Nutritionist Guide to Direct-to-Consumer Genetic Tests and Precision Nutrition

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Analogous to precision medicine, precision nutrition aims to tailor nutritional recommendations based on personal needs to optimize health. The field of nutritional genomics, which refers to the bidirectional interplay between dietary nutrients and the genome, is providing some of the necessary scientific evidence for precision nutrition. However, the extent of the clinical utility of nutritional genomics largely depends on the mode of disease/trait inheritance and remains unclear for prevalent, complex diseases, such as obesity, heart disease, and type 2 diabetes. Because genomic technology is now readily accessible through affordable personal DNA tests, it is now critical for nutritionists to establish a basic understanding in nutritional genomics to evaluate the validity of genetics-related ''health claims'' being provided by direct-to-consumer genetic testing companies. In this review, we provide examples of successful nutritional genomics studies, review current limitations, provide guidelines to evaluate health claims, and lastly discuss possible avenues and future outlooks for precision nutrition. Nutr Today. 2019;54(5):188–194

INTRODUCTION TO NUTRIGENOMICS

The prevalence of noncommunicable diseases (NCDs), such as obesity, cardiovascular disease, diabetes, and cancer, continues to rise globally.[1] In the United States, recent estimates of these diseases range from 9.4% for diabetes[2] to 37.7% for obesity.[3] In addition to the major public health burden inflicted by NCDs is a substantial economic burden, estimated to cost a staggering $94.9 trillion for chronic conditions in 2015-2050 in the United States.[4] Pharmacological and lifestyle interventions, including dietary, constitute the major effective strategies for the prevention, management, and treatment of several NCDs, as agreed upon by global health guidelines, such as the World Health Organization's Guidelines for the Prevention of Cardiovascular Disease.[5] Whether these strategies could be tailored and personalized to meet an individual's need is a major area of interest, which fueled the recent ''precision medicine'' movement.[6]

Precision medicine is largely focused on genetics as a result of the completion of the Human Genome Project in 2003,[7] along with other significant advancements in bioinformatics.[8] Through studying family pedigrees and twin pairs, population geneticists have identified that genetics is a substantial contributor, with varying importance, to many NCDs and personal traits including those of nutrition relevance.[9] For example, a classic twin study from the 1990s compared the correlation of body mass index (BMI) between pairs of identical and fraternal twins who were raised together and those who were raised apart and identified that up to 70% of the variation in BMI is influenced by genetics.[10] Because susceptibility to nutrition-related NCDs and dietary preference is in part also regulated by genetics, it became evident that nutritional needs and advice may need to vary from person-to-person based partly on one's genetic profile. Thus, analogous to precision medicine, precision nutrition aims to craft and tailor nutritional recommendations based on personal needs to optimize health.[11]

The field of nutritional genomics, which refers to the bidirectional interplay between dietary nutrients and the genome,[7] is providing some of the necessary scientific evidence for precision nutrition. The field deals with how genes may influence and modify the health impact of dietary nutrients (nutrigenetics) and also how nutrients may alter the expression or programming of specific genes (nutrigenomics). Nutritional genomics can serve 2 main purposes: biological and clinical. First, insights from nutritional genomics studies can advance our understanding of biological mechanisms that link dietary nutrients to disease. For example, a finding that sugar-sweetened beverages (SSBs) lead to a 12% increased risk for gout among those with a specific defective form of the *SLC2A9* gene, which encodes a transporter that eliminates uric acid, helped advance our understanding of the contribution of fructose-containing SSBs in increasing blood levels of uric acid (a risk factor for gout).[12] These mechanistic understandings, however, are mostly possible when

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the genes being investigated have a known biological function, which is often not the case. It is important to note that other defective forms of the *SLC2A9* gene exist, and not all have been evaluated for a response by fructose consumption. Second, findings from nutritional genomics research can inform clinical practice for personalized nutrition recommendations or precision nutrition. The clinical application of nutritional genomics is currently at its infancy.

CLINICAL UTILITY OF NUTRIGENOMICS

The extent of the clinical utility of nutritional genomics largely depends on the mode of disease/trait inheritance, that is, how much of the disease/trait is regulated by genetics and known genes.[8] For Mendelian diseases/traits, specific genes, often with known functions, are dominantly or recessively passed down from parent to offspring and directly influence the disease/trait.[13] In these cases, a genetic mutation results in the altered function, localization, or presence of proteins that are involved in molecular pathways essential to the disease/trait biology.[13] For example, in sickle cell anemia, a mutation in *HBB*, a gene responsible for making hemoglobin in red blood cells, impairs the functionality of this oxygen-carrying protein.[14] A nutrition-related example is lactase persistence or the continued production of the lactase enzyme past childhood, which enables dairy tolerance during adulthood.[15] Carrying one of several genetic forms of *LCT*, the gene encoding the lactase enzyme directly enhances the expression of the lactase enzyme at the jejunal brush borders in the small intestines. Carrying the form of *LCT* that enhances lactase enzyme enables dairy tolerance during adulthood without abdominal pain and distension.[15] Because of the known effect of the *LCT* gene on the lactase enzyme, the known biological role of this enzyme on lactose digestion, and the known consequences of a mutated form of the gene with lactose consumption on health and well-being, personalizing dietary recommendations based on the form of *LCT* is, for the most part, intuitive. These links, however, are often less apparent for most other diseases/traits as their genetic components are complex.

Most nutrition-related diseases/traits, particularly NCDs of great public health concern such as obesity, have non-Mendelian modes of inheritance as they are influenced by numerous (tens, hundreds, and possibly thousands) genes and are further shaped by the environment and are therefore complex.[8] Recent advancements in genetics, ranging from candidate gene association studies and large genome-wide association studies, have enabled the genetic mapping of specific genetic variants that partly contribute to the complex diseases/traits that manifest as NCDs. These genetic variants, that is, nucleotide alterations to the DNA sequence, are called single-nucleotide polymorphisms (SNPs) and constitute one of several sources of variation in the human genome.[7] Since 2007, when the first genome-wide association study for age-related macular degeneration was published,[16] more than 5500 genome-wide association studies have been conducted for various traits and diseases. These studies have identified more than 71 500 genetic variant-trait or disease associations described in more than 3500 publications and cataloged in the NHGRI-EBI GWAS Catalog (https://www.ebi.ac.uk/gwas/home).[17] These associations include SNPs for diseases, such as obesity, heart disease, and insomnia, and traits, such as body weight, eye color, and sleep duration. Similarly, genetic studies for nutrition-related traits have all unraveled contributing genetic variants such as macronutrient intake,[18] fish intake,[19] and circulating vitamin K concentrations.[20] Unfortunately, in most cases, the biological mechanism explaining the link between the identified genes and the disease or trait of interest is not yet known. As a result, a clear and "intuitive" relationship linking nutrient to genetic variant to disease cannot be established easily. With complex genetic architectures and unclear underlying biology involving genetics and the environment, the clinical utility of nutritional genomics for some of the most pertinent diseases remains indiscernible.

Nevertheless, few nutritional genomics studies investigating complex diseases, such as heart disease, have provided compelling evidence suggesting that diet may still be successfully personalized based on genetics. These findings indicate that certain foods or nutrients are beneficial for some with a specific genetic profile, but detrimental for others with a different genetic profile. We have compiled a list of such published nutritional genomics studies.[21] Here, we provide 2 examples to demonstrate 2 different forms of those studies.

The first example is related to coffee intake, *CYP1A2*, and myocardial infarction.[22] *CYP1A2* is a gene that encodes an enzyme that metabolizes caffeine and exists in 2 forms: a rapid metabolizing and a slow metabolizing form. In this study, the investigators find that among those with the genetic variant encoding the slow metabolizing form of the enzyme there is 64% higher odds of having myocardial infarction when consuming 4 cups of coffee per day compared to less than 1 cup of coffee per day. Among those with the fast metabolizing form of the enzyme, however, there is no apparent link between cups of coffee and myocardial infarction. The recommendation based on these findings is limiting coffee intake for those with the slow metabolizing form of the gene.

The second example is related to SSBs, an obesity genetic risk score, and obesity.[23] Rather than investigating single genes, the investigators have generated a score that aggregates multiple genes that predispose to obesity. The findings indicate that, for individuals with a genetic

predisposition to obesity, consuming SSBs results in a much higher risk of becoming obese. In other words, a genetic profile predisposing to obesity was exacerbated by higher consumption of SSBs. Unlike the first example, rather than focusing on a single gene, a score was developed aggregating multiple genes all known to influence the obesity, the outcome, rather than the nutrient. Furthermore, although the genes are known to associate with obesity, their exact biological mechanisms are unknown.

These 2 examples, as well as others like them, should be treated as preliminary for several reasons of which we describe 4. First, unlike our Mendelian example, many nutritional genomics findings for complex traits have weak underlying biological mechanisms convincingly supporting the interaction findings. Indeed, in most cases, potential mechanisms are merely speculated, but not rigorously tested. Second, few discovered gene-diet interactions have been reevaluated, replicated, and independently validated in additional studies. A recent study aimed at evaluating the robustness of existing findings on gene-diet interactions for type 2 diabetes failed to replicate all 8 previously identified findings despite mirroring the analytical approach.[24] Even the widely accepted coffee-*CYP1A2* interaction discovered in a Costa Rican population has recently failed to replicate in a British population.[25] While the lack of replication does not invalidate the original findings, it begs the question whether findings from one population (ie, Costa Rican population) are biologically and clinically relevant for another population (ie, British population). Third, the magnitude of an interaction indicates whether it necessitates clinical translation. Some interactions, despite being statistically significant, have very small effects on an outcome of interest and, if so, are meaningless to be brought forth to the clinic. For example, we have observed that the influence of carbohydrate consumption on your glucose levels varies depending on the form of *MTNR1B*, a gene encoding a melatonin receptor.[26] Despite significance, this difference in glucose levels is, however, only 0.003 mmol/L per each additional 1% additional intake of carbohydrate in the diet. Thus, while this interaction may be revealing something about the underlying biological link between carbohydrates, *MTNR1B*, and glucose levels, it likely will not have a clinical effect considering how small the effect is. Fourth, most of these findings have been conducted using cross-sectional data, when diet and a trait/disease were measured at the same timepoint. Findings from cross-sectional analyses do not translate to future change as the putative links between diet, gene, and health outcome from association studies do not imply cause and effect, and the involvement of other genes cannot be ruled out.[27] Thus, we cannot imply that changing behavior today (ie, reducing SSB intake) will result in improved health outcomes in the future (ie, lower future risk of developing obesity). Double-blind randomized controlled trials have been conducted in the past, such as for a common polymorphism in *MTHFR*, which encodes an enzyme necessary for the digestion and absorption of folate.[28] The trial found that that treating patients homozygous for this polymorphism with riboflavin elicited a significant reduction in blood pressure. Future randomized controlled trials are needed for rigorous evaluation of interactions. For these reasons and others, the benefits of nutrigenomics for complex nutrition-related traits/diseases remain unclear because often the underlying biological mechanisms are weak, the gene-diet interactions that have been discovered have often not been replicated, the magnitude of the interactions is often clinically irrelevant, and the identified cross-sectional interactions do not guarantee that changing behavior will result in better health outcomes in the future.

ROLE OF THE NUTRITIONIST

Genomic technology initially limited to research and healthcare settings is now readily accessible through affordable personal genomic tests, also known as direct-to-consumer (DTC) or personal DNA tests. For this reason, and the general public's growing interest in personal genetic information, it is now critical for nutritionists to establish a basic understanding in nutritional genomics to evaluate the validity of genetics-related "health claims" being provided by DTC companies. In brief, DTC companies function by having customers send biological samples to the company, which then extracts DNA from the sample and genotypes-specific genomic regions of interest, and lastly renders a health report providing (almost always) definitive "personalized" health reports.[27] Too often, unregulated nutrition-related DTC genetic testing companies promise to deliver healthy diets best suited for an individual's genetic makeup and lifestyle and use exaggerated, unscientific phrases such as "diet type recommendations" and "genotype-specific shopping list" to market their products. This is unsurprising considering the growing and competitive market anticipated to surpass $2.5 billion by 2024, according to data from the Global Market Insights, Inc.[29] Therefore, nutritionists need to critically evaluate precision nutrition claims.

FIVE QUESTIONS TO ASK ABOUT NUTRITION GENOMICS CLAIMS

Five questions may be asked about nutrition genomics claims to help guide conversations with clients and to evaluate whether a "health claim" is warranted. Those questions are described in the following section and summarized in the Table.

"Can you show me the genes?" For each interaction "health claim," a corresponding list of gene(s) should be identified

TABLE Five Questions to Ask About Nutrition Genomics Claims and Corresponding Rationale

Question	Rationale
1. Which genes?	A corresponding list of gene(s) should be identified to understand the rationale for any health claim or recommendation.
2. How many genes regulate the trait or disease?	Understanding the mode of inheritance (Mendelian vs non-Mendelian) and complexity of the trait can help determine whether recommendations are reliable.
3. Who was assessed in the publication?	Understanding the characteristics of the population where the original finding was made is an important step in evaluating whether a DTC health claim is applicable to a patient.
4. How much difference will it make?	It is important to evaluate whether the difference discovered in the main finding is substantial enough for the health claim to be emphasized. Only those findings that are both statistically significant and clinically relevant because of their large effects are worth pursuing for precision nutrition.
5. How does the recommendation fit with other accepted health recommendations?	When evaluating DTC health reports, it is important to consider whether the recommendation conflicts with well-accepted health recommendations or essentially reinforces them.

to understand the rationale for the recommendation and to identify the source study. This, however, is not always easy to retrieve. Whereas some companies, like 23andMe and DNAfit, are transparent about what genes serve as the basis for each recommendation, other companies, such as Habit and myDNAHealth, are less transparent and instead use umbrella phrases like "metabolism-related genes," possibly as it constitutes part of their intellectual property. Ambiguity at the level of the gene precludes the ability to evaluate a health claim, and for that reason, a recommendation with no corresponding gene list can be deemed unsuitable.

"How many genes regulate the trait or disease?" Considering trait or disease heritability, the extent that variation in a trait or disease is due to variation in genetics and polygenicity, the number of genes contributing to the genetic variation are important factors when determining whether a DTC health claim is scientifically sound. As findings in nutritional genomics remain limited, DTC companies often base their recommendations for complex traits and diseases on a handful of genetic findings. For example, one company bases its recommendation for "carbohydrate metabolism" or "type 2 diabetes" on 1 or 2 published interactions. This oversimplification entirely disregards the complexity of human biology and physiology and the truth regarding our incomplete knowledge of the functionality of all our genes. How can we be certain that a recommendation to "increase carbohydrate" based on a single gene to lower diabetes risk, for instance, will not be detrimental when considering another gene also involved in diabetes risk? Thus, understanding the mode of inheritance (Mendelian vs non-Mendelian) and complexity of the trait can help determine whether recommendations are reliable.

"Who was assessed in the published finding?" Understanding the characteristics of the population where the original finding was made is an important step in evaluating whether a DTC health claim is applicable to a patient. Visiting the original publication and replication studies (if available) can help determine important population characteristics including age, sex, race, and ethnicity. Essentially, discoveries can often only be extended or generalized to people or patients of similar demographics, and also, the larger the sample size included in the analysis (ie, more people investigated in the study), the more likely the results are valid rather than driven by chance. For example, a study identified that the form of *PPARG*, a gene involved in regulating adipogenesis, might influence the effect of dietary fat on BMI based on data from 2141 women from the Nurses' Health Study, a predominantly European cohort.[30] Considering the demographic of that population, it is more possible to extend those findings to other women of European ancestry residing in New England, but less clear whether those findings can be generalized to other demographics, such as an East Asian man living in Singapore. Unfortunately, there is currently a disproportionately larger number of genetic discoveries conducted only in cohorts of predominantly European ancestry compared with other ethnicities.[31] Generalizing genetic findings from a particular ethnicity to another is particularly difficult. First, the

relevant gene found in one ethnicity might not be prevalent in another ethnicity. In the case of *PPARG*, whereas it has a 12% prevalence in European ancestry, it is rare in African ancestry (only 0.05% prevalence). Visiting dbSNP, a database of genomic variation, can help identify prevalence across ethnicities (https://www.ncbi.nlm.nih.gov/snp) to determine whether one finding is relevant to another ancestry. Second, the SNP identified to interact with diet often serves as a marker tagging another piece of genetic data, and there is often uncertainty of the actual "causal" genetic SNP causing the interaction.

"But how much difference will it make?" For a recommendation to be worthwhile, it is important to evaluate whether the difference discovered in the main finding is substantial enough for the health claim to be emphasized. Statistically significant findings and clinically relevant findings are 2 different concepts. Only those findings that are both statistically significant and clinically relevant because of their large effects are worth pursuing for precision nutrition. Often, statistically significant nutritional genomics findings have very small effects, and more often than not, DTC companies do not reveal to what extent the recommendation will likely have an impact based on the original findings. In the case of *PPARG*, the original finding indicated a difference of 1.9 kg/m^2.[30] Again, revisiting original sources of these findings can help determine whether effort should be placed on the DTC health claim or whether it is more effective to shift focus on other well-known recommendations that are known to substantially improve human health.

"How does the recommendation fit with other well-accepted health recommendations?" With few exceptions, nutritional genomics discoveries essentially corroborate current messages and recommendations from major health guidelines. Many nutritional genomics studies tend to indicate that genetic predisposition to disease may be attenuated through positive lifestyle changes, whether it be increasing fruit and vegetable intake, reducing intake of SSBs, reducing red meat intake, increasing physical activity, or better sleep hygiene.[26,32–36] Thus, in evaluating DTC health reports, it is important to consider whether the recommendation conflicts with well-accepted health recommendations or essentially reinforces them. Claims that conflict with widely accepted recommendations should be carefully examined.

Surprisingly, current studies repeatedly show that disseminating genetic data and information on genetic risk does not always motivate behavioral change such as improvements in diet and exercise.[37–39] Indeed, the largest human intervention personalized genomic trial of diet, genes, and health outcomes to date, the Food4Me study, did not modify dietary behaviors in response to simple personalized dietary advice delivered electronically.[40,41] Thus, it is possible that placing too much emphasis on genetics will likely result in a failed nutritional intervention.[27] Instead, nutritionists should continue to effectively personalize dietary recommendations based on individualized needs and goals identified from in-depth patient assessments, as is the current nutrition care process standard.[42] Nutritional genomics should currently be mostly used merely to reinforce health messages and possibly motivate patients. Other sets of guidelines to aid in evaluating DTC results also exist and are set to be reviewed every 2 years to include advancements in the field.[43] Resources such as this review and other guidelines should be considered when making personalized genetic recommendations.

FUTURE TRENDS IN NUTRITIONAL GENOMICS

As the field of nutritional genomics continues to evolve with emerging data, the role of nutritionists will likely adapt and mature. Based on current trends, we provide some possible avenues and future outlooks for precision nutrition.

In recognition of the complexity and polygenicity of common traits and diseases (ie, that traits/diseases may be genetically regulated by multiple SNPs), nutritional genomics studies are moving toward gene scores. These scores, termed genetic risk scores or polygenic risk scores, represent a count of the number of genes that predispose to a disease or exhibit a certain trait. We provided an earlier example pertaining to the study on SSBs, obesity genetics, and obesity. Another example is a recent study that assessed whether the efficacy of omega-3 fatty acid supplementation differed among people with different genetic risk scores for triglycerides.[44] Thus, it is very conceivable that future DTC recommendations will be based on genetic risk scores, such as scores for vitamin or mineral deficiencies, food intolerances, and other gut health issues, and health reports will provide nutrition care plans and personalized therapies based on these genetic profiles. Currently, 23andMe is providing scores for type 2 diabetes, a common and life-threatening NCD genetically regulated by more than 120 SNPs, and subsequently offering optional online health coaching tools, at an additional cost, for those who desire guidance on how to attenuate their genetic risk through lifestyle changes. Similar trends will likely continue as more scores, aggregating a handful of genes or even genes spanning the entire genome (termed genome-wide polygenic scores[45]), are being generated by genetic epidemiologists. Worthy of noting is that the same disease, such as type 2 diabetes, may have multiple scores associated with them as complex NCDs may result from different "genetic signatures." In the case of type 2 diabetes, for example, 5 different clusters of genes, each related to a different physiological pathway leading to type 2 diabetes, may

result in the disease.[46] The relevance of nutrition in each of these distinct type 2 diabetes scores needs to be evaluated.

Whereas current genotyping platforms only assess specific regions of the genome, emerging technologies are having better genetic resolution and coverage and are designed to sequence every specific genetic variation in the genome. Direct-to-consumer companies will likely shift to whole genome sequencing as this technology becomes better tested and more affordable. In addition, whereas precision medicine and precision nutrition are slanted toward genetics because it is measurable with current technologies, developments in other technologies including the epigenome and the gut microbiome will enable other factors to be integrated into precision medicine and nutrition. In fact, several studies have successfully personalized nutrition without genetics based on other factors such as the microbiome.[47] In the future, DTC companies will likely expand beyond genetic variation to measure sources of human variation, such as epigenetics, and provide personalized dietary recommendations based on an entire host of genetic and nongenetic data.

There is a push toward expanding human genetic studies beyond only individuals of European ancestry. This will be made possible by large genetic biobanks that are designed to capture genetic diversity such as the US-based All-of-Us study, the China Kadoorie Biobank, and the Qatar Biobank. These large global initiatives will enable testing whether findings discovered in predominantly European populations hold true in large non-European populations. The larger the population, the better, as larger studies are more likely to lend robust results rather than be driven by chance or error. Thus, it is conceivable for DTC companies to start providing ancestry-specific precision nutrition recommendations.

In addition, future studies in the field will also likely emphasize on randomized controlled trials and longitudinal study designs in recognizing limitations of current cross-sectional nutritional genomic studies.[44,48] Randomized controlled trials may be risky and costly, but when completed, they will provide irrefutable evidence of the utility of some SNPs in DTC. As most studies rely on self-reported dietary intake, which is prone to various limitations and inaccuracies, future studies may involve more objective assessment of dietary intake using biomarkers. Advancements in both study design and dietary assessment will likely yield more robust and impactful nutritional genomics findings and address various current limitations in the field.

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REFERENCES

1. Riley L, Gouda H, Cowan M, World Health Organization. *Noncommunicable Diseases Progress Monitor*. 2017.
2. Statistics About Diabetes: American Diabetes Association®. http://www.diabetes.org/diabetes-basics/statistics/. Accessed August 17, 2018.
3. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(25 suppl 2):S102–S138.
4. Chen S, Kuhn M, Prettner K, Bloom DE. The macroeconomic burden of noncommunicable diseases in the United States: estimates and projections. *PLoS One*. 2018;13(11):e0206702.
5. Prevention of Cardiovascular Disease Guidelines for Assessment and Management of Cardiovascular Risk WHO Library Cataloguing-in-Publication Data. 2007. www.inis.ie. Accessed August 17, 2018.
6. Hesketh J. Personalised nutrition: how far has nutrigenomics progressed? *Eur J Clin Nutr*. 2013;67(5):430–435.
7. Camp KM, Trujillo E. Position of the Academy of Nutrition and Dietetics: nutritional genomics. *J Acad Nutr Diet*. 2014;114(2):299–312.
8. Guasch-Ferré M, Dashti HS, Merino J. Nutritional genomics and direct-to-consumer genetic testing: an overview. *Adv Nutr*. 2018;9(2):128–135.
9. Tenesa A, Haley CS. The heritability of human disease: estimation, uses and abuses. *Nat Rev Genet*. 2013;14(2):139–149.
10. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. The body-mass index of twins who have been reared apart. *N Engl J Med*. 1990;322(21):1483–1487.
11. Ordovas JM, Ferguson LR, Tai ES, Mathers JC. Personalised nutrition and health. *BMJ*. 2018;361:bmj.k2173.
12. Batt C, Phipps-Green AJ, Black MA, et al. Sugar-sweetened beverage consumption: a risk factor for prevalent gout with SLC2A9 genotype-specific effects on serum urate and risk of gout. *Ann Rheum Dis*. 2014;73(12):2101–2106.
13. Chong JX, Buckingham KJ, Jhangiani SN, et al. The genetic basis of Mendelian phenotypes: discoveries, challenges, and opportunities. *Am J Hum Genet*. 2015;97(2):199–215.
14. Strouse J. Sickle cell disease. *Handb Clin Neurol*. 2016;138:311–324.
15. Deng Y, Misselwitz B, Dai N, Fox M. Lactose intolerance in adults: biological mechanism and dietary management. *Nutrients*. 2015;7(9):8020–8035.
16. Klein RJ, Zeiss C, Chew EY, et al. Complement factor H polymorphism in age-related macular degeneration. *Science*. 2005;308(5720):385–389.
17. Buniello A, MacArthur JAL, Cerezo M, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res*. 2019;47(D1):D1005–D1012.
18. Merino J, Dashti HS, Li SX, et al. Genome-wide meta-analysis of macronutrient intake of 91,114 European ancestry participants from the cohorts for heart and aging research in genomic epidemiology consortium. *Mol Psychiatry*. 2018.
19. Mozaffarian D, Dashti HS, Wojczynski MK, et al. Genome-wide association meta-analysis of fish and EPA+DHA consumption in 17 US and European cohorts. *PLoS One*. 2017;12(12):e0186456.
20. Dashti HS, Shea MK, Smith CE, et al. Meta-analysis of genome-wide association studies for circulating phylloquinone concentrations. *Am J Clin Nutr*. 2014;100(6):1462–1469.
21. Parnell LD, Blokker BA, Dashti HS, et al. CardioGxE, a catalog of gene-environment interactions for cardiometabolic traits. *BioData Min*. 2014;7:21.
22. Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. *JAMA*. 2006;295(10):1135–1141.

23. Qi Q, Chu AY, Kang JH, et al. Sugar-sweetened beverages and genetic risk of obesity. *N Engl J Med*. 2012;367(15):1387–1396.
24. Li SX, Imamura F, Ye Z, et al. Interaction between genes and macronutrient intake on the risk of developing type 2 diabetes: systematic review and findings from European Prospective Investigation into Cancer (EPIC)-InterAct. *Am J Clin Nutr*. 2017; 106(1):263–275.
25. Zhou A, Hyppönen E. Long-term coffee consumption, caffeine metabolism genetics, and risk of cardiovascular disease: a prospective analysis of up to 347,077 individuals and 8368 cases. *Am J Clin Nutr*. 2019;109(3):509–516.
26. Dashti HS, Follis JL, Smith CE, et al. Gene-environment interactions of circadian-related genes for cardiometabolic traits. *Diabetes Care*. 2015;38(8):1456–1466.
27. Loos RJF. From nutrigenomics to personalizing diets: are we ready for precision medicine? *Am J Clin Nutr*. 2019;109(1):1–2.
28. Horigan G, McNulty H, Ward M, Strain JJ, Purvis J, Scott JM. Riboflavin lowers blood pressure in cardiovascular disease patients homozygous for the 677C–>T polymorphism in MTHFR. *J Hypertens*. 2010;28(3):478–486.
29. Global Market Insights I. Direct-to-consumer genetic testing market to hit $2.5 Bn by 2024: Global Market Insights, Inc. *PRNewswire*.
30. Memisoglu A, Hu FB, Hankinson SE, et al. Interaction between a peroxisome proliferator-activated receptor gamma gene polymorphism and dietary fat intake in relation to body mass. *Hum Mol Genet*. 2003;12(22):2923–2929.
31. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet*. 2019;51(4):584–591.
32. Dashti HS, Follis JL, Smith CE, et al. Habitual sleep duration is associated with BMI and macronutrient intake and may be modified by CLOCK genetic variants. *Am J Clin Nutr*. 2015; 101(1):135–143.
33. Khera AV, Emdin CA, Kathiresan S. Genetic risk, lifestyle, and coronary artery disease. *N Engl J Med*. 2017;376(12):1194–1195.
34. Fretts AM, Follis JL, Nettleton JA, et al. Consumption of meat is associated with higher fasting glucose and insulin concentrations regardless of glucose and insulin genetic risk scores: a meta-analysis of 50,345 Caucasians. *Am J Clin Nutr*. 2015;102(5): 1266–1278.
35. Kilpeläinen TO, Qi L, Brage S, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med*. 2011;8(11):e1001116.
36. Haslam DE, McKeown NM, Herman MA, Lichtenstein AH, Dashti HS. Interactions between genetics and sugar-sweetened beverage consumption on health outcomes: a review of Gene-Diet Interaction Studies. *Front Endocrinol (Lausanne)*. 2018; 8:368.
37. Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. *N Engl J Med*. 2011;364(6):524–534.
38. Gray SW, Gollust SE, Carere DA, et al. Personal genomic testing for cancer risk: results from the Impact of Personal Genomics Study. *J Clin Oncol*. 2017;35(6):636–644.
39. Nielsen DE, Carere DA, Wang C, Roberts JS, Green RC, PGen Study Group. Diet and exercise changes following direct-to-consumer personal genomic testing. *BMC Med Genomics*. 2017;10(1):24.
40. O'Donovan CB, Walsh MC, Forster H, et al. The impact of MTHFR 677C → T risk knowledge on changes in folate intake: findings from the Food4Me study. *Genes Nutr*. 2016;11:25.
41. Celis-Morales C, Livingstone KM, Marsaux CF, et al. Effect of personalized nutrition on health-related behaviour change: evidence from the Food4Me European randomized controlled trial. *Int J Epidemiol*. 2017;46(2):578–588.
42. Writing Group of the Nutrition Care Process/Standardized Language Committee. Nutrition care process and model part I: the 2008 update. *J Am Diet Assoc*. 2008;108(7):1113–1117.
43. Grimaldi KA, van Ommen B, Ordovas JM, et al. Proposed guidelines to evaluate scientific validity and evidence for genotype-based dietary advice. *Genes Nutr*. 2017;12:35.
44. Vallée Marcotte B, Guénard F, Lemieux S, et al. Fine mapping of genome-wide association study signals to identify genetic markers of the plasma triglyceride response to an omega-3 fatty acid supplementation. *Am J Clin Nutr*. 2019;109(1):176–185.
45. Khera AV, Chaffin M, Wade KH, et al. Polygenic prediction of weight and obesity trajectories from birth to adulthood. *Cell*. 2019;177(3):587–596.e9.
46. Udler MS, Kim J, von Grotthuss M, et al. Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: a soft clustering analysis. *PLoS Med*. 2018; 15(9):e1002654.
47. Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. *Cell*. 2015;163(5):1079–1094.
48. Lankinen MA, Fauland A, Shimizu B-I, et al. Inflammatory response to dietary linoleic acid depends on FADS1 genotype. *Am J Clin Nutr*. 2019;109(1):165–175.