data on other sources of heterogeneity to predict individual glycemic response to a meal (Zeevi et al. 2015). Using subcutaneous glucose sensors in people, researchers detected high interindividual variability of postprandial glycemic response. These data were combined with data on food intake, physical activity, medical histories, anthropometric measures, and microbiota profiling, and an algorithm to predict glycemic response to a meal was developed. The predictive performance of the algorithm was then examined in a blinded randomized controlled trial with new participants in which the algorithm predicted with 70–80% accuracy the glycemic response to a test meal.

Another study observed that carrying a particular set of alleles in several genes influenced the response to a dietary intervention (Abdullah et al. 2018, Vazquez-Vidal et al. 2019). After normolipidemic people ate three servings per day of dairy foods for four weeks, carriers of ATP-binding cassette subfamily G member 5 (*ABCG5*) rs6720173-GG, who also carried cytochrome P450 family 7 subfamily A member (*CYP7A1*) rs3808607-G, had greater increases in total cholesterol and LDL-C concentrations compared to C-allele carriers of *ABCG5* rs6720173-C who also carried 7-dehydrocholesterol reductase (*DHCR7*) rs760241-TT. In addition, carriers of *ABCG5* rs6720173-C with *CYP7A1* rs3808607-TT and *DHCR7* rs760241-GG had reductions in LDL-C concentrations compared to those who carried *ABCG5* rs6720173-GG, *CYP7A1* rs3808607-G and *DHCR7* rs760241-A.

In all the above examples, polymorphisms in known pathways related to the metabolism of the nutrient were related to altered function. However, polymorphisms in unexpected pathways can sometimes modify the effects of nutrients. Although there was a lack of an overall effect of vitamin E on cardiovascular disease (CVD) or cancer in the Women's Genome Health Study (a 10-year trial using aspirin and vitamin E with 10-year follow-up), a subgroup of people with a polymorphism in catechol-*O*-methyltransferase (*COMT*) rs4680-AA halved their risk of developing CVD (Hall et al. 2014) and reduced their risk of developing cancer by 14% (Hall et al. 2019) when treated with vitamin E compared with people without this variant who were unresponsive to vitamin E. The mechanism linking *COMT* to vitamin E metabolism is unknown but may be due to the regeneration of a vitamin E radical via the donation of a hydrogen from vitamin C; *COMT* variants that alter vitamin C concentrations have been reported (Shin et al. 2014).

Obviously, building a catalog of metabolically functional SNPs is going to be challenging, but at this time such variants number in the hundreds (de Toro-Martin et al. 2017), and thousands are likely to be contributors to metabolic heterogeneity.

Diet Challenges Can Reveal the Effects of Genetic Variation

When studying genetic variation as a source of metabolic heterogeneity, it is important to realize that genetically caused metabolic inefficiencies can be revealed by diets that challenge the capacity of pathways altered by the effects of SNPs. When the capacity to make or use an essential nutrient is diminished, diets that contain excess precursor to push through the metabolic bottleneck or provide the metabolites that are decreased by the bottleneck can overcome the effect of the SNPs. For example, premenopausal women with the *PEMT* rs12325817 variant have impaired endogenous synthesis of choline but can overcome this problem by eating more choline in their

diet. Alternatively, some gene variants can be revealed when people eat too much of a nutrient. For example, in the choline–fatty liver study discussed below, SNPs cause diminished capacity for fat export from the liver, but this was problematic only when fat production in the liver was high because of high-calorie intake (high BMI) making the capacity for fat export rate limiting (Corbin et al. 2013). It was only when people ate diets high in calories that hepatic lipogenesis exceeded the rate at which fat could be exported by the liver, and this resulted in fat accumulation within the liver. Thus, measuring genotype is not sufficient to identify individuals who will suffer an adverse outcome; diet intake information needs to be integrated with genotype to predict such risk.

Genome-wide association studies (GWASs) have identified remarkably few gene variants associated with metabolic heterogeneity because most GWASs are based on data sets that do not include diet intake. A recent study found many gene variants that contributed to a polygenic risk score for obesity, and that most of the gene variants that contributed to these risk scores were not previously identified using standard GWAS approaches (Khera et al. 2019). It is hard to find genetic studies that also collected data on dietary intake; without such information, there is no understanding of diet–gene interactions that can inform precision nutrition. An example of a helpful diet–gene study is the National Health and Nutrition Examination Survey (NHANES) conducted by the US Centers for Disease Control and Prevention; it now collects phenotypic, genetic, and dietary data (Wallace & Fulgoni 2016).

Patterns of Genetic Variation Rather Than Single Polymorphisms Are Important

Many published papers study the effects of genetic variation on metabolic heterogeneity by considering the effects of individual gene variants, but it would be better if a pattern of variants that affected multiple points in a pathway or in related pathways were the basis for predicting metabolic heterogeneity because the sum of all the effects of the multiple polymorphisms best predicts metabolic function. To accomplish this approach, the field needs to develop appropriate data and better computational models and tools. An algorithm-based approach was used to identify SNPs that, when considered as an integrated grouping, predicted which people were at higher risk for developing fatty liver when they ate more calories (had higher BMI). When pathways in one-carbon metabolism, including choline metabolism pathways, are perturbed, the capacity of the liver to export accumulated fat is diminished (da Costa et al. 2006; Fischer et al. 2007; Yao & Vance 1988, 1989). People who are inefficient at exporting fat from the liver are prone to develop fatty liver. Multiple pathways contribute to altered capacity to export fat from the liver, including pathways that transport choline into the liver, transport phosphatidylcholine out of the liver into bile, phosphorylate choline, oxidize choline to make metabolites that can donate methyl groups, and synthesize phosphatidylcholine de novo (the PEMT pathway) (Corbin et al. 2013). Gene variants in each of these pathways are relatively common, and a model that integrates the effects of SNPs across these different pathways accurately predicted which people developed fatty liver as their BMI increased and was much better than using single polymorphisms alone (Corbin et al. 2013).

Because an individual's genetic code stays constant, the power of such gene-variant-based predictions is that they are measurable at any time in life. Excellent molecular tools are available for assessing gene sequence variants. For this reason, nutrigenetics/nutrigenomics has advanced more rapidly in making contributions to precision nutrition. However, genetic variation is only one contributor to metabolic heterogeneity, and although mathematical models based on gene variation alone are an excellent start, they do not provide the best estimates of an individual's dietary requirements.

EPIGENETIC DIFFERENCES AS A SOURCE OF METABOLIC HETEROGENEITY

Cells in different tissues have highly diverse functions despite sharing a common genetic code. This is because gene expression is regulated by epigenetic mechanisms that are mediated by noncoding RNAs and by marks placed on genes or histone tails. The writing and erasing of epigenetic marks are guided by a complex set of interactions in which DNA modifications, histone tail modifications, and other epigenetic marks influence each other and function in a synergistic fashion (Jeltsch & Jurkowska 2014, Strahl & Allis 2000). Food intake can significantly modify epigenetic marks (reviewed in Ideraabdullah & Zeisel 2018).

DNA methylation (formation of 5-methylcytosine primarily at CG dinucleotides) is the best understood epigenetic mark (Szyf 2005). DNA methylation at each site is determined by the local activity of DNA methyltransferases (writers) and DNA demethylases (erasers) (Jeltsch & Jurkowska 2014). DNA methylation usually suppresses a gene's expression, but exceptions occur (Jones 2012). DNA methylation is erased at most sites during early embryogenesis and then replaced with new marks. It is during fetal development and early postnatal life that genes are most likely to undergo changes in DNA methylation, and these marks are then sustained throughout life (Jones 2012). *S*-adenosylmethionine is the methyl donor for DNA methyltransferases, and it is formed by pathways that metabolize a number of nutrients [methionine, 5-methyltetrahydrofolate, betaine (from choline), vitamin B12, and vitamin B6]; for this reason, DNA methylation is modulated by dietary intake (Dolinoy et al. 2006; Dominguez-Salas et al. 2014; Ideraabdullah & Zeisel 2018; Mehedint et al. 2010; Waterland et al. 2006, 2007; Wolff et al. 1998). Diets high in methyl-group donors increase DNA methylation of specific genes (Zhang 2015) and can result in a permanent change in phenotype [e.g., coat color in the *Agouti* mouse (Waterland 2006) or twisted tails in *Axin fused* mice (Waterland et al. 2006)]. In people, seasonal variation in methyl-group content of diets is associated with different patterns of DNA methylation, raising the possibility that babies born at different times of the year may be epigenetically different (Dominguez-Salas et al. 2014). Other dietary variations, including intake of the fat docosahexaenoic acid (DHA) (Ideraabdullah & Zeisel 2018), protein restriction (Lillycrop et al. 2005), and ingestion of some bioactives (e.g., epigallocatechin-3-gallate, genistein, polyphenols), can modify DNA methylation. A review of methods for assessing DNA methylation is available (Shen & Waterland 2007).

Histone proteins H2A, H2B, H3, and H4 make up the nucleosome around which DNA is coiled (Lai & Pugh 2017). These histones contribute to the structure of chromatin (open/active versus closed/inactive) and this structure changes depending on posttranslational histone modifications to the amino-terminal tails of these proteins (Strahl & Allis 2000). These modifications include methylation, acetylation, biotinylation, propionylation, succinylation, citrullination, butyrylation, glutathionylation, malonylation, formylation, crotonylation, ADP-ribosylation, GlcNAcylation, phosphorylation, hydroxylation, and oxidation (Zhao & Garcia 2015). Many of these histone modifications depend on products of nutrient metabolism and therefore are sensitive to dietary intake (Ideraabdullah & Zeisel 2018). For example, histone methylation is modulated by intake of dietary methyl donors (Davison et al. 2009, Jiang et al. 2012, Mehedint et al. 2010), and histone demethylases are dependent on α-ketoglutarate and iron derived from the diet and nutrient metabolism (Inoue et al. 2015, Kaelin & McKnight 2013, Leung et al. 2016). Multiple components of the diet and of microbial metabolism of the diet (such as butyrate) inhibit histone deacetylases (Rajendran et al. 2011).

Diet can also modulate expression of noncoding RNAs that regulate gene expression and/or post-transcriptional activity (Deveson et al. 2017, Holoch & Moazed 2015). MicroRNAs (miRs)

bind to mRNAs that contain a targeting sequence for the miR, and mark them for cleavage, degradation, or translational repression depending on the gene target (Saetrom et al. 2007). The transcription of perhaps 60% of miRs is regulated by DNA or histone methylation (Sengupta et al. 2016). Specific miRs regulate almost all gene products involved in metabolism. Some of the effects of dietary choline on fetal brain development are mediated by a choline-sensitive miR (159-5p; under adequate choline conditions, expression of this miR is kept low). In the fetal brain, miR159-5p suppresses the formation of the epidermal growth factor receptor, which is needed for normal brain development (Trujillo-Gonzalez et al. 2018, Wang et al. 2016).

Epigenetic marks and expression of noncoding RNAs are changeable during sensitive time frames during early development and thereafter are usually maintained by mechanisms that assure faithful copying of DNA during cell replication. It is possible that the sensitive development windows during which epigenetic signals are modifiable are there to provide the opportunity to retune metabolism if a baby is born into a dietary environment that is markedly different than expected based on life in utero (Ideraabdullah & Zeisel 2018). Certain epigenetic marks remain modifiable throughout the life span depending on a number of environmental exposures, including nutrition; thus, the timing of sample collection is important. Epigenetic signals regulate genes of nutrient metabolism, but nutrient metabolism modifies epigenetic signaling (Ideraabdullah & Zeisel 2018). The methods for assessing epigenetic changes are relatively mature (Shen & Waterland 2007, Waterland 2006); however, epigenetic marks and noncoding RNAs are usually tissue specific, and investigators do not always have access to the target tissue. Epigenetic analyses of DNA from lymphocytes likely will not show the same marks as would be detected if, for example, liver, muscle, and brain DNA were analyzed. Perhaps it will soon be possible to use circulating cell-free DNA that is released from such tissues to assess epigenetic marks within those tissues (Oussalah et al. 2018).

MICROBIOME AS A SOURCE OF METABOLIC HETEROGENEITY

Humans exist in symbiosis with many gut microbiota that evolved over time to thrive in the human gastrointestinal tract (Qin et al. 2010). These microbiota can metabolize almost any substrate that is presented to them (Goodman & Gordon 2010). Often, they access nutrients before they are available to the host (competing for nutrient supply). Gut microbiota also produce small molecules unique to microbial pathways of metabolism that people then absorb (Daliri et al. 2017, Hall & Versalovic 2018, Manor et al. 2014).

Using high-throughput sequencing technologies, researchers can characterize the functional diversity of the human gut microbiota (Bauer & Thiele 2018). The microbes within the intestine vary between people (Eckburg et al. 2005), and this is an important source of metabolic heterogeneity between people. How much energy people derive from foods (Scheithauer et al. 2016) depends on gut microbiota; for example, polysaccharide fermentation by gut bacteria generates propionate, butyrate, and acetate, which are energy substrates (den Besten et al. 2013). Gut microbiota can increase nutrient requirements by competing with the human host; for example, choline-consuming gut bacteria result in lower serum concentrations of choline in the human host (Romano et al. 2017). Gut microbiota provide people and animals with essential vitamins (e.g., vitamin K) (Ramakrishna 2013). They can also produce potentially harmful molecules such as phenols, *p*-cresol, and phenylacetic acid (derived from amino acids), trimethylamine (derived from choline and creatinine) (Zeisel & Warrier 2017), and sulfides (derived from the catabolism of sulfur amino acids and taurine) (De Filippis et al. 2018).

The composition of the gut microbiome is influenced by environmental factors such as diet (De Filippis et al. 2018), and host genetics has a small influence (Rothschild et al. 2018). Only

2% of the variability in the microbiome between people is related to genetic ancestry (Rothschild et al. 2018, Wu et al. 2011). The effects of dietary intake on gut microbiota composition can be rapid (David et al. 2014, De Filippis et al. 2018), and the microbiome has a diurnal rhythm (Hor et al. 2018). This makes the timing of sampling important for assessing the gut microbiome's contributions to metabolic heterogeneity (Manor et al. 2014), and many current studies do not control for timing of sampling relative to meals or time of day. Methods for the study of the microbiome are under development, and new methods can functionally characterize the microbiota in terms of metabolic activity. These include meta-transcriptomic, metabolomic, and metaproteomic analyses (Daliri et al. 2017, Hor et al. 2018, Jin et al. 2017, Lamichhane et al. 2018, Zmora et al. 2016). Adding up the contributions of individual species of bacteria does not accurately predict metabolism in the microbiome because of the metabolic interactions that occur between microbes, as well as the interactions that occur between microbiota and the human gut (Bauer & Thiele 2018, Manor et al. 2014). Despite this, mathematical models based on gut microbiota data and several other easily measurable variables (e.g., blood metabolite measures, dietary habits, anthropometrics, physical activity) have provided better estimates of heterogeneity between individuals in postprandial glycemic response to meals and of the rate of postdieting weight regain than did models that use only host genetic and environmental data (Korem et al. 2017, Rothschild et al. 2018, Thaiss et al. 2016, Zeevi et al. 2015).

ENVIRONMENTAL EXPOSURES AS A SOURCE OF METABOLIC HETEROGENEITY

The environmental exposure that is likely the largest modifier of metabolism in people is food intake. It is necessary to obtain valid information about the habitual dietary intake of people so that this can be included in mathematical models developed for precision nutrition. Unfortunately, current methodology has shortcomings; 24-h diet recalls, food frequency questionnaires, and four-day food records are commonly used but are error prone (Cade 2017, Tabacchi et al. 2014, Tasevska et al. 2014). Twenty-four-hour diet recalls provide limited information on the day-to-day variation in dietary intake throughout longer periods (e.g., day of the week, season) and 24-h recall data are subject to errors because of poor memory, approximation errors in standard portion sizes, and recall bias (Brouwer-Brolsma et al. 2017, Gibson et al. 2017). Food frequency questionnaires are relatively easy and inexpensive to process, but it is challenging to develop a valid and reliable one that accurately estimates intake for a wide variety of foods (Brouwer-Brolsma et al. 2017). Many web-based applications that enable dietary self-monitoring likely suffer from the same sources of error, and there are few evaluations of the quality and reliability of these apps with regard to dietary assessment (Cade 2017). The web-based Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24) developed by the US National Cancer Institute includes a multipass web-based recall of diet intake using digitized images to estimate portion size and it addresses some of the sources of error in diet estimation, but significant residual errors remain (Kirkpatrick et al. 2016).

Some biomarkers can help improve estimates of the intake of calories and certain nutrients [e.g., doubly labeled water method (Westerterp 2017), 24-hour urinary sodium (Cogswell et al. 2015)]; however, for most nutrients such biomarkers have yet to be developed. Metabolomics-based analyses show promise for assessing dietary intake of fruits, vegetables, meat, fish, bread, whole-grain cereals, nuts, wine, coffee, tea, cocoa, and chocolate (Guasch-Ferre et al. 2018) and appear to differentiate people's dietary patterns (e.g., vegetarian, omnivorous, Western, prudent, Nordic, and Mediterranean) (Beger et al. 2016, Guasch-Ferre et al. 2018, Kinross et al. 2014, Menni et al. 2013, Pallister et al. 2016). However, metabolic heterogeneity, which is due to the

various sources discussed in this review, causes individuals who habitually consume the same diets to differ in the small molecules appearing in blood, urine, or tissues; thus, metabotype is not directly substitutable for dietary intake information. It is possible that appropriate computational models can be developed that integrate information about the various sources of metabolic heterogeneity to provide adjusted metabolomic data that reflect dietary intake (essentially reverse-engineering the models for precision nutrition discussed below). Other methods might be used in conjunction with metabolomics. Stable isotope ratios (ratios of light/heavy elements) vary naturally and reproducibly among foods, and the analysis of isotopomers may be useful in improving estimates of dietary intake (O'Brien 2015). Before this approach is viable for use in precision nutrition, controlled feeding studies are needed to establish the dose–response relationships between isotopomers and specific food intakes and dietary patterns (O'Brien 2015).

It is important that molecular assessment of food intake also captures the timing of food intake (meal and snack patterns), as circadian rhythms in metabolism are entrained, in part, by meal patterns (Eckel-Mahan & Sassone-Corsi 2013). Many studies use fasting samples to minimize this source of variation, but fasting is itself a challenge that alters metabolism (Patterson et al. 2015). The peripheral clocks regulating local metabolic rhythms are determined by feeding–fasting cycles, and the local clock genes control downstream metabolic processes (Oike et al. 2014). The circadian rhythms of metabolism are also entrained by light-sensitive mechanisms in the hypothalamic suprachiasmatic nucleus (Versteeg et al. 2016). Because the effects of light are so important in setting this metabolic cyclicity, the timing relative to day/night when biomarkers of metabolism are collected needs to be carefully controlled. The area of molecular clocks and their interactions with nutrition was reviewed by Oike et al. (2014). An example of the importance of these circadian rhythms comes from the ONTIME (obesity, nutrigenetics, timing, Mediterranean) study, which focused on the interaction between meal timing, genetics, and weight loss and found that carriers of variants in the gene encoding periolipin1 (*PLIN1*) lost less weight when placed on a meal plan that served lunch late (after 15:00) than did early lunch eaters (before 15:00) (7.21 ± 0.67 kg versus 10.63 ± 0.56 kg; $p = 0.001$) (Garaulet et al. 2016). Carriers of variants in *PER2*, *CLOCK*, and *CRY1* circadian genes have altered feeding behaviors in response to low-fat and low-carbohydrate diets (Dashti et al. 2014, Garaulet et al. 2010, Gomez-Delgado et al. 2015). Another example of a metabolically important circadian rhythm is the diurnal variation in blood glucose concentrations and in glucose tolerance. Glucose tolerance is higher in the morning than in the afternoon; both insulin sensitivity and insulin secretion are reduced in the evening compared to the daytime (Jarrett et al. 1972).

Human and microbiota metabolisms are sensitive to environmental exposure to chemicals (or their metabolites). Obesogenic environmental chemicals (Baillie-Hamilton 2002), which include endocrine disrupter chemicals, are a source of human metabolic heterogeneity that arises because they modify hormonal signaling and other receptors that modify metabolism (Heindel et al. 2017). Many endocrine disrupter chemicals, including bisphenol A (BPA), which increases weight gain and body fat after developmental exposure (Amin et al. 2019, Stojanoska et al. 2017, Yang et al. 2016) and induces insulin resistance (Heindel et al. 2017), have been described. Phthalates (used in the manufacture of plastics) modify peroxisome proliferator-activated receptor (PPAR)-modulated pathways in carbohydrate and lipid metabolism because they activate PPARs (Kim & Park 2014).

PRECISION NUTRITION IMPLEMENTATION

Applications

An obvious component of the practice of precision nutrition is genetic testing. The field is in a transition between chip-based technology and gene-sequencing technology. Gene chips use short

sequences of complementary DNA (oligos) as hooks that bind to the sequences being sought. Millions of oligos can be attached to a chip, and these chips can be custom designed. At present, many of these commercially available chips detect known common polymorphisms that derive from a diverse group of ancestries and detect many, but not all, variants relevant to nutritional heterogeneity. However, many companies allow the construction of custom chips that add additional oligos. Gene sequencing, in contrast, provides information about the entire genome, identifying not only known gene variants but also unknown variants. Gene sequencing is currently two to three times more expensive than chip technology, but as prices fall it likely will make chip technology obsolete. Chip technology is currently used in almost all the genetic testing that is available directly to consumers.

Once the many gene variants in a person are identified, the functional meaning of these variants needs to be determined. Because this involves recognizing the effects of complex patterns of gene variants, computational models are used (as discussed above). Although there are excellent algorithms for using gene variants to determine a person's ancestry, such computational tools are just being developed for precision nutrition. As these are refined, there will likely be more commercially available genetic tests that offer health care providers and consumers precision nutrition–relevant information. Similar considerations about microbiome testing suggest that once computational models are developed that convert complex patterns of data about the microbiome (likely RNA sequencing data) into precision nutrition–relevant functional meaning, commercially available tests will be marketed directly to the consumer. These computational tools are already being developed (Manor et al. 2014).

Genetically guided nutrition interventions are also likely to increase in number. An excellent example is the development of foods designed to be tolerated by children with a gene mutation in the metabolism of phenylalanine. In this case, a problematic nutrient is removed from the diet. However, interventions can be developed in which nutrients, their precursors, or their metabolites are purposely added. Once multiple functional polymorphisms in a person have been identified, they can be mapped to metabolic pathways, and treatments containing constituents that bypass or correct metabolic flow can be administered, thereby overcoming the effects of the polymorphisms. Although prebiotics and probiotics are commercially available, similar considerations about more targeted microbiome-based nutrition interventions suggest that they too will soon be commercially available (Manor et al. 2014).

Precision nutrition is not about developing unique prescriptions for individual people but rather about stratifying people into different subgroups of the population on the basis of biomarkers and therapeutic efficacy. Thus, precision nutrition can be applied to public policy so that the application of precision nutrition enables better targeting of diet recommendations. Rather than just making nutrition recommendations based solely on age or gender, relevant genetic (e.g., the microbiome) information can be used to refine them. For example, if a reasonable portion of people have increased requirements for a nutrient because they have genetic polymorphisms, then a targeted recommendation can be made that reflects that these people have a higher dietary reference intake.

Ethical Issues

Precision nutrition shares many ethical issues with precision medicine (Blasimme & Vayena 2016, Minari et al. 2018, Sankar & Parker 2017). The technologies used in precision nutrition generate targeted results that have a clinical meaning but also results whose implications are not yet well understood. The field advances as scientists study different populations, collect a larger set of data, use better tools to identify new associations, and create clinical meaning out of data of previously

unknown importance. Such a precision nutrition learning process raises the moral and legal possibility that the new understanding may require that people be recontacted to revise/improve recommendations. This means that it is difficult to anticipate and explain all the potential findings along with their associated risks and benefits, creating important issues for patient informed consent. Are we morally and legally required to reach out and inform a mother who we now realize is at higher risk for having a baby with a birth defect because they have a polymorphism in a choline-producing gene? How good must the data be before we are ethically obligated to warn or prevent adverse risk? In addition, when broad swaths of data are collected, it is possible that risks of diseases will be uncovered as incidental findings (especially with genetic sequencing). If we incidentally discover a patient has a genetic mutation or variant that greatly increases their risk of breast cancer, must we tell them? The knowledge base that underlies precision nutrition has been created using data from studies in limited populations. If samples are collected without broad public participation, the members of groups that abstain from participation are less able to share in the benefits of the resulting data and precision nutrition interventions. As precision nutrition learns more about the importance of gene signatures (patterns of gene variations), will such signatures mean the same among people of different ancestry? If not, how do we avoid giving inappropriate recommendations?

At this time, it is unclear whether precision nutrition will have a health professional as a gatekeeper or will be delivered directly to the consumer. The existing investments by commercial interests and the current open-access ethos make direct-to-consumer applications most likely. However, the huge volume of information involved and the ethical considerations discussed above seem to make the gatekeeper model appropriate.

WHY CALL IT PRECISION NUTRITION INSTEAD OF PERSONALIZED NUTRITION?

Precision nutrition is not about developing unique prescriptions for individual people, but rather about stratifying people into different subgroups of the population on the basis of biomarkers and therapeutic efficacy. It would be inappropriate to suggest that precision nutrition can offer individually customized recommendations when it is based on data developed from larger-than-one-person subgroups. The hope is that we will be able to subcategorize people into ever smaller groups that can be more targeted in terms of recommendations, but we will never achieve this at the individual level; the word personalized suggests that we will be able to achieve this, whereas the word precision suggests that we can be more precise in our recommendations than traditional nutrition approaches have been.

CHALLENGES

Precision nutrition applications, both in research and in commercial products, are already in use. Because of the continuous quality improvement in the science underlying precision nutrition, better research tools and better commercial products will follow. The greatest challenge that limits the refinement of precision nutrition is that few data sets are available that include diet intake, genetics, epigenetics, microbiome, environmental exposure, and metabolic phenotype data measured at the same time. It would be even better if these study designs included a nutrition challenge meant to reveal metabolic roadblocks (e.g., feeding subjects a high-calorie diet to reveal those with genetic variants that make them develop fatty liver). In addition, generating this data requires improvements in ‘omic methods for assessing metabolic function (e.g., there is a need for better standardization of diet conditions and timing of sampling in studies making ‘omic

measurements) (Beger et al. 2016, Kinross et al. 2014). Once these data sets are available, the mathematical and computational modeling tools needed to improve the estimation of metabolic differences between people can be refined and thereby enhance the precision nutrition knowledge base. Such knowledge- and data-driven models will provide mechanistic insights for generating hypotheses, designing interventions, and making recommendations (Wolkenhauer 2014).

DISCLOSURE STATEMENT

The author has an equity interest in SNP Therapeutics (a company using gene-guided medical foods to treat health problems). Beyond this, he is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This work was supported by the US National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases grants DK056350 and DK115380.

LITERATURE CITED

Abdullah MMH, Eck PK, Couture P, Lamarche B, Jones PJH. 2018. The combination of single nucleotide polymorphisms rs6720173 (ABCG5), rs3808607 (CYP7A1), and rs760241 (DHCR7) is associated with differing serum cholesterol responses to dairy consumption. *Appl. Physiol. Nutr. Metab.* 43:1090–93

Ahn J, Yu K, Stolzenberg-Solomon R, Simon KC, McCullough ML, et al. 2010. Genome-wide association study of circulating vitamin D levels. *Hum. Mol. Genet.* 19:2739–45

Amin MM, Ebrahim K, Hashemi M, Shoshtari-Yeganeh B, Rafiei N, et al. 2019. Association of exposure to bisphenol A with obesity and cardiometabolic risk factors in children and adolescents. *Int. J. Environ. Health Res.* 29:94–106

Baillie-Hamilton PF. 2002. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J. Altern. Complement. Med.* 8:185–92

Barry EL, Rees JR, Peacock JL, Mott LA, Amos CI, et al. 2014. Genetic variants in CYP2R1, CYP24A1, and VDR modify the efficacy of vitamin D3 supplementation for increasing serum 25-hydroxyvitamin D levels in a randomized controlled trial. *J. Clin. Endocrinol. Metab.* 99:E2133–37

Bashiardes S, Godneva A, Elinav E, Segal E. 2018. Towards utilization of the human genome and microbiome for personalized nutrition. *Curr. Opin. Biotechnol.* 51:57–63

Bauer E, Thiele I. 2018. From network analysis to functional metabolic modeling of the human gut microbiota. *mSystems* 3:e00209-17

Beger RD, Dunn W, Schmidt MA, Gross SS, Kirwan JA, et al. 2016. Metabolomics enables precision medicine: "a white paper, community perspective." *Metabolomics* 12:149

Bilgin Sonay T, Carvalho T, Robinson MD, Greminger MP, Krutzen M, et al. 2015. Tandem repeat variation in human and great ape populations and its impact on gene expression divergence. *Genome Res.* 25:1591–99

Blasimme A, Vayena E. 2016. Becoming partners, retaining autonomy: ethical considerations on the development of precision medicine. *BMC Med. Ethics* 17:67

Boeke CE, Gillman MW, Hughes MD, Rifas-Shiman SL, Villamor E, Oken E. 2013. Choline intake during pregnancy and child cognition at age 7 years. *Am. J. Epidemiol.* 177:1338–47

Brouwer-Brolsma EM, Streppel MT, Van Lee L, Geelen A, Sluik D, et al. 2017. A National Dietary Assessment Reference Database (NDARD) for the Dutch population: rationale behind the design. *Nutrients* 9:E1136

Cade JE. 2017. Measuring diet in the 21st century: use of new technologies. *Proc. Nutr. Soc.* 76:276–82

Caudill MA, Strupp BJ, Muscalu L, Nevins JEH, Canfield RL. 2018. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. *FASEB J.* 32:2172–80

Cent. Medicare Medicaid Serv. 2009. *National coverage determination (NCD) for pharmacogenomic testing for warfarin response (90.1)*. Rep., Cent. Medicare Medicaid Serv., Baltimore, MD

Cogswell ME, Maalouf J, Elliott P, Loria CM, Patel S, Bowman BA. 2015. Use of urine biomarkers to assess sodium intake: challenges and opportunities. *Annu. Rev. Nutr.* 35:349–87

Colin EM, Weel AE, Uitterlinden AG, Buurman CJ, Birkenhager JC, et al. 2000. Consequences of vitamin D receptor gene polymorphisms for growth inhibition of cultured human peripheral blood mononuclear cells by 1,25-dihydroxyvitamin D3. *Clin. Endocrinol.* 52:211–16

Corbin KD, Abdelmalek MF, Spencer MD, da Costa KA, Galanko JA, et al. 2013. Genetic signatures in choline and 1-carbon metabolism are associated with the severity of hepatic steatosis. *FASEB J.* 27:1674–89

Corella D, Peloso G, Arnett DK, Demissie S, Cupples LA, et al. 2009. APOA2, dietary fat, and body mass index: replication of a gene-diet interaction in 3 independent populations. *Arch. Intern. Med.* 169:1897–906

Corella D, Tai ES, Sorli JV, Chew SK, Coltell O, et al. 2011. Association between the APOA2 promoter polymorphism and body weight in Mediterranean and Asian populations: replication of a gene-saturated fat interaction. *Int. J. Obes.* 35:666–75

da Costa KA, Corbin KD, Niculescu MD, Galanko JA, Zeisel SH. 2014. Identification of new genetic polymorphisms that alter the dietary requirement for choline and vary in their distribution across ethnic and racial groups. *FASEB J.* 28:2970–78

da Costa KA, Kozyreva OG, Song J, Galanko JA, Fischer LM, Zeisel SH. 2006. Common genetic polymorphisms affect the human requirement for the nutrient choline. *FASEB J.* 20:1336–44

Daliri EB, Wei S, Oh DH, Lee BH. 2017. The human microbiome and metabolomics: current concepts and applications. *Crit. Rev. Food Sci. Nutr.* 57:3565–76

Dashti HS, Smith CE, Lee YC, Parnell LD, Lai CQ, et al. 2014. *CRY1* circadian gene variant interacts with carbohydrate intake for insulin resistance in two independent populations: Mediterranean and North American. *Chronobiol. Int.* 31:660–67

David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, et al. 2014. Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505:559–63

Davison JM, Mellott TJ, Kovacheva VP, Blusztajn JK. 2009. Gestational choline supply regulates methylation of histone H3, expression of histone methyltransferases G9a (Kmt1c) and Suv39h1 (Kmt1a), and DNA methylation of their genes in rat fetal liver and brain. *J. Biol. Chem.* 284:1982–89

De Filippis F, Vitaglione P, Cuomo R, Berni Canani R, Ercolini D. 2018. Dietary interventions to modulate the gut microbiome: how far away are we from precision medicine. *Inflamm. Bowel Dis.* 24:2142–54

den Besten G, Van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. 2013. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J. Lipid Res.* 54:2325–40

de Toro-Martin J, Arsenault BJ, Despres JP, Vohl MC. 2017. Precision nutrition: a review of personalized nutritional approaches for the prevention and management of metabolic syndrome. *Nutrients* 9:E913

Deveson IW, Hardwick SA, Mercer TR, Mattick JS. 2017. The dimensions, dynamics, and relevance of the mammalian noncoding transcriptome. *Trends Genet.* 33(7):464–78

Dolinoy DC, Weidman JR, Waterland RA, Jirtle RL. 2006. Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. *Environ. Health Perspect.* 114:567–72

Dominguez-Salas P, Moore SE, Baker MS, Bergen AW, Cox SE, et al. 2014. Maternal nutrition at conception modulates DNA methylation of human metastable epialleles. *Nat. Commun.* 5:3746

Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, et al. 2005. Diversity of the human intestinal microbial flora. *Science* 308:1635–38

Eckel-Mahan K, Sassone-Corsi P. 2013. Metabolism and the circadian clock converge. *Physiol. Rev.* 93:107–35

Elkum N, Alkayal F, Noronha F, Ali MM, Melhem M, et al. 2014. Vitamin D insufficiency in Arabs and South Asians positively associates with polymorphisms in *GC* and *CYP2R1* genes. *PLOS ONE* 9:e113102

Fischer LM, da Costa KA, Kwock L, Galanko J, Zeisel SH. 2010. Dietary choline requirements of women: effects of estrogen and genetic variation. *Am. J. Clin. Nutr.* 92:1113–19

Fischer LM, da Costa K, Kwock L, Stewart P, Lu T-S, et al. 2007. Sex and menopausal status influence human dietary requirements for the nutrient choline. *Am. J. Clin. Nutr.* 85:1275–85

Ganz AB, Klatt KC, Caudill MA. 2017. Common genetic variants alter metabolism and influence dietary choline requirements. *Nutrients* 9:E837

Garaulet M, Corbalan-Tutau MD, Madrid JA, Baraza JC, Parnell LD, et al. 2010. PERIOD2 variants are associated with abdominal obesity, psycho-behavioral factors, and attrition in the dietary treatment of obesity. *J. Am. Diet. Assoc.* 110:917–21

Garaulet M, Vera B, Bonnet-Rubio G, Gomez-Abellan P, Lee YC, Ordovas JM. 2016. Lunch eating predicts weight-loss effectiveness in carriers of the common allele at PERILIPIN1: the ONTIME (Obesity, Nutrigenetics, Timing, Mediterranean) study. *Am. J. Clin. Nutr.* 104:1160–66

Gibson RS, Charrondiere UR, Bell W. 2017. Measurement errors in dietary assessment using self-reported 24-hour recalls in low-income countries and strategies for their prevention. *Adv. Nutr.* 8:980–91

Gomez-Delgado F, Garcia-Rios A, Alcala-Diaz JF, Rangel-Zuniga O, Delgado-Lista J, et al. 2015. Chronic consumption of a low-fat diet improves cardiometabolic risk factors according to the *CLOCK* gene in patients with coronary heart disease. *Mol. Nutr. Food Res.* 59:2556–64

Goodman AL, Gordon JI. 2010. Our unindicted coconspirators: human metabolism from a microbial perspective. *Cell Metab.* 12:111–16

Guasch-Ferre M, Bhupathiraju SN, Hu FB. 2018. Use of metabolomics in improving assessment of dietary intake. *Clin. Chem.* 64:82–98

Hall A, Versalovic J. 2018. Microbial metabolism in the mammalian gut: molecular mechanisms and clinical implications. *J. Pediatr. Gastroenterol. Nutr.* 66(Suppl. 3):S72–79

Hall KT, Buring JE, Mukamal KJ, Vinayaga Moorthy M, Wayne PM, et al. 2019. COMT and alpha-tocopherol effects in cancer prevention: gene-supplement interactions in two randomized clinical trials. *J. Natl. Cancer Inst.* 111(7):684–94

Hall KT, Nelson CP, Davis RB, Buring JE, Kirsch I, et al. 2014. Polymorphisms in catechol-*O*-methyltransferase modify treatment effects of aspirin on risk of cardiovascular disease. *Arterioscler. Thromb. Vasc. Biol.* 34:2160–67

Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, et al. 2017. Metabolism disrupting chemicals and metabolic disorders. *Reprod. Toxicol.* 68:3–33

Holoch D, Moazed D. 2015. RNA-mediated epigenetic regulation of gene expression. *Nat. Rev. Genet.* 16:71–84

Hor J, Gorski SA, Vogel J. 2018. Bacterial RNA biology on a genome scale. *Mol. Cell* 70(5):785–99

Ideraabdullah FY, Zeisel SH. 2018. Dietary modulation of the epigenome. *Physiol. Rev.* 98:667–95

Inoue S, Honma K, Mochizuki K, Goda T. 2015. Induction of histone H3K4 methylation at the promoter, enhancer, and transcribed regions of the *Si* and *Sglt1* genes in rat jejunum in response to a high-starch/low-fat diet. *Nutrition* 31:366–72

Jarrett RJ, Baker IA, Keen H, Oakley NW. 1972. Diurnal variation in oral glucose tolerance: blood sugar and plasma insulin levels morning, afternoon, and evening. *Br. Med. J.* 1:199–201

Jeltsch A, Jurkowska RZ. 2014. New concepts in DNA methylation. *Trends Biochem. Sci.* 39:310–18

Ji Y, Skierka JM, Blommel JH, Moore BE, Vancuyk DL, et al. 2016. Preemptive pharmacogenomic testing for precision medicine: a comprehensive analysis of five actionable pharmacogenomic genes using next-generation DNA sequencing and a customized CYP2D6 genotyping cascade. *J. Mol. Diagn.* 18:438–45

Jiang X, Yan J, West AA, Perry CA, Malysheva OV, et al. 2012. Maternal choline intake alters the epigenetic state of fetal cortisol-regulating genes in humans. *FASEB J.* 26:3563–74

Jin P, Wang K, Huang C, Nice EC. 2017. Mining the fecal proteome: from biomarkers to personalised medicine. *Expert Rev. Proteom.* 14:445–59

Johnson AR, Lao S, Wang T, Galanko JA, Zeisel SH. 2012. Choline dehydrogenase polymorphism rs12676 is a functional variation and is associated with changes in human sperm cell function. *PLOS ONE* 7:e36047

Jolliffe DA, Walton RT, Griffiths CJ, Martineau AR. 2016. Single nucleotide polymorphisms in the vitamin D pathway associating with circulating concentrations of vitamin D metabolites and non-skeletal health outcomes: review of genetic association studies. *J. Steroid Biochem. Mol. Biol.* 164:18–29

Jones PA. 2012. Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nat. Rev. Genet.* 13:484–92

Josse AR, Da Costa LA, Campos H, El-Sohemy A. 2012. Associations between polymorphisms in the AHR and CYP1A1-CYP1A2 gene regions and habitual caffeine consumption. *Am. J. Clin. Nutr.* 96:665–71
Kaelin WG Jr., McKnight SL. 2013. Influence of metabolism on epigenetics and disease. *Cell* 153:56–69
Khera AV, Chaffin M, Wade KH, Zahid S, Brancale J, et al. 2019. Polygenic prediction of weight and obesity trajectories from birth to adulthood. *Cell* 177:587–96.e9
Kiddy CA. 1979. A review of research on genetic variation in physiological characteristics related to performance in dairy cattle. *J. Dairy Sci.* 62:818–24
Kim SH, Park MJ. 2014. Phthalate exposure and childhood obesity. *Ann. Pediatr. Endocrinol. Metab.* 19:69–75
Kinross J, Li JV, Muirhead LJ, Nicholson J. 2014. Nutritional modulation of the metabonome: applications of metabolic phenotyping in translational nutritional research. *Curr. Opin. Gastroenterol.* 30:196–207
Kirkpatrick SI, Potischman N, Dodd KW, Douglass D, Zimmerman TP, et al. 2016. The use of digital images in 24-hour recalls may lead to less misestimation of portion size compared with traditional interviewer-administered recalls. *J. Nutr.* 146:2567–73
Kohlmeier M. 2013. *Nutrigenetics: Applying the Science of Personal Nutrition*. Amsterdam: Elsevier
Kohlmeier M, da Costa KA, Fischer LM, Zeisel SH. 2005. Genetic variation of folate-mediated one-carbon transfer pathway predicts susceptibility to choline deficiency in humans. *PNAS* 102:16025–30
Korem T, Zeevi D, Zmora N, Weissbrod O, Bar N, et al. 2017. Bread affects clinical parameters and induces gut microbiome-associated personal glycemic responses. *Cell Metab.* 25:1243–53.e5
Lai WKM, Pugh BF. 2017. Understanding nucleosome dynamics and their links to gene expression and DNA replication. *Nat. Rev. Mol. Cell Biol.* 18(9):548–62
Lamichhane S, Sen P, Dickens AM, Oresic M, Bertram HC. 2018. Gut metabolome meets microbiome: a methodological perspective to understand the relationship between host and microbe. *Methods* 149:3–12
Leung A, Trac C, Du J, Natarajan R, Schones DE. 2016. Persistent chromatin modifications induced by high fat diet. *J. Biol. Chem.* 291:10446–55
Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. 2005. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *J. Nutr.* 135:1382–86
Liu F, Struchalin MV, Duijn K, Hofman A, Uitterlinden AG, et al. 2011. Detecting low frequent loss-of-function alleles in genome wide association studies with red hair color as example. *PLOS ONE* 6:e28145
Ma Y, Follis JL, Smith CE, Tanaka T, Manichaikul AW, et al. 2016. Interaction of methylation-related genetic variants with circulating fatty acids on plasma lipids: a meta-analysis of 7 studies and methylation analysis of 3 studies in the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium. *Am. J. Clin. Nutr.* 103:567–78
Manor O, Levy R, Borenstein E. 2014. Mapping the inner workings of the microbiome: genomic- and metagenomic-based study of metabolism and metabolic interactions in the human microbiome. *Cell Metab.* 20:742–52
Mehedint MG, Niculescu MD, Craciunescu CN, Zeisel SH. 2010. Choline deficiency alters global histone methylation and epigenetic marking at the Re1 site of the calbindin 1 gene. *FASEB J.* 24:184–95
Menni C, Zhai G, Macgregor A, Prehn C, Romisch-Margl W, et al. 2013. Targeted metabolomics profiles are strongly correlated with nutritional patterns in women. *Metabolomics* 9:506–14
Miller WL. 2017. Genetic disorders of vitamin D biosynthesis and degradation. *J. Steroid Biochem. Mol. Biol.* 165:101–8
Minari J, Brothers KB, Morrison M. 2018. Tensions in ethics and policy created by national precision medicine programs. *Hum. Genom.* 12:22
Nissen J, Vogel U, Ravn-Haren G, Andersen EW, Madsen KH, et al. 2015. Common variants in *CYP2R1* and *GC* genes are both determinants of serum 25-hydroxyvitamin D concentrations after UVB irradiation and after consumption of vitamin D_3-fortified bread and milk during winter in Denmark. *Am. J. Clin. Nutr.* 101:218–27
O'Brien DM. 2015. Stable isotope ratios as biomarkers of diet for health research. *Annu. Rev. Nutr.* 35:565–94
Oike H, Oishi K, Kobori M. 2014. Nutrients, clock genes, and chrononutrition. *Curr. Nutr. Rep.* 3:204–12

Oussalah A, Rischer S, Bensenane M, Conroy G, Filhine-Tresarrieu P, et al. 2018. Plasma mSEPT9: a novel circulating cell-free DNA-based epigenetic biomarker to diagnose hepatocellular carcinoma. *EBioMedicine* 30:138–47

Overbeek R, Begley T, Butler RM, Choudhuri JV, Chuang HY, et al. 2005. The subsystems approach to genome annotation and its use in the project to annotate 1000 genomes. *Nucleic Acids Res.* 33:5691–702

Pallister T, Jennings A, Mohney RP, Yarand D, Mangino M, et al. 2016. Characterizing blood metabolomics profiles associated with self-reported food intakes in female twins. *PLOS ONE* 11:e0158568

Palomba S, Orio F Jr., Russo T, Falbo A, Tolino A, et al. 2005. BsmI vitamin D receptor genotypes influence the efficacy of antiresorptive treatments in postmenopausal osteoporotic women. A 1-year multicenter, randomized and controlled trial. *Osteoporos. Int.* 16:943–52

Patterson RE, Laughlin GA, Lacroix AZ, Hartman SJ, Natarajan L, et al. 2015. Intermittent fasting and human metabolic health. *J. Acad. Nutr. Diet.* 115:1203–12

Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, et al. 2010. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 464:59–65

Rajendran P, Williams DE, Ho E, Dashwood RH. 2011. Metabolism as a key to histone deacetylase inhibition. *Crit. Rev. Biochem. Mol. Biol.* 46:181–99

Ramakrishna BS. 2013. Role of the gut microbiota in human nutrition and metabolism. *J. Gastroenterol. Hepatol.* 28(Suppl. 4):9–17

Rasmussen BB, Brix TH, Kyvik KO, Brosen K. 2002. The interindividual differences in the 3-demethylation of caffeine alias CYP1A2 is determined by both genetic and environmental factors. *Pharmacogenetics* 12:473–78

Reiter T, Jagoda E, Capellini TD. 2016. Dietary variation and evolution of gene copy number among dog breeds. *PLOS ONE* 11:e0148899

Resseguie M, Song J, Niculescu MD, da Costa KA, Randall TA, Zeisel SH. 2007. Phosphatidylethanolamine N-methyltransferase (PEMT) gene expression is induced by estrogen in human and mouse primary hepatocytes. *FASEB J.* 21:2622–32

Resseguie ME, da Costa KA, Galanko JA, Patel M, Davis IJ, Zeisel SH. 2011. Aberrant estrogen regulation of PEMT results in choline deficiency-associated liver dysfunction. *J. Biol. Chem.* 286:1649–58

Romano KA, Martinez-Del Campo A, Kasahara K, Chittim CL, Vivas EI, et al. 2017. Metabolic, epigenetic, and transgenerational effects of gut bacterial choline consumption. *Cell Host Microbe* 22:279–90.e7

Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, et al. 2018. Environment dominates over host genetics in shaping human gut microbiota. *Nature* 555:210–15

Sabeti PC, Varilly P, Fry B, Lohmueller J, Hostetter E, et al. 2007. Genome-wide detection and characterization of positive selection in human populations. *Nature* 449:913–18

Sachse C, Brockmoller J, Bauer S, Roots I. 1999. Functional significance of a C→A polymorphism in intron 1 of the cytochrome P450 *CYP1A2* gene tested with caffeine. *Br. J. Clin. Pharmacol.* 47:445–49

Saetrom P, Snove O Jr., Rossi JJ. 2007. Epigenetics and microRNAs. *Pediatr. Res.* 61:17–23

Sankar PL, Parker LS. 2017. The Precision Medicine Initiative's All of Us research program: an agenda for research on its ethical, legal, and social issues. *Genet. Med.* 19:743–50

Scheithauer TP, Dallinga-Thie GM, de Vos WM, Nieuwdorp M, Van Raalte DH. 2016. Causality of small and large intestinal microbiota in weight regulation and insulin resistance. *Mol. Metab.* 5:759–70

Sengupta D, Deb M, Rath SK, Kar S, Parbin S, et al. 2016. DNA methylation and not H3K4 trimethylation dictates the expression status of *miR-152* gene which inhibits migration of breast cancer cells via DNMT1/CDH1 loop. *Exp. Cell Res.* 346:176–87

Sharma AK, Eils R, Konig R. 2016. Copy number alterations in enzyme-coding and cancer-causing genes reprogram tumor metabolism. *Cancer Res.* 76:4058–67

Shaw GM, Carmichael SL, Laurent C, Rasmussen SA. 2006. Maternal nutrient intakes and risk of orofacial clefts. *Epidemiology* 17:285–91

Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. 2004. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. *Am. J. Epidemiol.* 160:102–9

Shen L, Waterland RA. 2007. Methods of DNA methylation analysis. *Curr. Opin. Clin. Nutr. Metab. Care* 10:576–81

Shin SY, Fauman EB, Petersen AK, Krumsiek J, Santos R, et al. 2014. An atlas of genetic influences on human blood metabolites. *Nat. Genet.* 46:543–50

Shukla H, Mason JL, Sabyah A. 2018. A literature review of genetic markers conferring impaired response to cardiovascular drugs. *Am. J. Cardiovasc. Drugs* 18(4):259–69

Silver MJ, Corbin KD, Hellenthal G, da Costa KA, Dominguez-Salas P, et al. 2015. Evidence for negative selection of gene variants that increase dependence on dietary choline in a Gambian cohort. *FASEB J.* 29:3426–35

Smith CE, Ordovas JM, Sanchez-Moreno C, Lee YC, Garaulet M. 2012. Apolipoprotein A-II polymorphism: relationships to behavioural and hormonal mediators of obesity. *Int. J. Obes.* 36:130–36

Stojanoska MM, Milosevic N, Milic N, Abenavoli L. 2017. The influence of phthalates and bisphenol A on the obesity development and glucose metabolism disorders. *Endocrine* 55:666–81

Strahl BD, Allis CD. 2000. The language of covalent histone modifications. *Nature* 403:41–45

Szyf M. 2005. DNA methylation and demethylation as targets for anticancer therapy. *Biochemistry* 70:533–49

Tabacchi G, Amodio E, Di Pasquale M, Bianco A, Jemni M, Mammina C. 2014. Validation and reproducibility of dietary assessment methods in adolescents: a systematic literature review. *Public Health Nutr.* 17:2700–14

Tasevska N, Midthune D, Tinker LF, Potischman N, Lampe JW, et al. 2014. Use of a urinary sugars biomarker to assess measurement error in self-reported sugars intake in the Nutrition and Physical Activity Assessment Study (NPAAS). *Cancer Epidemiol. Biomark. Prev.* 23:2874–83

Thaiss CA, Itav S, Rothschild D, Meijer M, Levy M, et al. 2016. Persistent microbiome alterations modulate the rate of post-dieting weight regain. *Nature* 540(7634):544–51

Trujillo-Gonzalez I, Wang Y, Friday WB, Vickers KC, Toth CL, et al. 2018. MicroRNA-129-5p is regulated by choline availability and controls EGF receptor synthesis and neurogenesis in the cerebral cortex. *FASEB J.* 33(3):3601–12

van Ommen B, van den Broek T, de Hoogh I, van Erk M, van Someren E, et al. 2017. Systems biology of personalized nutrition. *Nutr. Rev.* 75:579–99

Vazquez-Vidal I, Desmarchelier C, Jones PJH. 2019. Nutrigenetics of blood cholesterol concentrations: towards personalized nutrition. *Curr. Cardiol. Rep.* 21:38

Versteeg RI, Stenvers DJ, Kalsbeek A, Bisschop PH, Serlie MJ, La Fleur SE. 2016. Nutrition in the spotlight: metabolic effects of environmental light. *Proc. Nutr. Soc.* 75:451–63

Wallace TC, Fulgoni VL 3rd. 2016. Assessment of total choline intakes in the United States. *J. Am. Coll. Nutr.* 35:108–12

Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, et al. 2010. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet* 376:180–88

Wang Y, Surzenko N, Friday WB, Zeisel SH. 2016. Maternal dietary intake of choline in mice regulates development of the cerebral cortex in the offspring. *FASEB J.* 30:1566–78

Waterland RA. 2006. Assessing the effects of high methionine intake on DNA methylation. *J. Nutr.* 136:1706S–10

Waterland RA, Dolinoy DC, Lin JR, Smith CA, Shi X, Tahiliani KG. 2006. Maternal methyl supplements increase offspring DNA methylation at *Axin fused*. *Genesis* 44:401–6

Waterland RA, Travisano M, Tahiliani KG. 2007. Diet-induced hypermethylation at *agouti viable yellow* is not inherited transgenerationally through the female. *FASEB J.* 21:3380–85

Westerterp KR. 2017. Doubly labelled water assessment of energy expenditure: principle, practice, and promise. *Eur. J. Appl. Physiol.* 117:1277–85

Wolff GL, Kodell RL, Moore SR, Cooney CA. 1998. Maternal epigenetics and methyl supplements affect *agouti* gene expression in A^{vy}/a mice. *FASEB J.* 12:949–57

Wolkenhauer O. 2014. Why model? *Front. Physiol.* 5:21

Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, et al. 2011. Linking long-term dietary patterns with gut microbial enterotypes. *Science* 334:105–8

Yang M, Chen M, Wang J, Xu M, Sun J, et al. 2016. Bisphenol A promotes adiposity and inflammation in a nonmonotonic dose-response way in 5-week-old male and female C57BL/6J mice fed a low-calorie diet. *Endocrinology* 157:2333–45

Yao ZM, Vance DE. 1988. The active synthesis of phosphatidylcholine is required for very low density lipoprotein secretion from rat hepatocytes. *J. Biol. Chem.* 263:2998–3004

Yao ZM, Vance DE. 1989. Head group specificity in the requirement of phosphatidylcholine biosynthesis for very low density lipoprotein secretion from cultured hepatocytes. *J. Biol. Chem.* 264:11373–80

Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, et al. 2015. Personalized nutrition by prediction of glycemic responses. *Cell* 163:1079–94

Zeisel SH. 2006. Choline: critical role during fetal development and dietary requirements in adults. *Annu. Rev. Nutr.* 26:229–50

Zeisel SH, Blusztajn JK. 1994. Choline and human nutrition. *Ann. Rev. Nutr.* 14:269–96

Zeisel SH, Mar MH, Howe JC, Holden JM. 2003. Concentrations of choline-containing compounds and betaine in common foods. *J. Nutr.* 133:1302–7

Zeisel SH, Warrier M. 2017. Trimethylamine N-oxide, the microbiome, and heart and kidney disease. *Annu. Rev. Nutr.* 37:157–81

Zhang N. 2015. Epigenetic modulation of DNA methylation by nutrition and its mechanisms in animals. *Anim. Nutr.* 1:144–51

Zhao Y, Garcia BA. 2015. Comprehensive catalog of currently documented histone modifications. *Cold Spring Harb. Perspect. Biol.* 7:a025064

Zmora N, Zeevi D, Korem T, Segal E, Elinav E. 2016. Taking it personally: personalized utilization of the human microbiome in health and disease. *Cell Host Microbe* 19:12–20