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PLANNING COMMITTEE FOR A WORKSHOP ON NUTRIGENOMICS AND THE FUTURE OF NUTRITION

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **HUGH H. TILSON**, University of North Carolina. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteur and the National Academies.
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On December 5, 2017, the Food Forum of the National Academies of Sciences, Engineering, and Medicine hosted a public workshop titled Nutrigenomics and the Future of Nutrition in Washington, DC, to review current knowledge in the field of nutrigenomics as it relates to nutrition. Workshop participants explored the influence of genetic and epigenetic expression on nutritional status and the potential impact of personalized nutrition on health maintenance and chronic disease prevention (see Box 1-1 for the workshop’s complete Statement of Task).¹

In her welcoming remarks, Food Forum chair Sylvia Rowe, SR Strategy, LLC, described how the Food Forum, through public workshops such as this, convenes scientists, administrators, and policy makers from academia, government, industry, and the public sector to discuss problems and issues related to food, food safety, and regulation and to identify possible approaches for addressing these problems and issues. She emphasized that while the forum compiles information, develops options, brings interested parties together, and provides a rapid way to identify areas of concordance among workshop participants, it does not make recommendations, nor does it offer specific advice. She noted that, in addition to diverse and ex-

¹ The role of the workshop planning committee was limited to planning the workshop, and this Proceedings of a Workshop was prepared by the rapporteur as a factual account of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine. They should not be construed as reflecting any group consensus.
BOX 1-1
Statement of Task

An ad hoc committee will plan and conduct a 1-day public workshop that will review current knowledge in the field of nutrigenomics as it relates to nutrition. The workshop will explore the influence of genetic and epigenetic expression on nutritional status, including the potential impact of personalized nutrition on health maintenance and chronic disease prevention. The workshop will also investigate the clinical implications of nutrigenomics, key public health and regulatory policy considerations presented in the context of emerging nutrigenomics applications to personalized nutrition, and the challenges to globalization of public health guidance that may be informed by nutrigenomic research.

The committee will define the specific topics to be addressed, develop the agenda, and select and invite speakers and other participants. After the workshop, proceedings of a workshop in brief and full proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

pert presentations, the agenda for the workshop included built-in time for discussion.

This Proceedings of a Workshop is a factual summary of the presentations and discussions that took place during the workshop. It is not intended to serve as a comprehensive overview of the subject, nor are the citations herein intended to serve as a comprehensive set of references for any topic. Additionally and importantly, the information presented here reflects the knowledge and opinions of individual workshop participants and should not be construed as reflecting consensus on the part of the workshop planning committee; the Food Forum; or the National Academies.

SETTING THE STAGE: INTRODUCTION AND OVERVIEW

Following Rowe’s welcoming remarks, Patsy Brannon, Division of Nutritional Sciences, Cornell University, set the stage for the workshop by discussing the central role of a risk assessment framework in current, population-based dietary guidance and the challenges of transitioning to personalized nutrition guidance. Her presentation is summarized here, with highlights provided in Box 1-2.
INTRODUCTION

BOX 1-2
Highlights from Patsy Brannon in Her Introductory Presentation

- A risk assessment approach is central to current population-based dietary guidance. Dietary reference intakes (DRIs) are based on a distribution of nutrient intake, and it is impossible for any given individual to ascertain where in the distribution that individual falls.
- Therefore, it has been impossible to provide specific nutrition recommendations for individuals. “That’s at the heart of the change of what nutrigenomics opens up as a possibility,” Brannon said.
- The variety of ways in which different authoritative bodies have defined nutrigenomics reflects the complexity of the interrelationships among genetics, epigenetics, nutrient–gene interactions, and individual variations in nutritional kinetics and dynamics.
- Added to this complexity is the very important role of consumer and food behavior. Taste, not health, is often the primary force driving food choices.
- Because of these complexities, instead of thinking about population-based and personalized dietary guidance as an either-or situation, the two approaches will likely need to be integrated.


Brannon began by discussing the risk assessment framework, which she said underlies many, though not necessarily all, current population-based dietary guidance. She explained that the first step in risk assessment is to identify, based on a review and synthesis of evidence in the literature, what is known in the field of risk assessment as the “hazard identification,” which, in the context of nutrition, is a health outcome. The second step, she continued, is to characterize the dose-response relationship between the exposure, which in this case is a nutrient or diet, and the health outcome. “These two steps are central to why we use a population-based approach,” she said. She then discussed each step in detail.

Step 1: Synthesizing the Evidence

In addressing the process of synthesizing the evidence, Brannon cited two sources: (1) food-based dietary guidance from the European Food Safety Authority (EFSA) and also, to some extent, from the U.S. Dietary Guidelines for Americans, particularly the Nutrition Evidence Library; and (2) nutrient requirements, including the dietary reference intakes (DRIs),
particularly the traditional DRI model (that is, before chronic disease endpoints were proposed).

EFSA’s population approach, as reflected in its *Scientific Opinion on Establishing Food-Based Dietary Guidelines* (EFSA, 2010), focused explicitly on dietary patterns, which Brannon noted is comparable to the focus of the *U.S. Dietary Guidelines for Americans* (HHS/USDA, 2015), emphasizing “desirable food and nutrient intakes.” But, she added, EFSA’s focus also was on diet and disease relationships of relevance to a specific population. She explained that the EFSA (2010) panel used a stepwise approach in reviewing the evidence and identifying diet–health relationships, country-specific diet-related health problems (in contrast to the U.S. focus on nationwide health problems and their public health significance), nutrients of public health concern, foods relevant for food-based dietary guidelines, and food consumption patterns. She commented that, other than the focus on country-specific diet-related health problems, EFSA’s approach was comparable to that used to establish the *U.S. Dietary Guidelines for Americans*.

Brannon then turned to the analytical frameworks used for the synthesis of evidence in establishing the *U.S. Dietary Guidelines for Americans*, which, like the EFSA approach, reflected a population-based approach. She cited the example of the framework used to evaluate adherence to a dietary pattern in relation to outcomes for breast, colorectal, prostate, and lung cancers.

*Step 2: Characterizing Dose-Response Relationships*

Brannon next considered how an understanding of the DRIs is helpful for understanding why the U.S. population-based approach is different from what is possible with nutrigenomics. The DRIs, she explained, are based on a distribution of intake requirements, so that it is impossible to ascertain where in the distribution a given individual falls (IOM, 2006).2

As shown in Figure 1-1, the DRI values include the estimated average requirement (EAR) for 50 percent of the population, a recommended dietary allowance (RDA) for 97.5 percent of the population, and an upper level (UL) at which adverse effects begin to be seen. The European approach, Brannon noted, uses comparable values. She added that the proposed chronic disease DRIs (NASEM, 2017a) are based on acceptable ranges of intakes instead of singular dietary reference values (see Figure 1-2).

Because of this distribution-based approach, Brannon observed, “we have been unable to give a specific recommendation for an individual, and that is at the heart of the change of what nutrigenomics opens up as a possibility.” This is true, she noted, for both the current model (left distribution in Figure 1-3) and the proposed expanded model with chronic

---

2 More about the DRIs can be found at www.nas.edu/dris (accessed April 23, 2018).
**INTRODUCTION**

The distribution of intake requirements (bell-shaped curve) upon which the dietary reference intakes (DRIs) (estimated average requirements [EARs], recommended dietary allowances [RDAs], and tolerable upper intake levels [ULs]) are set, with intake on the x-axis and frequency of risk of adverse health outcome on the y-axis.

SOURCE: Presented by Patsy Brannon on December 5, 2017.

**FIGURE 1-1**

Two possible distributions of intake ranges (horizontal bars) when chronic disease risk decreases with increasing intake (left) and when chronic disease risk increases with increasing intake (right).

NOTE: RDA = recommended dietary allowance; UL = tolerable upper intake level.

disease endpoints (right distribution in Figure 1-3). She suggested that this distribution of requirements raises the question of why there is variability in requirements for a nutrient or in the response to a nutrient or dietary component related to health promotion or disease prevention.

**Nutritional Kinetics, Dynamics, and Requirements**

Brannon chose to frame her consideration of the question of variability in terms of nutritional kinetics, dynamics, and requirements because she believes it is useful to step back and ask, Why do people actually vary? She explained that when people consume food, there are both kinetic and dynamic aspects to the nutrient concentration at the site of action.

Brannon listed several different processes related to kinetics: absorption (e.g., processes related to digestion and bioavailability); distribution throughout the tissues (e.g., processes related to the volume of circulating fluids, the volume of the compartments into which they are being distributed, and body composition); metabolism, including metabolic rates; and excretion, including rates of excretion.

Likewise, Brannon continued, there are several different processes involved in dynamics that affect the actions of a nutrient. Among these processes are dose-response at the site of action (including complexities related to the differential distribution of nutrients in different compartment pools and their differential effects), maximal efficacy, and the temporal response...
as nutrients are consumed. Adverse or beneficial effects, Brannon observed, also depend on dose-response at the site of action and the target tissue, as well as on deficiency; toxicity; temporal response; and, for DRIs for chronic disease, the ranges of dose-response effects. Additionally, she noted, as more is learned about the inflammatory response, it is clear that the dynamics of nutrients, as well as some of their kinetics, can also be influenced by the inflammatory response.

Brannon then cited a number of factors that affect individual variation in nutritional kinetics and dynamics, including genetics, epigenetics, and nutrient–gene interactions. She explained that genetics encompasses both the mitochondrial genome and the nuclear genome, plus interactions between the two, as well as other factors including age, sex, and physiological state (e.g., growing, pregnancy, lactation, stress, disease). Also relevant are nutrient–diet interactions, nutrient–environment interactions, and drug–nutrient interactions. When one considers all of these processes and factors, Brannon observed, “it becomes quite clear why nutrigenomics can help us understand what an individual needs as opposed to an average for the population.”

Definitions of Nutrigenomics

Upon searching for definitions of nutrigenomics, Brannon found that what she thought nutrigenomics meant agreed largely with how it was defined, including by such authoritative sources as Nature and medical dictionaries. However, she noted, although all of the definitions included nutrients, their impact on health, and the interaction between nutrients and genetics, they varied in how they characterized those relationships. For example, some focused on nutrients affecting health, with the effect being mediated through genetics, whereas what she described as more reflective definitions pointed out, first, that nutrients and the genome interact with each other and are mutually influencing and, second, that nutrients and health influence each other.

Additionally, Brannon found variability in whether a definition included nutrients, diet, foods, or food components. She sees this variability, coupled with the mutuality of nutrient–health and nutrient–genome relationships, as reflecting the complexities of nutrigenomics and their impact on how nutritional and dietary guidance would be provided to a specific individual. She pointed to Figure 1-4 as making these complexities readily evident, noting that the dietary and genetic interrelationships depicted in this figure are multiple and complex, affecting different phenotypes for, in this example, cardiovascular disease. She suggested that all of these complexities will need to be addressed as nutrigenomics begins to be applied to specific, personalized nutrition.
Consumer and Food Behavior

Adding to the complexity illustrated in Figure 1-4, Brannon continued, is the reality that consumer and food behavior is “very, very difficult to fully elucidate and understand.” She noted that each consumer is a complex psychological unit that informs both poor and good food behavior choices. She stressed that, based on the body of literature on consumers and food behavior, one issue that will need to be addressed is the reality that health is not the only driving force in food choices, and likely not even the major one. She acknowledged that, based on the theory of self-determination, health can be an important driving force in food choices, and it is known that as individuals’ health changes, their willingness to think about their health and the framing of their food choices can also change. However, she added, she knows many clinical dietitians who wish effecting change in
food choices were as simple as telling a patient, “You have this disease and you need to make this change in your diet.” “The reality is far different and more difficult to understand and influence,” she stated.

Rather than health, Brannon continued, taste is often the primary force behind food choices. Even when dining with fellow nutritionists, she may hear them say, almost with a guilty chuckle, such things as, “Well, I know I shouldn’t eat this, but I really like the way it tastes.” That is the reality of how people choose their foods, she asserted, and while nutrigenomics may change how people frame their choices and influence how they prioritize health, taste will remain an important factor.

Another issue Brannon believes will need to be addressed is that behavior change is neither easy nor fully understood. Nor are professionals necessarily as effective as they would like to be in facilitating behavior change in their clients and customers.

Finally, Brannon observed, individual consumers face a barrage of conflicting information about the risks of disease and diet and what to do about them both, and now they are faced with conflicting information about nutrigenomics as well. She stressed the importance of remembering that consumers want simplicity, clarity, and direction. In sum, she said, “As we move forward in nutrigenomics and the future of nutrition and diet advice, we are going to need to keep in mind what consumers are going to want.”

**Integrating Population-Based and Personalized Dietary Guidance**

Brannon next reflected on the many discussions related to nutrigenomics that pose guidance as either population-based or personalized for the individual, observing that the world is not that simple or clear cut. She argued that population-based and personalized dietary guidance will need to be integrated.

Brannon commented on the fact that 43 nutrients need to be supplied in the diet and that these nutrients exist in variable amounts in different foods. For example, she elaborated, the reason there is more protein in MyPlate than is actually required in the DRI is that some food groups rich in protein are rich in micronutrients, such as riboflavin, that are not abundant in the food supply. Thus, she explained, achieving a personalized dietary pattern meeting the needs for all of these nutrients would involve modeling a very complex set of multifactorial, interactive issues while also considering other bioactive food components. In sum, she said, much will have to be learned about nutrigenomics and its complexities before it can be applied as a sole approach.
Nutrigenomics and the Future of Nutrition: Complexities and Opportunities

In closing, Brannon presented an outline for the remainder of the workshop. Session 1 would focus on the interrelationships among diet, genomics, and health or disease prevention. Session 2 would focus on ways of applying nutrigenomics to diets tailored to individuals. Session 3 would turn to policy and ethical implications, with a close look at the nature and strength of the evidence—both what it needs to be and what it is—in terms of consumer perspective and behavior. Lastly, Session 4 would conclude with a panel discussion on the opportunities for nutrigenomics and the future of nutrition.

ORGANIZATION OF THIS PROCEEDINGS

The organization of this Proceedings of a Workshop parallels that of the workshop (see Appendix A for the workshop agenda). Chapter 2 summarizes the first portion of session 1 on Nutrigenomics and Chronic Disease Endpoints, which included two presentations. Chapter 3 summarizes the remainder of session 1 on Personalized Nutrition in the Real World. Chapter 4 turns to session 2 on Nutrigenomics Applications: Dietary Guidance and Food Product Development. Chapter 5 describes the presentations of session 3 on Nutrigenomics: Regulatory, Ethical, and Science Policy Considerations. Finally, Chapter 6 summarizes session 4, the panel discussion on Rethinking the Relationship Between Diet and Health: Can Nutrigenomics Help?
In session 1, moderated by Naomi Fukagawa, U.S. Department of Agriculture, speakers discussed the interrelationships among diet, genomics, and health or disease prevention. This chapter summarizes the first portion of the session, which included presentations by José Ordovás, Tufts University, and Douglas Wallace, Perelman Medical School, University of Pennsylvania. (The remainder of the session is summarized in Chapter 3.) Highlights from the presentations of Ordovás and Wallace are provided in Box 2-1.

**GENOTYPES AND DISEASE RISK: WHAT IS CURRENTLY KNOWN ABOUT NUTRITION AND EPIGENETICS?**

The genome contains more than 3 billion base pairs, Ordovás observed, in contrast to the epigenome’s 30 million CpG dinucleotides\(^1\) in various states of methylation. Although the smaller size of the epigenome may make it appear easier to work with than the genome, he stated that it in fact poses a greater challenge. According to Ordovás, this is the case because unlike single nucleotide polymorphisms (SNPs), which either do or do not exist across all cells in an organism, the epigenome changes over time and across organs and cell types. “So we have something much more difficult to deal

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\(^1\) CpG is a coupling of a cytosine and guanine nucleotide in linear sequence; the cytosines in CpG dinucleotides can be methylated, unmethylated, or hemimethylated, with methylation status affecting gene expression.
BOX 2-1
Overview of Points Presented by Individual Speakers*

- The root of personalized therapies is newborn screening. Each year in the United States, for example, more than 1,000 babies are born with congenital hypothyroidism (CH), a monogenic disease whose treatment requires specific foods. (Ordovás)
- A less extreme example than CH is what scientists have been learning about APOA2. Several replicated studies have demonstrated that, under low saturated fat conditions, APOA2 genotype does not matter. But when consuming a diet high in saturated fat, which stresses the physiology, individuals with the CC genotype gain more weight relative to those with either the CT or TT genotype. (Ordovás)
- In addition to what scientists have learned about the genome in relation to nutrition, evidence that in humans, nutrition-related epigenetic changes can influence adult-onset diseases is beginning to emerge. (Ordovás)
- The basic assumptions made by the scientific community in studying disease need to be reconsidered. Instead of focusing only on nuclear DNA and inheritance, it is important to think about mitochondrial DNA and inheritance as well. (Wallace)
- Because they are maternally inherited, the different components of the mitochondrial “wiring diagram” have co-evolved and have remained tightly coupled over evolutionary time, making energy production more efficient than it would otherwise be. (Wallace)
- However, mitochondria are constantly replicating, and as they do so, mutations accumulate, the “wiring” loosens, and energy output decreases. Results of several studies suggest a central role for mitochondrial mutations and bioenergetic dysfunction in human disease. (Wallace)

* This list is the rapporteur’s summary of the main points made by individual speakers (noted in parentheses). The statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they are not intended to reflect a consensus among workshop participants.

with in terms of using the epigenome as part of this task of nutrigenomics, or nutrigenetics,” he said.

Moreover, Ordovás continued, scientists have studied the genome more than they have the epigenome. The SNP database\(^2\) now contains more than 300 million of what he called “needles in this haystack.” And there has been enough research in this area, he added, to know that the genome can

\(^2\) The SNP database (dbSNP) is a public domain archive of SNP and other small-scale genetic variations, not just in humans but in all species. See https://www.ncbi.nlm.nih.gov/snp (accessed February 20, 2018).
indicate what people can eat, as well as what people want to eat. But there has also been enough research to know the complexity of the road ahead, he cautioned. Thus, to provide some context for his discussion of the epigenome in relation to nutrition, he began by speaking briefly of the genome in relation to nutrition.

**Nutrition and the Genome**

The root of personalized medicine and nutrition, Ordovás said, is newborn screening, which he considers the simplest example of genomic screening for specific personalized treatments. In the United States, he reported, about 12,000 of the 4.2 million babies born each year are born with a monogenic disease—a disease that if not detected in time, usually at birth, can mean death or a life with severe disabilities. One of the most common such diseases is congenital hypothyroidism (CH), which is detected in more than 1,000 infants annually in the United States. According to Ordovás, the approximate cost of screening for CH is $20 million, compared with $400 million in benefits (i.e., later costs avoided by having diagnosed and treated the disease).3 “So the benefit [of genetic screening] is obvious—it’s 20 times the cost,” he said. Regardless of the economic costs and benefits, he added, “what we know is that, based on genotype, individuals need to receive specific therapies and either can eat or cannot eat certain foods.”

Ordovás acknowledged that CH is an extreme case. As a broader example of how the genome and health influence one another, he pointed to past positive selection as a significant driver of nutrition-related genetic variation. He cited the lactase persistent gene as the classic example of this phenomenon, with different ethnic groups having more or less prevalence of the gene depending on past access to dairy products. The same is true of the fat-related *APOE* gene, he noted, with respect to its prevalence among groups with a hunter-gatherer versus agricultural history, as well as of alcohol-related *ADH1B*. All three examples, he observed, illustrate that what individuals from different cultures eat is determined partly by how their genomes have been responding to selective pressures in their nutritional environments.

Ordovás went on to explain that past exposure to different nutrition-related environments has impacted genetic variation in taste and food preference as well (e.g., Chmurzynska and Mlodzike, 2017). To illustrate

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3 Another one of these diseases with an important nutritional implication, Ordovás noted, is phenylketonuria (PKU), which is detected in about 400 infants born each year in the United States. The approximate cost of screening per child with PKU detected is $2,500, and the cost of dietary treatment for 10 years is approximately $8,000. In comparison, the expected cost of institutionalization over a 30-year period is estimated to be $162,000 (Grosse, 2015).
this point, he described what scientists have been learning about APOA2, a gene that is expressed primarily in the liver and that produces APOA2, a protein present in high-density lipoprotein (HDL). He noted that, although scientists have known about this protein and its abundance in plasma for some 40 years, only when the genetic work began did they start to see some of what it actually does. He pointed to one of the initial findings from the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) nutri-pharmacogenomic study, which enrolled more than 1,000 people. The researchers found that APOA2 has a common polymorphism in the promoter region of the gene (APOA2 m265T>C), and individuals who are homozygous for the C allele, which is the less common of the two alleles, eat more and weigh more relative to individuals with the TT and TC genotypes (Corella et al., 2007). He described the polymorphism as “an example of a genetic variant that predisposes you to obesity because it drives you to eat more of certain foods.”

In later GOLDN and other studies (Correla et al., 2009, 2011; Delgado et al., 2007; Smith et al., 2012), Ordovás and his team replicated a gene–diet interaction between the APOA2 polymorphism and saturated fat and found that under low saturated fat conditions, one’s genotype does not matter; body mass index (BMI) is the same. It is only when the physiology, or genome, is stressed by a diet high in saturated fat that individuals with the CC genotype have higher BMIs, whereas for individuals with the TT or TC genotype, the amount of saturated fat in the diet does not matter for their BMI. In the past, Ordovás added, lack of validation, or replication, has been a problem with gene–environment interaction studies. The fact that this same pattern has been seen in six independent populations and five ethnicities across the world indicates, he said, that “this is a polymorphism that may have a significant impact in terms of personalized recommendations.” However, he again cautioned that this is only one piece of the complex nutrigenomics puzzle, which he predicted probably will not be completed any time soon. “But at least we have a better idea of where the pieces fit together,” he said.

Epigenetics in Nutrition Research

Ordovás reiterated that, compared with genetics, epigenetics is more difficult to study with respect to its importance in nutrition because it is what he described as a “moving target,” with different organs, different tissues, and different cells having different epigenetic patterns. Moreover, he explained, because the study of epigenetics is restricted primarily to those cells researchers can access, much of the progress in understanding epigenetics in relation to nutrition has been made in experimental animal models. That said, he added, evidence in humans is beginning to emerge.
As an example of this evidence, Ordovás highlighted what is being learned about the famous Dutch Hunger Winter of 1944–1945 in the Netherlands, when people had to survive on rations as low as 400–800 calories per day. An estimated 22,000 people died. But those deaths were not the end of the story, Ordovás noted. He explained that investigators studied individuals who were still in the fetal state during that time and found, for example, that their birthweight had been different relative to those not exposed to the Hunger Winter. Moreover, individuals exposed to the famine, particularly those exposed during middle and late gestation, had impaired glucose tolerance even at age 60 years (e.g., de Rooij et al., 2006a, b; Ravelli et al., 1998). According to Ordovás, researchers have found other differences as well, such as problems with obesity and neurological disorders among those exposed to the Hunger Winter during fetal development, and highly significant differences in the epigenetic profiles of individuals who were and were not born during the Hunger Winter (e.g., Tobi et al., 2014).

Ordovás then turned from the Dutch Hunger Winter, a set point in history, to parts of the world that experience yearly seasonalities, reporting that investigators have found similar changes in the DNA methylation patterns depending on the season of conception. In The Gambia, for example, there are two seasons—dry and wet. Waterland and colleagues (2010) found that individuals born during the wet, or harvest, season have different DNA methylation patterns from those born during the dry, or hungry, season. Ordovás remarked that these differences may play a significant role in survival and disease.

As another example of nutrition-related epigenetic differences, Ordovás cited whole fruits versus fruit juices. He observed that whole fruits are typically presented as being rich in fiber and low in energy and containing intact vitamins and minerals, whereas fruit juices are portrayed as being deficient in fiber and high in energy because of added sugar, and lacking in most vitamins and minerals found in whole fruits (although in some cases, he noted, the lost vitamins and minerals are replenished). But, he asked, how true are these characterizations? Using data from the Framingham study, Nicodemus-Johnson and Sinnott (2017) examined the epigenomes of individuals who consumed whole fruits and those who consumed fruit juices and found significant differences in the epigenetic signatures associated with pathways involved in the immune system. More specifically, the whole fruit–specific epigenetic signature was enriched for adaptive immune system genes but not innate immune system genes, and for genes involved in telomere maintenance and other aging-related pathways. In contrast, the juice-specific epigenetic signature was enriched for both adaptive and immune system genes, so for genes involved in proinflammatory pathways. Based on these findings, Ordovás said, “it’s better to eat fruits, thanks to the epigenome.”
The Integration of Genetics and Epigenetics in Nutrition Research

Ordovás observed that methylation, on which he had been focusing during his presentation to this point, is only a small fraction of the complex epigenome. That said, he continued, methylation is dependent on two factors within the context of nutrition: (1) what one eats and (2) what one’s genome is. Regarding the latter, he explained that any time a gene variant removes either the C or the G from a CpG site, that site will no longer be methylated. Conversely, if a variant introduces a new CpG site, methylation will emerge in a place where it did not exist before. So it is not only the environment, or diet, that affects methylation, Ordovás stated, but also the genome itself (Zhi et al., 2013).

To illustrate, Ordovás described how \textit{ABCA1}, which is involved with HDL metabolism, is a common genetic variant that sits atop a differentially methylated 5′ CpG region of the genome. By sitting there, it can not only change the methylation of that CpG but also affect the methylation of all the other neighboring CpGs. Ordovás described the results of a meta-analysis of methylation data from more than 10,000 individuals from different cohorts showing that a change in EPA\textsuperscript{4} in the diet resulted in either decreased methylation and increased HDL cholesterol or increased methylation and decreased HDL, depending on the \textit{ABCA1} genotype (Ma et al., 2016). More specifically, with a 1 percent increase in EPA, individuals with the CC genotype experienced decreased methylation, increased gene expression, and increased HDL cholesterol, in contrast to the increased methylation, reduced gene expression, and lowered HDL cholesterol experienced by individuals with the GG genotype under the same conditions. (Ordovás noted that decreased methylation is usually associated with increased gene expression.) Thus, he said, this is a case in which both genetics and epigenetics need to be considered. Otherwise, he stated, a general recommendation to increase one’s EPA levels would have a positive effect in some individuals with respect to HDL cholesterol but a negative effect in others.

As another example of a nutrition-related gene–epigenetic interaction, Ordovás cited perilipin, a protein that surrounds lipid droplets in adipocytes. Many studies have shown, he reported, that variation in the perilipin genes affects obesity risk. His research team found that one of these genes, \textit{PERILIPIN4} (\textit{PLIN4}), is not in the promoter region of the gene, as are the other polymorphisms, but in the 3′ region of the gene (Richardson et al., 2011). It turns out, he explained, that microRNAs (miRNAs), which are another type of epigenetic phenomenon, can bind to the 3′ region and decrease expression. This particular polymorphism is at a site where there normally is no bound miRNA, but when a G is

\textsuperscript{4} EPA is eicosapentaenoic acid, an omega-3 fatty acid.
replaced with an A, miRNA suddenly binds and decreases the expression of \textit{PLIN4}. The question, Ordovás suggested, is whether something can be done about this. In fact, his team has observed that when individuals with the less common allele—that is, with bound miRNA at that site—are placed on a diet rich in omega-3s, their phenotype reverts from that of the less common allele to that of the more common allele. So again, he said, this is an example of gene–diet interaction that works through a combination of genomics and epigenomics. He noted that there are thousands of miRNAs, many of which scientists know very little about, although they are beginning to make progress, especially in terms of understanding miRNAs in relation to cancer.

\textbf{The Future}

In closing, Ordovás remarked that the microbiome plays a role in nutrition and that personalized nutrition will require not just combining genomics and epigenomics but also considering the microbiome, as well as the metabolome. “I don’t know that we’ll ever get to perfect,” he observed, meaning perfect personalized nutrition. However, quoting Voltaire,\textsuperscript{5} who in turn borrowed from an old Italian proverb, Ordovás said, “perfection is the enemy of good.” There is enough evidence now, in his opinion, to begin putting the pieces of the puzzle together and to control some of what he described as the “snake oil” being sold by some consumer ventures.

\textbf{MITOCHONDRIAL GENETICS AND DISEASE RISK: EXPLORING CURRENT EVIDENCE}

“Why can’t we understand or cure the common metabolic and degenerative diseases?” Wallace asked, noting that there is an enormous number of such diseases, including neurodegenerative and neuropsychiatric disorders (e.g., autism, Alzheimer’s disease), heart and muscle diseases (e.g., cardiomyopathy, chronic fatigue), visceral diseases (e.g., renal and hepatic diseases), metabolic diseases (e.g., diabetes, obesity, cardiovascular disease), cancer, and aging. He suspects that perhaps the problem is not the effort expended, given the trillions of dollars that have been spent trying to understand human disease, but the basic assumptions the scientific community is making in addressing the problem.

According to Wallace, the first basic assumption upon which Western medicine is premised is that disease is organ based, an assumption that goes back to Andreas Vesalius.\textsuperscript{6} For example, if one has a headache, one is

\textsuperscript{5} Voltaire was an 18th-century writer, historian, and philosopher.

\textsuperscript{6} Vesalius was a 16th-century anatomist and physician.
referred to a neurologist because the assumption is that a symptom in the head means there is something wrong with the head. “I call that the anatomical paradigm of disease,” Wallace said. The second basic assumption, he continued, goes back to Gregor Mendel: if a trait is inherited according to “the laws of Mendel,” then it is genetic, and if it is not inherited, then it must be environmental. He remarked that these ideas are the framework with which all medical students are taught and all basic scientists design their experiments.

According to Wallace, however, these ideas may not be sufficient. While it is true that anatomy is encoded by Mendelian genes and that there are specific disease mutations that gave rise to the newborn screening program, he observed, this knowledge does not appear to be helping with the common complex diseases. “It is not enough to have an anatomy,” he said. “One has to be animated.” He mentioned Newton’s work and the fact that mass does not change unless it is acted upon by energy. “Therefore,” he asserted, “if we are going to think about being alive, we have to think not only about anatomy, but also energy.” Furthermore, he argued, one must think not only about the information for anatomy, but also the information for energy, and when one begins to think this way, medicine becomes not just about anatomy but also about energetics. He believes bioenergetic dysfunction lies at the nexus of the genetic and environmental “causes” of the common complex diseases.

The Dichotomy Between Anatomy and Energy

Wallace then turned to how the dichotomy between anatomy and energy arose from the origin of the very cells that make up the human body, that is, the eukaryotic cells, which in turn arose from the symbiosis between Archaebacteria and the oxidative Alphaproteobacteria. It was the Archaebacteria that ultimately gave rise to the nuclear cytosol and the Alphaproteobacteria that gave rise to the mitochondria.

These different bacteria, Wallace continued, each had—and still have—their own information storage and retrieval systems. The nucleus has DNA, which is transcribed into RNA, which in turn is translated in the cytosolic ribosomes, producing about 20,000 to 25,000 proteins. An estimated 1,000 to 2,000 of these proteins make up the anatomy of the mitochondria. But the mitochondria have retained their own DNA as well, Wallace emphasized. Their DNA is replicated and transcribed in the mitochondria, and the messenger RNA is translated on mitochondria ribosomes in a bacteria-like way. Not only is mitochondrial translation initiated by N-formyl methionine, just as bacterial proteins are, but mitochondria ribosomes also are sensitive to chloramphenicol and aminoglycosides, just as bacterial ribosomes are.
Over evolutionary time, Wallace explained, the two originally co-equal genomes began to specialize, with the nuclear genome specializing in creating the anatomy not only of the cell but also of the mitochondria, and the mitochondrial genome specializing in energy and developing what he described as “the wiring diagram for the power plant.” More specifically, the mitochondrial DNA evolved to code for critical proteins involved in the energy process called oxidative phosphorylation, including 7 of the 45 respiratory complex I proteins, 1 of the 11 complex III proteins, 3 of the 13 complex IV proteins, and 2 of the 15 complex V proteins. Wallace explained that each of these complexes is a system by which the cell takes the nutrients in the diet and the oxygen that is being breathed and converts them into potential energy. That energy, he said, “you then use for everything that you want to do.”

With respect to how these complexes are involved in oxidative phosphorylation, Wallace explained that glucose goes through glycolysis to produce pyruvate, which can then be either reduced to produce lactate or amino-grouped to produce alanine. Alternatively, the pyruvate can be transported into the mitochondria through the pyruvate transporter, where it is converted by pyruvate dehydrogenase to make acetyl coA, driving the tricarboxylic acid (TCA) cycle. The purpose of the TCA cycle, Wallace continued, is to strip hydrogens off hydrocarbons and put them on the carrier nicotinamide adenine dinucleotide (NAD), creating NADH. The two hydrogens of NADH are then burned by what is called the electron transport chain, which is made up of complexes I, III, and IV, as well as coenzyme Q and cytochrome C. As they flow down this chain, the two electrons (of the two hydrogens) react with oxygen to produce water. The energy that is released is not just dissipated, Wallace clarified, but is used to create what is essentially a capacitor. As the electrons flow through the complexes (I, III, and IV), they pump protons from inside the mitochondrial matrix, across the mitochondrial inner membrane, and into the intermembrane space, thereby creating a positive, acid exterior and a negative, alkaline interior. This membrane potential can be used for many functions, Wallace added, one of which is to make adenosine triphosphate (ATP): protons flow through a proton channel in complex V (i.e., ATP synthase) to condense adenosine diphosphate (ADP) and phosphate and make ATP. This coupling of oxidation and phosphorylation is oxidative phosphorylation. The membrane potential can also be used in other ways, Wallace noted—for example, to regulate a positive cation, such as calcium, by electrophoresing into the negatively charged mitochondrial matrix.

“So sitting in your chair right now,” Wallace said, there are 100 trillion cells, each cell with about 1,000 mitochondrial bacteria—about 30 percent of one’s body weight—and each mitochondrion having a potential across its membrane of about 0.2 volts. “So the total energetics in your body right
now is the equivalent of a lightning bolt,” he said, “and that is the energy for everything that you do every day of your life . . . so this flow of energy is absolutely critical.”

However, like any furnace, Wallace continued, mitochondria also make smoke—the reactive oxidant species that form when not fully oxidized electrons bind with oxygen (O₂) to produce hydrogen peroxide. If the hydrogen peroxide is not reduced to water (i.e., by nicotinamide nucleoside transhydrogenase), then another electron, provided by a transition metal, will bind with it to produce a hydroxyl radical, a reactive oxygen species and a potent damaging agent. Wallace noted that some people take vitamin C, vitamin E, beta carotene, or coenzyme Q (CoQ) to prevent this from happening.

The mitochondria also have a self-destruct system (i.e., apoptosis). According to Wallace, there is active debate around what the structure of this system is, but its job normally is to maintain a closed door. He explained that when the membrane potential becomes low, high-energy phosphates decline, oxidative stress becomes excessive, or calcium load occurs, the self-destruct system senses these changes and ultimately pops into an open channel that short-circuits the membrane potential. As a result, fluids flow in, the inner membrane swells, and pro-apoptotic proteins flow out and degrade the cell from the inside out. Without enough energy, this self-destruct system fails. If bacteria are released into the bloodstream with all of their bacterial antigens, the result will be inflammation, which is believed to accompany all the metabolic and degenerative diseases.

In summary, Wallace said, the mitochondria generate most of the body’s energy; regulate the redox state of the cells; make reactive oxygen species, which are signaling molecules but at high levels are toxic; regulate calcium; regulate apoptosis; and generate all the intermediates for regulating the epigenome (e.g., ATP, acetyl CoA).

Wallace added that different tissues have different energetic demands. For example, the brain is about 3 percent of body weight but uses about 20 percent of all mitochondrial energy. So a 10 percent reduction in mitochondrial energy, Wallace said, “is going to give you a very bad headache.” The headache occurs not because the brain has altered, he clarified, but because there is a systemic defect, and the brain is specifically affected. The hierarchy of energetics, he explained, is brain, heart, muscle, renal, endocrine, and liver, which are the organs affected in all the common, complex diseases.

**Mitochondrial Inheritance**

The 13 proteins retained by the mitochondria that make up what Wallace described as the “electron and proton wires of the wiring diagram” must co-evolve, he argued, because if any one were to become leaky for
protons, it would “short the capacitor.” This is the case, he elaborated, because the wiring diagram is an integrated circuit, with all of the enzymes in the system relying on the same substrate, that is, the membrane potential. But how could such co-evolution occur, he asked, since nuclear genes undergo recombination? Thus, for example, if there were a polymorphism in complex I but not in complexes III and IV, recombination would be mixing and matching coupled and uncoupled variation.

To explain coupling, Wallace described someone who burns the least number of calories for the maximum amount of ATP as someone who is very good at taking in calories, burning them, making that membrane potential, and then converting the membrane potential to ATP. In other words, this person’s coupling system is tight. Because a calorie is a unit of heat, Wallace continued, that person also generates less heat. But, he added, someone who is less efficient at pumping protons out or converting protons into ATP must burn more calories for the same amount of ATP, plus that person generates more heat. In other words, this person’s coupling system is loose. “Your mitochondria is regulating your thermal and your energy balance based on the coupling efficiency,” Wallace said.

The wiring diagram of the mitochondria is inherited only from women, Wallace continued, thus ensuring that there will never be recombination. That is, mitochondrial DNA is transmitted from a mother to all of her children and from her daughters to the daughters’ children, and so on, while when a male’s mitochondria enter the egg, they are perceived as foreign and selectively destroyed.

Mitochondrial Mutations and Heteroplasmy

Wallace went on to explain that mitochondria are constantly replicating inside the cell. They are also constantly being eaten by mycophagy, and thus are in what he described as a colony in steady state. Nonetheless, as they replicate, mutations accumulate. Wallace observed that, because mitochondria have very high mutation rates—one or two orders of magnitude greater than that of nuclear DNA—they are characterized by a tremendous amount of genetic variation. Moreover, he added, as mutations accumulate, they create mixed populations of mutant and normal mitochondria within single cells. If one of these mixed, so-called heteroplasmic cells were to divide down the middle, both new cells would have some mutant and some normal mitochondria, so they would both be heteroplasmic. But a cell could also divide such that one new cell would contain only normal mitochondria, the other containing twice as many mutant mitochondria. Thus, Wallace said, “the tissues in our bodies are a mosaic of different mitochondrial genotypes, with different tissues having different percentages of mutant and normal mitochondrial DNAs.” And as the number of mutant mitochondrial
DNAs increases, he noted, energy output declines, eventually falling below the minimum energy for that organ and reaching what he characterized as the equivalent of an energetic disease.

Three Types of Mitochondrial Mutations

Wallace next described three categories of mitochondrial mutations. First are mutations that arise along the maternal lineage and give rise to maternally inherited diseases. For example, if an individual inherits a mutation in the \textit{ND4} gene at nucleotide position 11778, he or she will be fine throughout midlife, but then will suddenly go blind in one eye and then in the other because of what is known as Leber’s hereditary optic neuropathy. A mutation in the \textit{ND6} gene at 14484 causes the same Leber’s blindness, and a mutation in \textit{ND6} at 14459 causes a more severe Leber’s blindness when heteroplasmic and generalized dystonia when homoplasmic (i.e., pure mutant). As another example, Wallace cited a mutation in the \textit{ATPase6} gene at 8993, which causes retinitis pigmentosa at 70 percent mutant, olivopontocerebellar atrophy at 85 percent mutant, and death as an infant with Leigh’s syndrome at 90 percent mutant.

According to Wallace, there are also several (maternally) inherited protein synthesis mutations, including a mutation in the tRNA leucine gene at 3243, which causes diabetes at 20 percent mutant, cardiovascular disease at 50 percent, and lethality in childhood at 100 percent. A mutation in the tRNA glutamine gene accounts for about 3–5 percent of late-onset Alzheimer’s and Parkinson’s disease. And a mutation in the tRNA lysine gene causes myoclonic epilepsy. Added to these are many kinds of cancer mutations.

Wallace then described a second class of mitochondrial mutations—the ancient polymorphisms. For example, one variant in the \textit{ND1} gene is found in three-quarters of sub-Saharan Africans (“macrohaplogroup L”); another variant (H) is found in half of Europeans; and four variants (A, B, C, and D) arose in central Asia and then crossed the Bering land bridge, allowing people to colonize the Americas. “We believe these are markers for mitochondrial lineages that adapted human energy metabolism to live in different environments,” Wallace said.

Finally, Wallace explained, as people age, they accumulate somatic mutations. This, he said, is “the aging clock.”

The Mitochondrial Etiology of Complex Diseases: An Energetic Approach to Medicine

Wallace reiterated, “Once we begin to think energetically, then all the common diseases have the same etiology: a bioenergetic defect due to
oxidative phosphorylation.” Nuclear mutations can affect this process, he noted, as can changes in the epigenome, as well as both ancient adaptive polymorphisms and recent deleterious mutations. Finally, he added, the calories and types of nutrients one ingests, or how one exercises and uses those nutrients, as well as whether one smokes or is exposed to other toxins, all impinge on energetics.

If energetics is affected, Wallace continued, then mitochondrial DNA damage accumulates over time, which leads to age-related decline and the delayed onset and progressive course of all the common diseases. Additionally, he explained, as the furnace is impaired, substrates (glucose, fatty acids, and cholesterol) build up, and that is what creates metabolic syndrome. When apoptosis fails, he noted, bacteria are released into the bloodstream, initiating all of the inflammatory processes that accompany the complex diseases. And finally, turning to cancer, he characterized it as “all about adjusting energy based on nutrients and oxygen. In fact, a bioenergetic way of looking at the disease takes us away from the anatomical approach and into an energetic approach to medicine.”

Studies of Mitochondrial Mutations

Wallace went on to describe results from studies of mitochondrial mutations, beginning with work he and his team did in the 1980s on a family in which the mother had lactic acidosis and growth retardation, and many of her children had lactic acidosis, growth retardation, progressive dementia, stroke-like episodes, hypertrophic cardiomyopathy, and cardiac conduction defects. Additionally, mitochondrial oxidative fibers degenerated in the muscle, although the glycolate muscle fibers were fine. All of these individuals had the same mutation in the tRNA dileucine gene. However, Wallace noted, different percentages of heteroplasmy in this same mutation can cause different phenotypes. Thus, he explained, individuals with greater than about 70 percent of the mutant mitochondria have myopathy, cardiomyopathy, and stroke-like episodes; individuals with 10–30 percent have autism and type 1 or type 2 diabetes; and individuals with 100 percent die as infants from Leigh syndrome.

Wallace and his team wanted to know whether a change in heteroplasmy in a cell could affect these different phenotypes, so starting with normal cells, or cells with zero percent heteroplasmy, they made what are known as cytoplasmic hybrids, or cybrids—cells with the same nucleus but different percentages of mutant mitochondrial DNA. They characterized the cybrids physiologically, then performed RNA sequencing and examined all the transcription factors that were regulated in the different cell lines. The patterns they observed indicated to Wallace that phenotype (e.g., the diabetes and autism associated with 10–30 percent heteroplasmy) is in fact
determined by the mitochondrial signaling to the nucleus, which in turn determines gene expression and phenotype. “So, in fact,” he said, “the mitochondria is determining what the environmental challenges are and telling the nucleus how to respond, and that is telling the physician what he or she will see in the clinic.”

Wallace described another pedigree, which had a mutation in the ND6 gene—one of the complex I genes. A woman had 50 percent mutant mitochondria in her white blood cells, and she had optic atrophy and cerebellar ataxia (Malfatti et al., 2007). Her sister had 5 percent mutant mitochondria in her white blood cells and was perfectly normal, although every one of the sister’s children was 100 percent mutant and died. Wallace interpreted this case as an indication of the rapidity of segregation that occurs along the germline and an explanation for why this class of disease was never understood with a Mendelian conceptual framework. This particular mutation, he noted, changes proline at codon 25 to a leucine (P25L).

Wallace described how he and his team took cultured mouse cells, mutagenized the mitochondrial DNA, then sequenced all the mutants that were respiratory deficient. They found an array of different mitochondrial DNA mutations, one of which was exactly the same mutation as that observed in the human phenotype described above. Another was a cytochrome oxidase mutation that changes valine at codon 421 to alanine (V421A). The researchers then created pluripotent cytoplasmic hybrids by, first, taking a cell with mutant mitochondrial DNA, removing its nuclei, and keeping the cytoplasmic fragment with the mutations and, second, making a female embryonic stem cell, killing its mitochondria, and then using cell fusion to substitute the mutant mitochondria (from the cytoplasmic fragment) for the mitochondria. Next, they put these hybrids into blastocysts and then into a foster mother to create chimeric females. They then bred the females for transmission of the dominant agouti locus through the oocytes to pick up the mutant mitochondrial DNA.

According to Wallace, the researchers found that mice with the P25L mutation had increased axonal swelling, demyelination, and abnormal mitochondria. But what he found interesting was that when they looked biochemically at the synaptosomes of the brains of these mice, they saw that the problem was not with ATP—the ATP in the mice with and without the mutation was the same. They observed a 30 percent reduction in respiration, but, Wallace noted, if energy demand is increased, respiration will rise to near normal. Rather than an effect on ATP, he explained, the mice with the mutation were experiencing reactive oxygen species production “through the roof.” Wallace characterized this as a “disease of oxidative stress,” which kills the neurons.

Wallace added that mice with the cytochrome oxidase mutation had a 50 percent reduction in cytochrome oxidase in all of their tissues. Addi-
tionally, they had what he described as the “ragged red fibers” that were seen in the original human family with abnormal mitochondria, progressive cardiomyopathy with fibrosis, and type 2 diabetes with aging. So again, he pointed out, the mice showed the same phenotypes as those seen in humans with a single-point mutation.

The Effect of Heteroplasmy on Phenotype

Among all of these murine studies, Wallace cited as most interesting that in which the researchers took two perfectly normal mitochondrial DNAs, 129 and NZB, mixed them together, and then segregated the heteroplasmic animals with this same nucleus back into homoplasy and heteroplasmy groups. They then examined activity in the mice, which are normally active at night but not during the day. They found that both the 129 and NZB animals were active at night but not during the day, while the heteroplasmic animals “just sat there,” Wallace said. He characterized them as depressed.

Wallace went on to explain that if the researchers subjected the mice to a color-cued task—providing them with an open field with differently colored holes around the outside of the field, one of which contained a black box where a mouse could hide—the homoplasmic animals learned over successive days where the black box was. Mice do not like to be in open, exposed areas, he noted. The heteroplasmic mice learned where the black box was as well, he reported, but it took them longer. Moreover, after four trials, when the animals were removed from the field for 2 days and then returned, the homoplasmic mice immediately ran and jumped into the black box, having remembered where it was, but the heteroplasmic mice did not, having, Wallace noted, learned nothing because they had no long-term memory. “So simply converting a homoplasmic cell to a heteroplasmic cell, of perfectly normal mitochondrial DNAs,” he said, “severely altered the neuropsychiatric pattern of those animals.”

Geographic Constraints of Human Mitochondrial DNA

Wallace pointed out that because mitochondrial DNA can be transmitted only from mother to daughter, the only way it can change is by sequential mutations. So, he explained, if he were to sequence the mitochondrial DNA of any two individuals, the number of changes would be equivalent to the generations since those two individuals shared a common mother. Thus, he said, by sequencing the mitochondrial DNA from people around the world, one can reconstruct their genetic relationships and migration patterns.

According to Wallace, in humans, mitochondrial DNA arose about 200,000 years ago in sub-Saharan Africa. Today, he explained, the Khoisan
people in that region have the most ancient mitochondrial DNA lineage. Two lineages that arose in Ethiopia—M and N—left Africa and colonized the rest of the world. N went to the temperate zone and gave rise to a number of European lineages (I, J, T, U, K, W, and Z), and also went to the temperate zone of Asia, whereas M stayed in the tropics, south to Australia, and later acquired new mutations to live in the temperate zone of Asia as well. Lineages C and D from M and lineage A from N crossed the Bering land bridge, from Chukotka, and colonized the Americas.

For Wallace, this geographic pattern is astonishing because nuclear polymorphisms, in contrast, are found panmictically (occurring through random mating) throughout all populations. The fact that mitochondrial DNA variation is highly geographically constrained based on the geographic origin of people’s ancestors, he explained, is why 23andMe is able to analyze customers’ mitochondrial DNA and provide them with information about their relations in other parts of the world.

Wallace’s explanation for why geography constrains mitochondrial variation is that people’s human ancestors evolved different adaptive mutations that allowed them to live in different environments and cope with different problems. In Africa, for example, he imagines the need to run away from lions, which would have required a great deal of ATP and thus a tightly coupled mitochondrial system. In the north, by contrast, the problem was not predation, he said, but freezing temperatures. Individuals there accumulated mutations that decreased the efficiency of the mitochondria, so that they were eating more calories for the same amount of ATP and generating more heat. According to Wallace, this is why people in the north still consume a high-fat marine mammal diet. “That’s their niche,” he said.

As an example of adaptive mitochondrial variation in humans, Wallace mentioned lineage J, which he described as a tiny part of the European lineage founded by two cytochrome B mutations, 15257 and 14798. The latter mutation is conserved in all mesosomic animals, but is polymorphic otherwise. In contrast, 15257 is conserved across evolution, yet Wallace estimated that 5 percent of the workshop participants had a variant of this gene. “That’s unheard of,” he said. “That is antithetical to what we think about evolutionary biology. If something is conserved across evolution, it should be homogeneous within a population. Not so for mitochondrial variation.” He characterized mitochondrial variation as “our adaptive engine. It allows us to adapt our energy to environmental changes.”

Wallace went on to talk about an A-to-G mutation that arose 10,000 years ago in Europe in the tRNA glutamine gene (Hutchin and Cortopassi, 1995). This mutation is found in only 0.4 percent of modern Europeans, but in about 3 percent of individuals with Alzheimer’s disease, 5 percent of those with Parkinson’s disease, and 7 percent of those with both diseases. Wallace noted that other mutations are much more deleterious than even
this one—for example, ND1 methionine 31 valine (M31V), which causes both Alzheimer’s and Parkinson’s diseases. He reported further that in a study of European individuals with autism, mitochondrial variation was shown to be correlated dramatically with that condition, with mitochondrial haplogroups accounting for 55 percent of the risk. He added that mitochondrial DNA variation has been associated with a range of other common neurodegenerative, neurological, metabolic, and inflammatory diseases, as well as with altitude adaptation, cancer, aging, and athletic performance.

**Nuclear–Mitochondrial DNA Interaction**

As an example of a nuclear–mitochondrial DNA interaction, Wallace described a nuclear mutation, Ant1, in a Mennonite pedigree that affects the adenine nucleotide translocator isoform-1. The mutation arose in Switzerland about 500 years ago and was carried to North America. It was originally a recessive mutation, but then heterozygous individuals married each other and gave rise to the affected homozygous mutants. What is interesting about this mutation, in Wallace’s view, is that some people with the affected mutants have very mild cardiomyopathy, while others die of fulminant, dilated cardiomyopathy. Compared with the heartbeat of cultured cardiomyocytes derived from embryonic stem cells in a healthy individual, the heartbeat in a mutant individual is highly dysrhythmic. According to Wallace, the different phenotypes are explained by the fact that people with severe cardiomyopathy have European mitochondrial lineage U, while those with mild cardiomyopathy have European mitochondrial lineage H. “So it is the mitochondrial DNA that is determining the severity of the disease,” he said, “not the nuclear mutation.”

In mice with the same mutation, Wallace continued, it has been shown that wild type mice (Ant1+/+) will continue to exercise until giving up, while mutant animals (Ant1−/−) start running but fall down because of the progressive accumulation of abnormal mitochondria. The mutant mice also have been shown to exhibit highly dysrhythmic cardiomyopathy, as opposed to the wild type. When the Ant1−/− mutation is combined with a mitochondrial COI mutation, there is no significant change in phenotype, but when it is combined with a mitochondrial ND6 mutation, mice develop severe cardiomyopathy with half the life span. Wallace interpreted this to mean, again, that mitochondrial DNA, not nuclear DNA, is determining the phenotype.

In terms of behavior, Wallace continued, when these same mice were put into a restraint to see how they would respond, the Ant1−/− mice with the mitochondrial ND6 mutation had a much stronger corticosterone response relative to the wild type mice. Thus, he noted, this same mitochondrial variant also affects brain development.
Closing Thoughts on the Mitochondrial View of Disease

Wallace closed by describing mitochondria as “the environmental sensors.” That is, when the environment changes, the epigenome changes, which in turn reconfigures the mitochondrial genotype to maintain homeostasis. But if the environmental change is too great or if there are mutations in the nuclear cytoplasmic system, Wallace explained, the mitochondria are unable to adjust, leading to energetic deficiency and disease. Based on this mitochondrial view of disease, he and his colleagues are now looking at traditional Chinese therapeutics. For 5,000 years, he said, Chinese medicine has been based on the idea of Qi (Chi), which he described as “vital force.” He speculated that eastern therapeutics may act through mitochondrial biology.
Personalized Nutrition in the Real World

Continuing the session 1 discussion, four presenters discussed applications of nutrigenomics “in the real world.” This chapter summarizes their presentations and the discussion that followed, with highlights provided in Box 3-1.

EXPLORING PERSONAL, DENSE, DYNAMIC DATA CLOUDS AND THE FUTURE OF PERSONALIZED MEDICINE

Nathan Price, Institute for Systems Biology, addressed personalized nutrition in the clinical setting. He began by emphasizing the complexity of nutrition’s health effects, as reflected in the fact that different foods have been shown to both prevent and cause cancer (Schoenfeld and Ioannidis, 2013). Given this complexity, he argued, “there is a need for personalization, a need for understanding.” He referred to Patsy Brannon’s opening presentation in session 1 and her discussion of the complex interrelationships between diet and health, particularly when one considers the molecular details of how the body processes food and how these molecular details are related to disease (see Chapter 1 for a summary of Brannon’s presentation). Additionally, he emphasized how the many different biological systems add to this complexity and the many different ways to think about it, citing Douglas Wallace’s perspective on mitochondria and their impacts as an excellent example (see Chapter 2 for a summary of Wallace’s presentation).
BOX 3-1
Overview of Points Presented by Individual Speakers*

- In contrast to the wellness industry, which has a mixed reputation because of the many non-scientifically based approaches being applied, the goal of “scientific wellness” is to provide an underpinning of rigorous science and dense, dynamic data for the study of wellness, and to predict and prevent disease before it happens. To launch scientific wellness, the 100K Wellness Project was conceived, focused on collecting a personal, dense, dynamic dataset for 100,000 individuals that can be observed over time for early warning signs of disease. (Price)
- Meanwhile, a 9-month feasibility study, the Pioneer 100 Wellness Project, has demonstrated improvements in a number of clinical markers. Along with data collection, wellness coaching was an important part of the study, reflecting the critical role of behavior change in personalized nutrition. (Price)
- Research has explained arginine deficiency syndromes, mostly in relation to sickle cell disease, an autosomal recessive inherited disease, but also trauma. Both have distinct nutritional requirements that develop because of metabolic abnormalities, and both may benefit from arginine replacement therapy. (Morris)
- Although the potential benefit of arginine therapy for sickle cell disease, as well as for trauma, has been demonstrated in both mice and humans, most of these studies are limited by methodological weaknesses. More research is needed, including the identification of subpopulations that would likely benefit the most from arginine replacement therapy. (Morris)
- Nutrigenomic studies are difficult not only because they are complex, but also because proving causation from association is especially challenging in the field of nutrition. Additionally, except for diseases caused by single gene defects, it is very difficult to isolate which components of a disease phenotype are related to nutrition. (Alpers)
- Because of these difficulties, many scientific approaches to studying links between genomics and nutritional phenotypes have relied on in vitro and in vivo animal studies. A long lag time can be expected before strong human data are available and nutrigenomics can be commercially implemented. (Alpers)
- Evidence from studies on the \textit{CYP1A2} genotype and coffee intake are “proof of concept” that a single nucleotide polymorphism (SNP) can modify the association between a dietary component and a variety of different health outcomes. (El-Sohemy)
- There are problems with the ways in which nutrigenomics is portrayed in the media and information about the field is communicated. An example is an article in which a pediatrician who was interviewed said he was unaware of evidence suggesting that people with different FTO gene variants respond differently to low-protein versus high-protein diets. Yet not only does such evidence exist, but it has been replicated. (El-Sohemy)

* This list is the rapporteur’s summary of the main points made by individual speakers (noted in parentheses). The statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they are not intended to reflect a consensus among workshop participants.
Scientific Wellness

The health care industry costs in the United States are approaching a staggering $4 trillion per year, according to Price. But it has been estimated that about 30 percent of a person’s lifetime health is attributable to genetics; about 60 percent to behavior and the environment, a large part of which is nutrition; and only about 10 percent to the health care system (Schroeder, 2007). “So there is a huge need, obviously, to focus on the 90 percent,” Price said. Yet, physicians receive only about 2 hours of training in nutrition, he observed, and the “wellness industry” has a mixed reputation, being characterized by many not very scientifically based approaches. Thus, he and his colleagues have been advocating what he called “scientific wellness.” He explained that the goals of scientific wellness are to provide a data-rich basis for rigorously quantifying wellness, to try to predict and prevent disease before it happens, and to focus on optimization of health in the individual.

To help launch this new scientific wellness industry, Price and his colleague, Leroy Hood, announced in 2014 a project called the 100K Wellness Project (Hood and Price, 2014). The project has one major goal: to collect a dataset enabling observation of enough people over time to detect all of the early warning signs for all of the major human diseases, and predict and prevent those diseases to the extent possible. The initial vision was to collect dense information on 100,000 individuals, including data on genomics, proteomics, metabolomics, the microbiome, and clinical chemistry, plus data from wearable devices.

Price explained that, to test whether he and his team could collect all the types of data they wanted to collect, they first conducted a prototype, or feasibility, study called the Pioneer 100 Wellness Project. The results of that 9-month longitudinal study of 108 individuals were published in *Nature Biotechnology* in 2017 (Price et al., 2017). As Price explained, multiple types of data were collected on the participants at three different times. Each time, the investigators measured about 150 clinical chemistries, about 700 metabolites, and about 400 proteins from blood; they also measured stress hormones from saliva over the course of a day. The initial data collection included whole-genome sequence data as well. In addition, individuals’ microbiomes were analyzed at three different times, and participants used wearable devices for continual self-tracking and lifestyle monitoring. With these data, Price and his team created what they call “personal, dense, dynamic data (PD3) clouds” for each participant—personal in the sense that they are individualized, dense because they include a large amount of information, and dynamic because they change over time.

In addition to the data collection, Price continued, participants received wellness coaching. He concurred with previous speakers on the critical role
of behavior change and the difficult challenge it presents, noting that his team’s study engaged a behavioral coach as well as a study physician.

Price stressed that a key to retaining participants in a program like this is making the data relevant. “How do you take these data,” he asked, and make them “actionable for the person, in the moment?” In the long run, he said, the researchers want to be able to mine PD3 clouds to enable new health discoveries that can then be returned back to the participants.

Meanwhile, Price reported, just over the course of the 9 months of the Pioneer 100 Wellness Project, the investigators saw improvements in a number of clinical markers, including a 21 percent improvement in markers for nutrition, a 33 percent improvement in markers for diabetes, a 12 percent improvement in markers for inflammation, and a 6 percent improvement in markers for cardiovascular disease. He noted that participants who have stayed with the program, through Arivale, have shown continued improvements; for example, improvement in markers for cardiovascular disease rose to 20 percent.

In addition to clinical markers, Price continued, his team monitored a number of dietary factors. Through this monitoring, they discovered, for example, that one individual who had high mercury levels also ate tuna sushi three times a week. When this person switched to salmon sushi, the amount of mercury in his blood had decreased by half within 3 months. After he had remained with the program for 1 year, his mercury blood level had normalized completely. According to Price, there were a number of such cases.

Scientific Wellness and Discovery: The Manifestation of Genetic Risk in the Body

In addition to mining the data and returning new health discoveries back to the Pioneer 100 Wellness Project participants, Price and his collaborators have been studying the nearly 4,000 correlations detected among the different types of data collected, including associations between the microbiome and metabolites, metabolites and proteins, proteins and lifestyle factors, and metabolites and genetic risk scores. “All these data types had never before been measured simultaneously on a population of people,” Price said. Given the complexity of the associations between these factors, he argued, “this is just the tip of the iceberg in terms of understanding how these things are interrelated.”

Price went on to acknowledge that some in the field of medicine believe his team is collecting too many measures, a view with which he strongly

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1 Price disclosed that he was co-founder of and on the board of directors at Arivale, a scientific wellness company that partially funded and may license discoveries from the Pioneer 100 Wellness Project.
disagrees. He explained, however, that it is important to distinguish what he and his collaborators do with respect to discovery—trying to understand how the human body is interconnected—from efforts focused on implementation in populations as the field moves forward. The basis for the initial study, he said, was the former. He clarified further that the relationships among different data types can be modularized into subsets, each having greater interconnectivity within than without, and those subsets then used for further study.

As an example, Price used the relationship between cystine, the dimer form of cysteine that is in the blood, and risk for inflammatory bowel disease (IBD). He and his collaborators found that it is not the disease itself but genetic risk for IBD that is related to differences in blood cystine levels. In this particular case, the correlation detected by his team was a negative one: on average, the higher the genetic risk score for IBD, the lower was the amount of cystine in the blood. Price noted that case control studies have shown that blood cystine level is also one of the best candidate biomarkers for the disease itself. But what Price found interesting was that even without the disease present, he and his collaborators found that this difference in blood cystine level preexists across the life span, in individuals ranging in age from their 20s through 89-plus, so the entire life span. He interprets this finding to mean that this deficiency in cystine is genetic.

Another interesting aspect of this cystine–IBD relationship for Price is that cystine lies upstream of the synthesis of glutathione, which is what combats oxidative stress in the body, and that depressed cystine can lead to an inability to process oxidative stress efficiently (Sido et al., 1998). Because oxidative stress is a trigger for IBD, he explained, this depressed ability to combat oxidative stress could be a potential mechanism for the association between cystine genetics and increased risk for IBD. He suspects that over a lifetime, individuals with a cystine deficiency are more likely to surpass what he called their “reservoirs of resiliency,” thereby transitioning to some sort of disease state. What is really fascinating to Price if this is true is that an individual at high genetic risk for IBD could potentially change to one at low risk for the disease through a shift in nutrition. Price termed this finding “the manifestation of genetic risk in the body.” “Gene variants do not mean anything in a test tube,” he remarked. “They mean something in the body.” In his opinion, using a resource such as the PD3 clouds created by his research team increases the chances of being able to see potential interventions not suggested directly by genetics.

**Personalized Nutrition in the Real World**

Price reported that Arivale, which, as noted above, was launched after the successful completion of the Pioneer 100 Wellness Project, and which
collects the same types of data and provides the same type of wellness coaching, now has 175 employees and has raised about $54 million, and thousands of people are participating in the program. He added that the Institute for Systems Biology has access to deidentified data from individuals who participate in the program and who agree to donate their data anonymously for research.

With respect to the value for participants, he said, “It’s really about empowering them with data.” The program provides coaching to help link the data collected with individuals’ behaviors so they can take action. Technologies such as mobile apps and dashboards are used to amplify the coaching relationship, Price noted, so that participants are receiving nearly daily texts from their coaches. His hope is that people will remain with the program over the course of their lifetime and that it will have an enormous impact on their health.

Already, Price continued, there have been many cases in which participants “have done the usual things,” such as lose weight and get healthier, but there have also been people who have been directed to their physicians because of early warning signs. As an example, he mentioned a woman who had an early warning sign that led to the discovery of a stage III colon cancer that was surgically removed just before it was likely to metastasize.

To provide workshop participants with a sense of other activities in the scientific wellness space, Price briefly shared what is being done by another personalized nutrition company, Habit, a spin-off of Campbell’s and a company for which Price sits on the scientific advisory board. For each individual, he reported, the company measures about 40–50 DNA variants and blood biomarkers in participants, collects metabolic data after they consume a “challenge shake” (a meal replacement drink), collects information on their habits and goals, and then analyzes all these data. Then, in a step Price characterized as very important, the company delivers personalized food back to participants. This is important, he explained, because integrating all of the information being provided and changing one’s behavior is difficult. Thus in addition to telling customers that they need to eat more x, y, or z, the company actually provides them with more x, y, or z.

In closing, Price observed, “We are starting to be able to gather immensely more kinds of data.” Additionally, the concept of the PD3 cloud is already being put into practice. Price believes that “this kind of data can be the foundation for the future of personalized medicine.”

SICKLE CELL DISEASE: AN ARGinine DEFICIENCY SYNDROME WITH DISTINCTIVE NUTRITIONAL REQUIREMENTS

Claudia Morris, Emory University School of Medicine, began by stating, “I am an emergency medicine physician. Most people scratch their
head wondering what I am doing talking about nutritional interventions.” She explained that essential amino acids are dietary dependent, whereas nonessential amino acids are not. But, she added, there are also conditionally essential amino acids, which are nonessential but indispensable under stress when the capacity of endogenous synthesis is surpassed. Arginine is one of these amino acids. Morris explained that although she would be talking mainly about arginine deficiency and its role in sickle cell disease (SCD), she would also be discussing the role of arginine deficiency in trauma. She noted that a number of other conditions are linked to acquired arginine deficiencies, including critical illness, burns, surgery, pregnancy (where Morris observed that the deficiency is probably protective), sepsis, pulmonary hypertension, asthma, and other hemolysis conditions in addition to SCD (e.g., thalassemia, malaria).

What Is Arginine?

Morris explained that arginine is found naturally in the diet, with high concentrations in meat, dairy products, seafood, nuts, and watermelon, but it is challenging to obtain enough arginine from the diet to reverse an acquired arginine deficiency. She noted that cardiovascular trials and her studies in SCD utilize 7–10 grams two to three times per day, whereas normal adult ingestion is about 2–7 grams per day. Arginine is available as a nutritional supplement with a low toxicity and, according to Morris, is now being marketed in the supplement world as a “natural alternative to Viagra” in addition to its touted role in cardiovascular health.

Ultimately, Morris explained, arginine is the obligate substrate for nitric oxide (NO) production via the NO synthase enzyme. NO, in turn, is a potent vasodilator with multiple functions: it plays a role in blood pressure modulation, but it also inhibits platelet aggregation, has immune response and anti-inflammatory properties, and can be a signaling molecule.

Arginine is a substrate for arginase as well, Morris continued, which means that arginase, an important intracellular enzyme in the urea cycle, competes with the NO synthase enzyme (see Figure 3-1 for a schematic of the metabolism of these different arginine processes). There are two mammalian isoforms of arginase: arginase I, which is cytosolic, and arginase II, which is mitochondrial. They are present in most cell types, including the red blood cells, which, for Morris, makes arginase a very intriguing enzyme to study in hemolytic disorders because when a red blood cell ruptures, the arginase “gets dumped” into circulation in a physiologically active form. It is also induced from inflammation by cytokines, she noted.

Morris went on to explain that in the presence of arginase, arginine is converted to ornithine and urea. Interestingly, she remarked, arginine and ornithine use the same amino acid transporters, CAT-1 and CAT-2, which
FIGURE 3-1 Metabolic pathways of the arginine processes, with arginine serving as a common substrate for both nitric oxide (NO) and arginase.

NOTE: Hb = hemoglobin; NOS = nitric oxide synthases; RNOS = reactive nitric oxide species.


means that when ornithine concentration is increased, it competitively inhibits cellular uptake of arginine, thus limiting arginine bioavailability and so decreasing NO bioavailability as well. As shown in Figure 3-1, the downstream by-products of arginase activity are the polyamines and prolines. The polyamines are involved in part in vascular smooth muscle proliferation and airway modeling. The prolines play a role in collagen production and deposition, lung fibrosis, and airway remodeling, which Morris identified as the kinds of structural changes seen in pulmonary hypertension and asthma and as common complications in SCD.

Arginine is semiessential, Morris continued, because the body has the ability to synthesize it through what is called “the intestinal renal axis.” The amino acid L-glutamine is taken up in the diet, then converted into citrulline in the enterocytes of the small intestine, and the citrulline is converted into arginine in the kidney. Morris mentioned that glutamine was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of SCD, which makes it the first FDA-approved drug for pediatric SCD and only the
second FDA-approved drug for adults with the disorder. Morris clarified that although glutamine is now considered a “drug” for treatment of SCD, it is still an amino acid and a nutritional supplement. It is also what she called “an arginine prodrug” through the intestinal–renal axis.

Turning to the bioavailability of arginine, Morris characterized it as much more complex than the amount of arginine in the plasma. She added that the term “global arginine bioavailability ratio”—arginine/(ornithine + citrulline)—was coined to take into account a number of different mechanisms that impact arginine bioavailability, such as the effects of arginase activity and renal dysfunction.

**Amino Acid Deficiencies: Sickle Cell Disease as a Model**

Morris defined SCD as an autosomal recessive inherited disease of the red blood cells. The genetic mutation responsible for SCD, she explained, is a single-point mutation, a substitution of valine for glutamic acid at the six position of the beta unit of the hemoglobin molecule, which causes the hemoglobin molecule to polymerize under stress or deoxygenation. This “sickling,” in turn, causes a cascade of effects that ultimately decrease blood flow. The tissue hypoxia that results causes both acute and chronic damage to nearly every organ system, according to Morris. She added that SCD affects about 100,000 individuals in the United States but millions of people worldwide, and comes at significant economic cost. Interestingly, she said, the clinical phenotype of SCD extends across a broad spectrum, from mild to severe, far exceeding what would be expected from a single-point mutation. So there are many other factors that come into play and that contribute to disease severity.

In Morris’s opinion, SCD is an excellent model for distinctive nutritional requirements that develop from a metabolic process, the metabolic process in the case of SCD being hemolysis. She noted that a decline in an amino acid does not necessarily translate to a clinically significant deficiency. Rather, a nutritional deficiency requires a biological process that is dependent on the nutrient that is being compromised. This compromise, in turn, must lead to an abnormal physiological response that causes a poor outcome, which needs to be reversible by replacement of the amino acid. In the case of SCD, Morris elaborated, the low arginine bioavailability that results from hemolysis is the nutritional deficiency; the endothelial dysfunction is the biological process that develops in the presence of low arginine bioavailability; pulmonary hypertension is one of the abnormal physiological responses that occurs as a result, and the one Morris said she would be using as a model for the remainder of her presentation; and in SCD patients, pulmonary hypertension is associated with increased mortality, which can be reversed by amino acid replacement.
According to Morris, in addition to being a model for distinctive nutritional requirements developing from a metabolic process, SCD is a model for vasculopathy and endothelial dysfunction, as it involves not only hemolysis but also inflammation, NO depletion, and arginine depletion. With SCD-related vasculopathy and endothelial dysfunction depletion, NO depletion takes “center stage,” she said. This is the case because with hemolysis, all of the contents that are normally packaged within a red blood cell dump into circulation when the cell breaks apart. These contents include hemoglobin, which, now cell-free, rapidly consumes NO, as well as arginase, which when dumped into circulation rapidly consumes the obligate substrate for NO production. As arginine level depletes, Morris continued, the NO synthase enzyme also begins to malfunction, uncoupling and producing superoxide in lieu of NO and adding to what she described as “this milieu of oxidative stress.” In sum, she said, there is a “global dysfunction of the arginine-NO pathway,” with many of these breakdowns occurring simultaneously.

Morris went on to explain that decreased NO bioavailability has several biological consequences, including endothelial activation, increased endothelin-1 (a potent vasoconstrictor), increased vasoconstriction, and increased platelet activation. There are several clinical consequences as well, she observed, including pulmonary hypertension, asthma, stroke, renal insufficiency, priapism, and leg ulcers. Although she said she would go on to focus on pulmonary hypertension in particular, she noted that all of these clinical manifestations are hemolytic subphenotypes of both SCD and low arginine bioavailability.

Also within the red blood cells, Morris noted, is lactase dehydrogenase (LDH). She explained that LDH is commonly thought not to be of clinical significance when dumped into circulation, but makes for a convenient biomarker of the hemolytic subphenotype of SCD first reported by Dr. Greg Kato and colleagues (Kato et al., 2006).

Arginine Deficiency and Sickle Cell Disease

Morris went on to discuss her work with SCD and arginine insufficiency, beginning with a 2005 study through which she and her research team discovered that patients with SCD have a plasma arginine insufficiency and elevated plasma arginase activity (Morris et al., 2005a). She clarified that because arginase is an intracellular enzyme, it is released only upon cell damage or cell death. “It just should not be in your plasma if you are a healthy individual,” she said. As part of the same study, Morris and colleagues (2005a) also examined the arginine-to-ornithine ratio, again because in the presence of arginase, arginine converts into ornithine, and they found a low arginine-to-ornithine ratio in patients with SCD compared
with normal controls. But “where it got interesting,” Morris said, was that the lowest levels were found in the patients at highest risk for pulmonary hypertension. She noted that not all patients with SCD develop pulmonary hypertension—only about 10 percent—but that these results led her to pay more attention to pulmonary hypertension.

Morris and her collaborators hypothesized, “if it is low, give it back.” So they conducted a small study of arginine replacement and observed a greater than 15 percent decrease in pulmonary systolic pressures, as estimated by Doppler echocardiography (Morris et al., 2003). Morris characterized this finding as “pretty impressive” (see Figure 3-2), noting that this decline is similar to that observed with on-the-market pulmonary hyperten-

sion medicine. She interprets this finding to mean that there is a condition of endothelial dysfunction, manifesting as pulmonary hypertension, that appears to be reversed with arginine therapy. In addition to being excited about the decline shown in Figure 3-2, Morris and her team observed, anecdotally, that leg ulcers started to heal on two of these patients, both of whom had been experiencing chronic leg ulcers for years.

The next step, Morris said, was to consider another hemolytic anemia, thalassemia, that was also known to be associated with a high prevalence of pulmonary hypertension. So her team looked at some of their patients in the thalassemia clinic and found a similar pattern of arginine dysregulation (Morris et al., 2005b). More specifically, compared with controls, patients with thalassemia had, on average, higher-than-normal arginase activity, lower arginine-to-ornithine ratios, and elevated levels of the downstream by-products proline and citrulline. The higher level of citrulline suggested to Morris that there might be problems with converting citrulline to arginine.

Morris reported, however, that it was not until her team returned to the thalassemia clinic 10 years later and looked specifically at patients who were at risk for pulmonary hypertension that they found that some of the thalassemia patients had completely normal arginine levels, and that it was mainly patients who were at risk for pulmonary hypertension who had dysregulated arginine metabolism (Morris et al., 2015). That is, compared with thalassemia patients who were not at risk for pulmonary hypertension, those who were at risk had low arginine levels, high arginase activity, low arginine-to-ornithine ratios, and low global arginine bioavailability ratios.

In her studies of both SCD and thalassemia, Morris observed that the severity of pulmonary hypertension and cardiopulmonary dysfunction correlated strongly with biomarkers of hemolytic rate. But what she characterized as “really fascinating” was that low global arginine bioavailability was also associated with increased risk of death in adults with SCD: there had been no deaths among patients with the highest bioavailability and the greatest number of deaths among those with the lowest bioavailability. She noted that Cox and colleagues (2018) obtained the same finding in children with SCD in Tanzania. Additionally, she said, low arginine bioavailability predicts early mortality in adults with malaria.

Morris reported that in separate work, Dr. Stan Hazen, a cardiologist, and his colleagues followed a group of nearly 1,000 patients who were at risk for cardiovascular disease and were undergoing right heart cardiac catheterization. After 3 years, they found that a reduced global arginine bioavailability ratio was prospectively associated with an increased incidence of major adverse cardiovascular events (Tang et al., 2009). The researchers looked at death, myocardial infarction, and stroke. Additionally, Morris said, they found that the global arginine bioavailability ratio was more predictive than cholesterol of cardiovascular disease, suggesting
to her, first, that this ratio is important for survival and, second, that it is a biomarker of vasculopathy that goes beyond SCD.

Morris pointed out that, while there are a number of different mechanisms of arginine dysregulation, many acting simultaneously, a common theme in arginine deficiency syndromes is excess arginase activity. So, she stated, whether hepatic, immune, or from hemolyzed red blood cells during hemolysis or transfusion reactions—that is, regardless of cellular origin—the physiological effects and clinical consequences of excess extracellular arginase are similar.

**Arginine Deficiency and Trauma**

In addition to conditions involving endothelial dysfunctions such as SCD, Morris continued, are arginine deficiency–related conditions related to T cell dysfunction, trauma being one example. Arginine is essential for naïve T cell activation, she explained, and T cells are “exquisitely sensitive” to arginine depletion. T cell proliferation is blunted and T lymphocyte–mediated cytotoxicity and memory responses are almost entirely abolished when arginine is depleted. But again, Morris said, “give it back, and you fix the problem.” Indeed, providing arginine to culture media restores T cell function.

As Morris had suggested earlier, T cell dysfunction may be protective in pregnancy, when a women needs to suppress her immune system to protect both herself and the fetus. But with trauma, she said, T cell dysfunction increases susceptibility to infection. Plasma arginine levels decrease within minutes to hours of a traumatic event and can remain low for up to a week or longer. Morris pointed out that it was one of the pioneers in the field, Dr. Juan Ochoa, who helped her and her team understand plasma arginase activity increases in trauma patients as a result of myeloid-derived suppressor cells that express arginase I after trauma. So in contrast to SCD, she continued, where it is the red blood cells that are dumping arginase from hemolysis, the cell source in trauma is different, but it similarly increases arginase. The increased arginase leads in turn to the arginine deficiency, ultimately translating into T cell dysfunction and increased susceptibility to infection.

Morris went on to observe that more than 15 million injuries occur each year in the United States, and about 10 percent of trauma patients develop wound infections. The infection rate increases to 30 percent for patients who have been in an intensive care unit (ICU) for more than 48 hours. Infections are the leading cause of late organ failure, Morris noted, and they contribute to about 10 percent of trauma deaths. Thus, she suggested, strategies aimed at infection prevention after trauma should result in significant decreased mortality, morbidity, and cost.
The Therapeutic Potential of L-Arginine

According to Morris, the therapeutic potential of arginine for SCD has been studied for 20 years. She reported that in a sickle cell mouse model, arginine supplementation has been shown to improve perfusion, increase glutathione levels (with an effect on oxidative stress), decrease inflammation, help heal lung injury, reverse micro-vascular vaso-occlusion, and decrease mortality. However, what Morris finds interesting about a sickle cell mouse model is that mice do not have arginase in their red blood cells as do humans, yet they have increased arginase activity. So the arginase is coming from a source other than the erythrocyte, she explained, and not necessarily through the process of hemolysis.

Morris noted further that several human phase II studies have shown that arginine therapy improves leg ulcers. Also in humans, she and her team conducted a vaso-occlusive pain trial in which children with SCD admitted to the hospital with acute SCD-related pain were treated with arginine versus placebo. She reported that those treated with arginine showed a 55 percent decrease in total opioid use (mg/kg) and lower pain scores at discharge. She mentioned that she was currently working with FDA to complete a second phase II trial, with plans for a phase III multicenter study. She also referred to data she had presented earlier showing decreased pulmonary hypertension with arginine therapy (see Figure 3-2). Anecdotally, she added, arginine has improved priapism in the emergency room the few times she has used it for that purpose.

With respect to trauma, Morris reported that arginine therapy has been shown to enhance wound healing after trauma and hemorrhagic shock; immunonutrition has been found to improve immune responses and T cell function; and high arginine formulas have been shown to decrease infection complications in critically ill patients, with the greatest benefit for surgical patients. However, she added, there is also evidence of harm in sepsis and following acute myocardial infarction. “So we don’t have all the answers yet,” she said. Moreover, most of these studies have had a number of methodological weaknesses, and, as discussed below, there is a paucity of data in children.

Immunonutrition in Critically Ill Children

Regarding immunonutrition in critically ill children, Morris said she was shocked by results of a 2009 Cochrane review that found insufficient evidence either for or against nutritional support in children during the first week of a critical illness, mainly because the appropriate studies had not been performed. She noted that some pediatric ICU doctors have interpreted this finding to mean that some of the sickest children in the hospital
should not be fed—even trauma patients, some of whom, she said, are basically being starved for days.

In addition to the Cochrane review, Morris mentioned a randomized controlled trial of arginine/glutamine-fortified formula among 40 children with traumatic brain injury (Briassoulis et al., 2006). The primary outcome measure was mortality. The authors found no difference in mortality compared with standard formula. According to Morris, however, fewer than 10 percent of pediatric trauma patients die, so the study was severely underpowered for its primary outcome. What she did find enlightening was that 69 percent of patients who received fortified formula had a positive nitrogen balance by day 5, compared with 31 percent of patients who received standard formula. Morris cited another, multicenter prospective cohort study of more than 1,000 mechanically ventilated children, in which Mehta and colleagues (2015) found decreased 60-day mortality among patients who had adequate protein intake. She reported that the same group recently published data showing similar findings in surgical trauma patients (Velazco et al., 2017). “This certainly gives me pause,” she said, “and it also suggests that we have gotten it wrong all these years. It is not overall calories, but it is enteral protein delivery [impacting important clinical outcomes].” She described enteral protein delivery as “a modifiable risk factor for mortality that is in dire need of a shift in our current practice, given the potential for improved outcomes.”

**Therapeutic Strategies**

Morris suggested several other therapeutic strategies to consider in addition to arginine supplementation: arginine precursors such as citrulline and glutamine; combination therapies that target multiple mechanisms; and immunonutrition, particularly targeted enteral formulas, although the ideal formulas for trauma, critical illness, hemoglobinopathies, and pediatrics do not yet exist. She urged more research in this area.

**Final Remarks**

Morris concluded by listing several final points:

- Arginine is a conditionally essential amino acid that becomes essential under conditions of stress and catabolic states, when the capacity of endogenous amino acid synthesis is exceeded. This occurs in such cases as critical illness, trauma, and hemolysis.
- SCD and trauma represent arginine deficiency syndromes, and they pose a distinct nutritional requirement that develops because of their metabolic abnormalities. Thus, they may benefit from arginine replacement therapy.
• There are at least two broad categories of arginine deficiency syndromes: (1) T cell dysfunction (e.g., trauma), and (2) endothelial dysfunction (e.g., SCD).
• The global arginine bioavailability ratio may be a novel biomarker of arginine deficiency, and as such warrants further study.
• Arginine-fortified immunonutrition may be a treatment for acquired arginine deficiencies. Morris called for future studies to identify subpopulations that would benefit most, with potential adverse events being minimized.

Morris closed by stating, “Nutrition is medicine!”

PERSONALIZED NUTRITION IN THE REAL WORLD: WHERE DO WE STAND?

David Alpers, Washington University School of Medicine, began his presentation by saying, “We are in this room to try to figure out where nutrigenomics is.” “We have heard a lot of evidence that has tremendous promise,” he added, including evidence indicating that behavior has an enormous influence on what people do in terms of nutrition and that this behavior may be modifiable (Meisel et al., 2015). Yet, he asserted, despite this evidence and despite the great number of genetic tests already available, most based on single nucleotide polymorphisms (SNPs), few studies are informative about how to influence clinical behavior in nutrition. He discussed why useful studies will be difficult, but not impossible, and why “we are just at the early stages of where we can utilize this information.”

According to Alpers, nutrigenomics studies are difficult, first, because they require isolation of the effects of different individual genes and different individual foods, initially by themselves and then in combination, using adequate control arms. Thus far, he said, upon examination of either isolated genes or isolated nutrients, such as antioxidants and vitamin A, the results “have not been very impressive.” A second reason for the difficulty of nutrigenomics studies is the challenge of proving causation from associations, a challenge he discussed in more detail, as summarized below.

The Challenge of Nutrigenomics Studies: Proving Causation

Alpers explained how the Bradford-Hill criteria for causal association are particularly difficult to achieve in nutrition-related studies (Bruemmer et al., 2009). He noted that while the Bradford-Hill criteria are not “absolute criteria,” they do provide a rough “scaling” of how to interpret associations.

For example, one of the Bradford-Hill criteria is that there be a strong association. According to Alpers, however, this is not the case for many of
the associations that have been reported between nutrition and either genetic or metabolic change. A second Bradford-Hill criterion is that the association be constant. But at present, Alpers said, most nutrigenomics associations are based on only a few studies, which makes it difficult to assess constancy. A third Bradford-Hill criterion, Alpers continued, is that there be one cause and one effect. He pointed out, however, that in nutrition, particularly in nutrigenomics, where the goal is to prevent disease in relatively healthy people, it is very difficult to narrow an association down to one cause and one effect because there are so many components to the diet and because those components interact, causing multiple metabolic changes to the diet. He added that this complexity extends even to inherited diseases caused by single genetic changes, such as what Morris had discussed. A fourth Bradford-Hill criterion is that there be a dose-response relationship. Alpers noted that although these relationships exist in genetic studies when one allele is variably knocked out, they are not usually available for the spontaneous SNPs found in association studies. A fifth Bradford-Hill criterion is that there be scientific justification for an association. According to Alpers, although there is always scientific justification for nutrition-related gene associations, some of it quite convincing in his opinion, few of these justifications are based on clinical data. Most are based on in vitro and animal data. A sixth Bradford-Hill criterion is that the association be coherent with other data. In nutrition, however, other data are often quite limited, Alpers explained. A final Bradford-Hill criterion is that interventions have been tested in randomized controlled trials. Again, however, such studies are very difficult to perform, Alpers said.

The Challenge of Nutrigenomics Studies: Isolating Nutrition-Related Phenotypic Effects

Alpers continued by pointing out that, in addition to the challenge of proving causation, another challenge to linking nutrition to genomics is the fact that, except for diseases caused by single gene defects, it is very difficult to isolate which components of the phenotype are related to nutrition and which to other factors. He elaborated on this challenge in the context of malnutrition, but remarked that his conclusions were just as applicable to the prevention of disease.

Alpers observed that, although a number of organizations have developed consensus criteria for malnutrition—that is, criteria that indicate whether a person is malnourished (White et al., 2012)—in clinical practice there are in fact two major types of malnutrition (Jensen et al., 2010). The first is pure starvation with no or limited inflammation, whereby if nutrients are given back, the phenotype is reversed. The second is malnutrition either in chronic disease, where mild or moderate inflammation and/or other fac-
tors are frequently superimposed, or in acute disease or injury with marked inflammation.

Alpers explained that chronic diseases with malnutrition include, for example, obesity, rheumatoid arthritis, inflammatory bowel disease, and cancer. But in the case of chronic disease, he noted, clinicians can have no idea what effect replacing nutrition will have on the phenotype. Although there are certainly differences among individuals, he said, “usually by the time we see a well-developed chronic disease, the effects of the disease itself are more potent than that of nutritional deficiencies.” Acute diseases or injuries with marked inflammation include trauma, as discussed by Morris, and major infections and burns.

According to Alpers, many of these same kinds of chronic disease/malnutrition conditions are the same disorders for which genomic links have been sought in past studies (e.g., obesity, cancer, type 2 diabetes, aging, even pregnancy). But again, he noted, most of these conditions have a component of inflammation, and only conditions with no or limited inflammation respond in a clear manner to nutrient supplementation. Thus, he observed, any change in phenotype may be related to nutritional supplementation only by chance or in part.

According to Alpers, the question then arises of what approaches have been used to try to link genetic or genomic effects to nutritional phenotypes. He referenced the large body of in vitro and in vivo animal studies carried out to support the rationale for such a link. He cited the example of cancer research, with many studies showing that curcumin, turmeric, garlic extract, and other nutrient components have potent roles in preventing some of the changes that occur during cancer in cells or in animals. But these findings have yet to be translated into human data, he cautioned.

Alpers went on to point out that the few human data that do exist are often less suggestive, citing studies on caffeine metabolism, omega-3 supplementation, and antioxidant supplementation. For example, he observed, even though the antioxidant pathway has been well explicated in a variety of diseases, including cancer and a number of degenerative diseases, the antioxidant theory of human disease, which was quite prevalent many years ago, has not yet been proven by clinical studies. He finds the mitochondrial story potentially a very powerful one (see Chapter 2 for a summary of Douglas Wallace’s presentation on mitochondria), but one without the necessary clinical data at present.

Alpers observed further that with human data, some genetic factors that can be detected—such as human leukocyte antigen (HLA) subtypes for celiac disease—are not sensitive enough. It is known, he pointed out, that the two subtypes found in almost all cases of celiac disease are also highly prevalent among individuals who do not have celiac disease. Sometimes, he noted, more information is needed than just the genetic change.
Alpers also pointed to other genetic factors that add little to clinical information. To illustrate this point, he explained that while it has been known for decades which genetic changes are determinative of lactose intolerance in humans, this same determination can be made clinically by removing milk products from an individual’s diet and seeing whether the person responds. “So we have not needed that information yet to get personalized in that particular condition,” he said.

Alpers cited as a final challenge to the scientific approaches linking genomics to nutrition that again, many chronic diseases—obesity in particular—are also related to the phenotype of chronic inflammation/malnutrition. He identified as the challenge with obesity and other nutritional disorders, including to some extent even diabetes, that management with the standard-of-care nutritional advice is difficult by itself and often is not fully implemented. While the use of individual coaches is, he said, “a wonderful thing” (see the summary of Price’s presentation earlier in this chapter), with such coaching being what trained dietitians provide, he believes the field will need to move much further along in terms of its use of cell phones and other technologies before individualized coaching becomes a widespread phenomenon.

Alpers expects a long lag time before strong nutrigenomics data become available, and he predicted that such data would become available one disease at a time. “There is not going to be any great breakthrough,” he said. “I think we need definite effects on a clinical basis before we can really implement these things fully commercially.”

Exploring Current and Future Directions of Personalized Nutrition

Alpers identified three current and future trends in personalized nutrition. First, many currently available personalized Internet services provide people with information based on an analysis of their dietary patterns, although, according to Alpers, none of these services have anything to do with genomics (Gibney and Walsh, 2013). Moreover, he asserted, the dietary patterns reported by individuals are often biased, although he believes this perhaps could be changed with education. He suggested that the difference between meal-based and food component–based information also will need to be addressed. He added that many of these services are mobile phone–based. Thus at present, the uptake of these systems has been much greater among adolescents, who have grown up with cell phones, than among adults, Alpers expects this situation will change with time and as the population becomes more accustomed to the technology. And despite these challenges, he predicts that in the future, personalized Internet services will become a potent method for modifying behavior, potentially leading to changes in clinical outcomes (once those changes in clinical outcomes have
been identified). He cautioned, however, that recidivism may be a problem, as it currently is with weight loss diets, noting that “it is very hard to keep up a change in behavior that hasn’t been lifelong up until now.” He added that while these programs have as yet nothing to do with genomics, if it can be shown that behavior is changed in a meaningful way, those lessons can be incorporated into what is learned in the future about the role of genetics in modifying disease phenotypes.

A second personalized nutrition trend discussed by Alpers is the use of phenotypic data. He remarked that although the phenotype is more difficult to study than the genome because of the difficulty of conducting a large phenotypic study with clear clinical relevance, there are a few examples of such studies. He cited a study in which monitoring urine sodium and decreasing sodium-containing foods was found to have an effect on blood pressure (Yamasue et al., 2006). This intervention appeared to work, he observed, although in the face of relatively high sodium intake, indicating that the effect of altering sodium intake is modest. He cited another example involving the use of a wristwatch accelerometer to monitor physical activity and deliver relevant information (Hurling et al., 2007). He described these studies as being among a number of wellness programs, suggesting that such programs do work. But again, he stressed, what is missing is knowledge of whether this type of program will actually change a disease phenotype, as well as how long people will stay with the program. As a final example, Alpers cited a number of studies of blood tests that are used to analyze metabolites and develop metabolic profiles. He clarified that these are metabolic analyses, not metabolomics analyses, which he said “are coming.” One of these studies looked at the effect of vitamin D supplementation, finding no effect on metabolites (O’Sullivan et al., 2011). In sum, Alpers stated that these types of studies have many problems that he did not have time to discuss during his presentation, but that such studies will be necessary to examine personalized nutrition with respect to phenotypic changes.

The third and final trend Alpers discussed is personalized nutrition based on genomic data. He observed that at present, most of the information in this area comes from observational studies linking SNPs to dietary patterns. “That’s not really enough in itself,” he argued. While it has been shown, he elaborated, that certain SNPs can cause metabolic changes—such as in the methylenetetrahydrofolate reductase gene, MTHFR—that have been shown to change homocysteine levels in TT individuals who receive riboflavin supplementation (McNulty et al., 2006), again that association has yet to be translated into a change in disease phenotype.

Alpers emphasized that, with all three of these approaches, it is difficult to predict the extent to which a user will want just a “one-off” result or will maintain the service in the long term. In his opinion, some of the
programs currently available are providing good incentives for people to stay with them, but what is needed is a service that can be delivered over the long term and will eventually show that its delivery leads to a change in disease progression or occurrence. While just making people feel good is worthwhile, he said, “that is not really what we are talking about [in this workshop].”

In closing, Alpers mentioned that some Food4Me studies under way in the European Union are developing data on consumer responses. These include a study just published in the *American Journal of Clinical Nutrition* in which individuals who were told that they had the *FTO* variant associated with risk of obesity lost more weight over 6 months relative to individuals who were not told whether they had the variant (Celis-Morales et al., 2017). The difference was small, Alpers said, but he suspected that it would have been greater if the study had lasted longer than 6 months. Additionally, he noted that members of the control group were told nothing about their genetic risk and that to serve as a real control group, they should have been told something definite but unrelated.

In closing, Alpers stated, “The concept of genomics for personalized nutrition is a sound one, and many of the strategies are in place. What is missing is the data that translate those strategies or the preclinical work to actual clinical outcomes. It will occur. It will be difficult but it will occur slowly. We just need to be patient.”

**IS GENETIC TESTING FOR PERSONALIZED NUTRITION READY FOR PRIME TIME?**

Ahmed El-Sohemy, University of Toronto, began by saying that he would be discussing some of the translational activities under way at a company, Nutrigenomix, he had founded and for which he serves as chief science officer. He also holds shares in the company. He clarified that Nutrigenomix is not a direct-to-consumer genetic testing company, but provides a service to health care practitioners, mainly registered dietitians but also some physicians who practice functional and integrative medicine. At the time of the workshop, the company was serving more than 6,000 practitioners in 35 countries and providing reports in 8 languages.

El-Sohemy asserted that genetic testing for personalized nutrition is indeed ready for prime time. While he agreed with many of Alpers’s comments, he said he would also be presenting evidence to support his opinion that many of the skeptics’ criticisms “are actually not true.” However, he acknowledged that the field is not without controversy, as there are many different kinds of operators, and the evidence base behind much of what is being offered is quite varied. He characterized some of what is being offered as “on the fringe or not really rooted in robust scientific evidence.”
He pointed to the many articles in the media questioning the validity of personalized dietary tests, and while he agrees that it is important to keep these companies honest, he asserted, “It is also not right to lump all of them in one basket and say that the whole field is all just snake oil.”

Part of the controversy, in El-Sohemy’s opinion, is due to the different kinds of tests on the market. He emphasized the importance of distinguishing between disease risk genes, which are often identified through genetic association studies, and what he refers to as modifier, or metabolic, genes. The latter are genes that are not by themselves related to any phenotype or health outcome, but modify the effect of an environmental factor on a phenotype or health outcome. El-Sohemy cited as an example that a genetic variant for a drug-metabolizing enzyme or a drug transporter does not necessarily cause any adverse effect by itself, but if someone with one of these particular genetic variants is prescribed a certain drug, he or she may experience an adverse reaction. He noted that although this analogy is from pharmacogenetics, it applies to nutrition as well.

### Why Are Genetic Differences Important for Nutrition?

With respect to why it is important to look at genetics in the field of nutrition, El-Sohemy remarked that if one looks at the link between virtually any nutritional factor and any health outcome for which there have been enough observational studies, one will see a heterogeneity of responses, with some studies showing increased effects, some no effect, and others completely opposite effects. There are, he observed, many reasons for the inconsistencies among studies, but an important consideration is the genetics of the groups or population being studied. For example, he noted, some people who go on a low-sodium diet actually experience an increase in blood pressure. These people used to be thought of as outliers, he said, but these so-called outliers are increasingly being recognized as very real. “So what if you are an outlier,” he asked, “and the advice that we are giving you is actually causing harm?” If there is a way to identify these individuals and find alternative strategies for them, he suggested, that is something to consider. “One size does not fit all,” he pointed out.

As proof of concept, El-Sohemy described some of his early work on caffeine and cardiovascular disease. He and his collaborators found that in fast metabolizers (CYP1A2 AA), moderate coffee consumption was associated with a lower risk of myocardial infarction, whereas in slow metabolizers (CYP1A2 AC + CC), consumption of even two to three cups per day was linked with a higher risk of that outcome (Cornelis et al., 2006; see Figure 3-3). A couple of years later, he reported, these findings were replicated by a research group in Italy, looking not at myocardial infarction but at the risk of developing hypertension (Palatini et al., 2009). Theirs was
FIGURE 3-3 The difference in risk of myocardial infarction between fast metabolizers (AA) and slow metabolizers (AA + AC).

SOURCES: Presented by Ahmed El-Sohemy on December 5, 2017, from Cornelius et al., 2006.

In addition to these observational studies, El-Sohemy and his team conducted a randomized controlled intervention trial of endurance performance in athletes. They recruited individuals and, based on genotype, randomized them to receive either placebo or one of two different doses of caffeine. They found that fast metabolizers benefited more from the caffeine, whereas slow metabolizers showed no improvement in performance (Guest et al., 2018).

In summary, El-Sohemy said, myocardial infarction, hypertension, prediabetes, and kidney function all show the same pattern. “If you are a slow...
metabolizer,” he observed, “you should probably limit your intake to no more than two cups a day. If you are a fast metabolizer, you are lucky. You can follow the general recommendations, which suggest that you can drink up to four cups a day.”

**Media Messages**

El-Sohemy then showed the image of a headline for a 2015 *The Washington Post* article: “Government panel said drinking coffee is harmless. Why that might be wrong.” The subheadline read: “A U.S. panel said coffee can be part of a healthy diet. That might be true for only half of us.” According to El-Sohemy, the journalist cited some of the work on fast versus slow metabolizers and wondered why these one-size-fits-all recommendations are still being issued when the science suggests otherwise (Whoriskey, 2015).

El-Sohemy added that one of the quotes in the article was from Sander Greenland, an epidemiology professor emeritus at the University of California, Los Angeles, who said, “There are spectacular metabolic differences in people, and to expect that coffee will have the same health effects on everyone is absurd.” El-Sohemy agreed with this assessment. He found it interesting that the journalist also interviewed a member of the government panel, who said, “Unfortunately, because genetic testing is expensive and rarely done, most people have little idea which gene variant they carry.” El-Sohemy agreed that this, too, was a fair observation, saying, “There is no point in making recommendations based on a bit of information that people do not have access to.”

For El-Sohemy, this quote by the panel member is significant because it implies that, if genetic testing were inexpensive and everyone knew what gene variant he or she had, the recommendation about drinking coffee would to some extent have taken the science into account. Such issues that relate to the economic and social aspects of genetic testing, such as how to make the information accessible to everyone, are very legitimate topics of discussion, in his view. He believes “there are some really good examples of proof of concept at how . . . a single SNP can modify the association between a dietary component and a variety of different health outcomes.”

El-Sohemy then cited a paper that appeared in *The BMJ* just prior to the workshop. Poole and colleagues (2017) conducted a review of about 200 meta-analyses of coffee consumption and multiple health outcomes and concluded that the totality of the evidence suggests a protective effect for a number of these outcomes. A *BBC News* article responding to this was headlined, “Three cups of coffee a day may have health benefits” (Roxby, 2017). Unfortunately, El-Sohemy said, “at the end of the day, people want to know what they can do for themselves, and when they see headlines like
this, they falsely assume that coffee is safe to consume.” But he emphasized that if slow metabolizers were to follow those recommendations, they would actually increase their risk for multiple health conditions. He asserted that the conclusion of the review suggests that the majority of participants in the studies included in the review were probably fast metabolizers. He pointed out that if a study population comprised only 60 percent fast metabolizers and 40 percent slow metabolizers, the fast metabolizer effect would still predominate. “We need to move away from these kinds of studies,” he argued. “Bigger is not necessarily better. You have to look at the quality of the scientific evidence.”

To this end, El-Sohemy and Raffaele De Caterina wrote what he said was the first consensus article of the International Society for Nutrigenetics and Nutrigenomics reviewing the scientific evidence that would enable DNA-based dietary advice on the consumption of caffeine (De Caterina and El-Sohemy, 2016). He mentioned another article, published recently in *Genes and Nutrition*, in which he and his co-authors propose certain guidelines for evaluating the scientific evidence for formulating DNA-based dietary advice (Grimaldi et al., 2017). He also cited an article that appeared in *The New York Times* headlined “For Coffee Drinkers, the Buzz May Be in Your Genes.” Although the research had been completed several years earlier, he added, the journalist reminded readers that the association between coffee and health appears to be dependent on individual genetic variation (O’Connor, 2016).

Still, El-Sohemy continued, there is no shortage of articles that question the validity of the entire field, referring in particular to an article that had appeared in the week just prior to the workshop titled “DNA-Based Diet Advice Is Big Business with Little Scientific Support” (Entis, 2017). He pointed out that one of the individuals interviewed in this article was a pediatrician and author of *The Bad Food Bible* (Carroll, 2017). The journalist wrote:

There’s no evidence that some people respond better to high-fat diets while others are more receptive to diets packed with protein or complex carbs. “It doesn’t exist,” [Carroll] says. Even if it did, “there’s no evidence we could detect it” through DNA sequencing. Metabolic illnesses and disorders such as celiac disease or lactose intolerance aside, humans’ genes are very similar. We have evolved to be able to eat the same foods.

El-Sohemy reminded the workshop participants, however, that José Ordovás had already presented evidence showing an association between *APOA2* and saturated fat (see Chapter 2 for a summary of Ordovás’s presentation). El-Sohemy cited other studies as well, such as the POUNDS LOST study, a 2-year randomized controlled trial comparing the effects of
a high-protein versus a low-protein diet, that have found similar associations. He reported that, as part of the POUNDS LOST study, Zhang and colleagues (2012) had found a significant loss of fat mass after 2 years of a high-protein diet, but only among individuals with an FTO AA genotype. Individuals with an AA genotype showed no change in fat mass on a low-protein diet, and individuals with either a TT or TA genotype showed no change in fat mass on either a high- or low-protein diet. “When it comes to the gold standard of scientific evidence,” El-Sohemy asserted, “I think this is pretty robust.” He added that this evidence has since been replicated in a distinct population in Spain. In that study, de Luis and colleagues (2015) showed that a high-protein diet is effective for weight loss only in individuals with the AA genotype. El-Sohemy and his team have replicated these findings yet again, in a distinct, East Asian population, in which individuals with the AA genotype had a waist circumference roughly 10 cm greater when not on a high-protein diet (Merritt et al., 2018). What these findings show, El-Sohemy argued, is that while FTO has been used in the past as a predictor for obesity, it is also a modifier gene that indicates whether someone is likely to benefit from a high-protein diet.

**Personalized Dietary Advice Versus Public Health Recommendations**

El-Sohemy agreed with Patsy Brannon’s prediction that the future would likely see the integration of personalized dietary advice with public health recommendations (see Chapter 1 for a summary of Brannon’s presentation). In the meantime, he said, there is some disagreement about whether providing people with genetic information is actually helpful. Some argue that if a person knows that something is “in my genes,” he or she will not be motivated to do anything in response. Others argue the opposite: that someone aware of having a particular gene will be motivated to watch what he or she eats. For example, people who knew they were slow metabolizers of coffee would cut back on coffee. Likewise, people told that they have the risk variant for salt-sensitive hypertension would lower their sodium intake.

El-Sohemy and his collaborators decided to put this notion to the test and conduct a randomized controlled trial comparing DNA-based dietary advice with standard recommendations (Nielsen and El-Sohemy, 2012). They found that those who received the DNA-based dietary advice actually understood the recommendations to a greater extent relative to those who received the standard recommendations, and were motivated to change their eating habits. In fact, El-Sohemy reported, they did change their eating habits and had maintained those changes 1 year later (Nielsen and El-Sohemy, 2014). The biggest effect, he noted, was with salt-sensitive hypertension in individuals told that they had the risk variant for that phenotype.
That DNA-based dietary advice can motivate behavior change has since been replicated by a group in Finland, El-Sohemy continued, with a different kind of genetic information and different outcomes (Hietaranta-Luoma et al., 2014), as well as in the Food4Me trial (Celis-Morales et al., 2017; Livingstone et al., 2016). He cited yet another study of behavior change in response to receiving genetic information, in which Green and Farahany (2014) showed that 42 percent of people surveyed reported positive changes in their health behavior. Many people reported changing their exercise habits (61 percent), and the vast majority reported changing their dietary patterns (72 percent). Finally, El-Sohemy cited a recent study by Nielsen and colleagues (2017), showing again that while not everyone changes behavior in response to receiving genetic information, providing people with the right kind of information can be a very useful way to get at least some people to change their eating habits.

What Do the Skeptics Say?

Again, El-Sohemy posed the question, What do the skeptics say? He mentioned the Academy of Nutrition and Dietetics’ position paper on nutritional genomics, which states: “Applying nutritional genomics in clinical practice through the use of genetic testing requires that registered dietitian nutritionists understand, interpret, and communicate complex test results in which the actual risk of developing a disease may not be known” (Camp and Trujillo, 2014). El-Sohemy questioned the use of the word “complex” and remarked that risk in nutrition is always relative, never actual, viewing this as a message to “spook” dietitians away from this type of testing. He noted that the position paper had been pulled a couple of months prior to the workshop so that the scientific evidence could be re-reviewed.

More generally, El-Sohemy continued, a frequent comment is that single SNPs are useless. In his opinion, there are a number of good examples of single SNPs that modify the effects of specific dietary factors. Another skeptics’ argument, he noted, is that people are not going to change their behaviors, and he reiterated that research has shown the contrary to be true. He also asked the question of when this has ever been an issue, pointing out that some people still smoke, and it is unlikely that they have not heard that smoking causes cancer. Finally, he observed, some skeptics argue that “it’s all about the microbiome.” Yet, he argued, there is good evidence that host genetics determines to a large extent the kinds of bacteria that colonize the gut (Blekhman et al., 2015; Goodrich et al., 2016; Turpin et al., 2016). Although he did not go into detail, he remarked that there are other criticisms that also are not necessarily valid.
Where Are We Today?

El-Sohemy closed by stating that, while the current dietary recommenda-
tions are based on science, he believes they are based on what he considers “old science.” The question this raises for him is, How much more science do we need before we can actually start using DNA-based information? “It is not meant to be revolutionary,” he said. “It is just meant to be evolutionary.” In his opinion, yes, DNA-based dietary advice is ready for prime time.

DISCUSSION

Following El-Sohemy’s presentation, he and the other session 1 speakers (including those whose presentations are summarized in Chapter 2) participated in an open discussion with the audience, summarized here.

Unintended Consequences of Information Provided to Consumers

Session moderator Naomi Fukagawa asked the speakers to reflect on the potential unintended consequences of providing consumers with genetic information and on ways to achieve a balance such that dietary recommendations do not end up being punitive—that is, with people feeling guilty about their dietary choices when they know they have an SNP that increases their risk for a particular health outcome.

Douglas Wallace replied that providing genetic information without genetic counseling can be highly problematic. He commented on recreational genetics companies that sequence various parts of an individual’s DNA, including mitochondrial DNA, and then provide that sequence to the consumer. It is quite common, he suggested, for people to search the Internet and scan the literature to see whether their nucleotides have been correlated with any kind of clinical problem. He receives phone calls from people who have done just that, asking him what they should do to “save themselves from this terrible disease.” People can find information on almost any nucleotide, he observed, with either positive or negative associations. “Without appropriate genetic counseling,” he said, “we are not doing people a real service to give them this kind of information.”

Fasting and the Mitochondria

Panelist Tim Morck commented on what he called a “new genre” of weight loss—fasting, not just fasting intended to mimic diets but also fast-

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2 Recreational genetics refers to direct-to-consumer genetic testing for genealogy and health diagnostic services.
ing itself, that is, going without any nutrients. He wondered whether fasting affects the mitochondria.

There is no question, Wallace replied, that periodic fasting changes one’s metabolic state, and it has been shown repeatedly in model organisms and in some primate studies to affect longevity and other risk factors. There is also clear evidence, he added, that fasting affects mitochondrial metabolism by increasing antioxidant defenses and respiration rate. Additionally, he explained, people make more mitochondria during fasting because they are trying to cope, first, with low carbohydrates, and then with what is basically a high-fat diet (from stored fats). According to Wallace, these aspects of fasting have generated a great deal of interest, as has the question of whether fasting increases mitophagy—the way the body pulls out the accumulation of defective mitochondrial DNA—and how it might be related to longevity. “But I think there is still a huge amount of unknown information that we need to really understand this in any causal way,” he said.

When Morck asked about potential stem cell stimulation in particular, Wallace replied that in fact, some of the most interesting studies have involved introducing mutations into the nuclear-encoded mitochondrial DNA polymerase that increased mitochondrial DNA mutation rates and caused premature aging. But the main effect, he said, was on stem cell biology. “So, yes,” he said, “there is a lot of interaction there.”

Behavior, Behavioral Feedback, and the Brain

In response to the emphasis placed by many speakers on the importance of behavior, Morck asked about the need for better markers of improvement that could help reinforce behaviors. He asked whether “true” metabolomics panels that show benefit might be sufficient to help motivate people. Nathan Price agreed that behavioral feedback is important and pointed out that it is a focus of Arivale and was emphasized in the Pioneer 100 Wellness Project. The risk of a disease in the far future is not very motivating to individuals, he observed, and at present, the company does not explicitly provide people information on disease risk. But with the markers provided, individuals can see changes in their body that are happening now. “In our experience,” he said, “we have seen that to be quite motivating for people.”

Wallace identified as a problem in clinical medicine that “if we don’t have a test, it is invisible to us.” In the field of what he called bioenergetic medicine, there are no good outcome variables, making it difficult to know whether an individual has a low- or high-energy state and whether a nutraceutical or other kind of intervention is actually having an effect. He mentioned that a great deal of time is currently being spent on developing microelectronic and nanoelectronic systems with which to monitor bioenergetics in tissues so there can be some kind of quantifiable outcome variable.
While the discussion was on the topic of behavior, David Alpers observed, “The organ that has been left out of this whole discussion is the brain.” He stressed that many behavior changes are dependent on an individual’s makeup. What drives or motivates a person to stay in a program is not always a test, he asserted; sometimes it is a feeling the person has or something about the way he or she looks. “So that is an enormously important part of the whole equation,” he said, “which usually isn’t looked into very often in this particular setting.”

**Behavior and Coaching**

An audience member asked about the longitudinal follow-up of the coaching that Price had described, wondering whether he and his team had followed participants beyond 6 months to see whether they continued to show improvement either with or without continued coaching. Price replied that many of the Pioneer 100 Wellness Project participants had entered Arivale’s commercial program. So yes, he and his collaborators do have a couple of years of follow-up data on those participants. But, he acknowledged, there was also a gap between the end of the Pioneer 100 Wellness Project and participants’ entry into the program, during which they received no coaching. During that period, many participants had reverted back, he said, so they had not done so well when they were not receiving coaching. When they reentered the program, however, they improved again.

**Questions About the Pioneer 100 Wellness Project**

In response to the previous question about whether the microbiome sequencing conducted during the Pioneer 100 Wellness Project was metagenomic sequencing, Price replied that, while metagenomic sequencing is better and he is advocating for a switch, 16S sequencing was used in the project because of cost considerations. Another audience member asked about the demographics of the project’s population, including diversity of socioeconomic status, and what Price hopes the demographics will be for the 100K Wellness Project. Price replied that the population in the Pioneer 100 Wellness Project was representative of Seattle, so in terms of ethnicity, it was heavily Caucasian, with some Asians and a few representatives of other lineages. With respect to the Arivale program, he explained that, because it is a commercial program, it is “definitely heavily biased socioeconomically.” He said the company would love to launch the program among groups of lower socioeconomic status and had attempted to do so in West Virginia, for example, but the financing had fallen through. He added that the company is exploring different
models of payment in cases where individuals, including those of low socioeconomic status, are at very high risk for disease, and there are other parties with a financial interest in their health.

**Caffeine Fast Metabolizers Versus Slow Metabolizers**

An audience member commented that most cardiologic health events are multifactorial, not single-factor events. She asked El-Sohemy whether studies on fast metabolizers versus slow metabolizers of caffeine had collected nutritional information other than caffeine intake, such as tea intake and overall diet, and whether they had considered the concentration of the coffee people were drinking. El-Sohemy acknowledged that many factors determine the “chemical soup” of a cup of coffee, such as type of bean, the extent of roasting, and other factors. In his opinion, however, those other factors are just “noise,” because whatever the fast metabolizers are drinking, or misreporting (e.g., their cup sizes), the slow metabolizers are drinking or misreporting as well. He explained that the gene he had discussed, CYP1A2, does not affect preference—for example, whether someone prefers Arabica, which has less caffeine than Robusta. Regarding other sources of caffeine, in one of his group’s study populations, 90 percent of caffeine intake came from coffee, even with the consumption of cola beverages and tea. With regard to consumption of other nutrients, he commented that in the myocardial infarction study he had referenced (Cornelis et al., 2006), the reported odds ratios were multivariate adjusted odds ratios that accounted for several confounding factors (e.g., sugar added to coffee, physical activity, smoking). Session moderator Fukagawa added that there are other bioactive compounds in coffee and coffee products that could have had salient interactions as well.

**Treating Specific Nutritional Deficiencies**

In response to a question about when the field will begin treating the type of very specific nutritional deficiencies discussed by Morris—that is, those with clear causality constructs—Morris reframed the question as, Are we really replacing a nutritional deficiency, or is arginine, or glutamine, working and functioning as a drug that works for everyone? Her personal experience in patients with SCD was that glutamine supplementation had the greatest effect on those who were the most glutamine deficient and that glutamine deficiency in those patients’ red blood cells was correlated strongly with their tricuspid regurgitant jet velocity on Doppler echocardiography (a measure of pulmonary hypertension risk). So her bias, she said, is that the patients who should be targeted first are those with the most severe deficiencies.
Additionally, Morris has learned from her studies that the global arginine bioavailability ratio is predictive of clinical outcome years ahead. Thus while children, for instance, have normal arginine levels at baseline, their levels drop acutely during times of pain crisis. Morris was involved with a phase II study that showed that administering arginine to these children during a pain crisis had an impact on pain outcomes.

Finally, when Morris and her collaborators gave arginine to SCD patients at baseline, they saw no effect on NO bioavailability. In fact, they observed a paradoxical decrease in NO that was not overcome by dose. But when they gave arginine to the same patients during a vaso-occlusive pain episode, they saw a rise in NO. “So again,” Morris said, “the patients who have a deficiency are probably the ones who are most likely to respond.”

Ordovás added that, regarding the genetic component, criticism is often raised that there is no clinical proof of benefit. He mentioned a long-term nutrition intervention study of people at high risk of cardiovascular disease, in which participants were administered either a Mediterranean or a low-fat diet. Using the gene TCF7L2, which is related to diabetes, Ordovás and colleagues found that even in people who were aged 60 and older, there was a benefit to using what he described as “the right diet for the right genotype” in terms of reducing the number of cardiovascular events that occurred over the 5 years of the study (Corella et al., 2016).
Before introducing the first speaker of session 2, moderator Wendy Johnson, Nestlé USA, reflected on a few highlights from the morning’s presentations and discussion that she found particularly interesting. She mentioned Patsy Brannon’s discussion of the circular relationship among the genome, diet, and health outcomes; José Ordovás’s description of evidence suggesting that where people live can influence their genetic makeup; Claudia Morris’s remarks on the elusive defined nutrition requirement that appears to change according to various disease states; discussion of how little is known about how behavior impacts nutrigenomics; and several participants’ thoughts on what can be done commercially with personalized medicine to help people, but also the complexity of making nutrigenomics a practical alternative for consumers. Now in session 2, Johnson continued, the focus would be shifting to “how we really take that information and move it forward in a way that makes a difference in people’s lives.” This chapter summarizes the session 2 presentations and discussion, with highlights provided in Box 4-1.

NUTRIENT REQUIREMENTS AS COMPLEX TRAITS: WHAT CONSUMERS NEED TO KNOW

Patrick Stover, Cornell University, began his presentation by describing an incident that had recently taken place when he missed a flight and was sent an Uber driver to accommodate his changed travel plans. It was about 1:00 AM, but the driver was quite chatty, he recalled. She told him about her family and how she had started a career as a personal training
BOX 4-1
Overview of Points Presented by Individual Speakers*

• The food environment has been one of the most powerful selective pressures on human evolution. (Stover)

• Not only does nutrition-related genetic variation exist, but it matters in public health. An example is how knowledge of an MTHFR polymorphism that affects folate status impacted World Health Organization guidelines for optimal folate levels. (Stover)

• In addition to matching diet to genotype, another “precision nutrition” strategy to consider is leveraging real-time, personalized readouts through the use of apps or point-of-care diagnostic devices. However, questions remain regarding what kind of guidance to provide to individuals and whether systems biology can be applied to the tremendous amount of data that individuals are collecting on themselves through these apps and devices. (Stover)

• Much is known about many of the metabolic pathways that nutrients must transit, the genes upon which those pathways depend, and how certain variants of some of these genes (i.e., single nucleotide polymorphisms [SNPs]) act as “roadblocks” in metabolism. Given this knowledge, one could develop nutritional solutions, or medical foods, to bypass roadblocks known to be associated with particular nutrition-related health outcomes. (Zeisel)

• An example is how premenopausal women with a polymorphism of the PEMT SNP require more dietary choline than premenopausal women without that polymorphism. (Zeisel)

• Single SNP analysis is useful, but as the field of nutrigenomics evolves, companies may need to start recognizing the complexity of metabolic pathways and the involvement of multiple SNPs. Nonetheless, one could still intervene with a medical food that delivers the nutrient(s) affected by a multiple SNP-defective pathway. (Zeisel)

* This list is the rapporteur’s summary of the main points made by individual speakers (noted in parentheses). The statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they are not intended to reflect a consensus among workshop participants.

couch and amassed a large clientele. When she learned that Stover was in the nutrition field, she told him that nutrition was the most important guidance she provided to her clients who were morbidly obese. “I use the blood type diet,” Stover remembered her saying, adding, “that’s the single most important thing that improves their health: the blood type diet.” Stover noted that the blood type diet is based on Peter D’Adamo’s book *Eat Right 4 Your Type*, and remarked that his experience with the Uber driver
reflects where he thinks a lot of consumers are in terms of their knowledge of nutrition and health.

Stover then showed a picture of the front cover of a 2010 issue of *Nature* with the headline “Can Science Feed the World?” That is, can science feed the 9 billion people who will be on this planet in 2050? The same issue, Stover continued, contains an article on diabetes. He explained that for him, the question is not whether we can feed that many people, but, “Can we feed them in a way that keeps diabetes off the cover of *Nature*?” He suggested that another way to frame the question, given today’s unprecedented capacity to formulate the food supply in any way desired, is, “What are our expectations of the food supply? That is, when we think about setting dietary and nutrient guidance and recommendations, what are the outcomes we really want to achieve? And what is achievable?” In fact, Stover observed, the U.S. federal government has asked these questions, as indicated by the request to the National Academies that a committee be assembled to develop a consensus report on developing guidance on dietary reference intakes (DRIs) based on chronic disease endpoints (NASEM, 2017a).

Stover went on to stress that making connections between food and disease prevention poses several challenges. He cited as the first of these that few chronic diseases are affected by a single nutrient or a single pathway. Thinking about the relationship between food and chronic disease, he argued, requires considering systems, or networks of pathways, rather than individual pathways, and how these pathways and nutrients converge and interact. This means, he observed, that thinking about biomarkers requires thinking not about single nutrient biomarkers, but about integrative biomarkers that are the endpoints of systems where pathways and nutrients interact and impact chronic disease. Additionally, he stated, as called for in the above-referenced National Academies report (NASEM, 2017a), it means considering DRIs as ranges, not point estimates. He noted further that, beyond considering integrative biomarkers, thinking about chronic disease endpoints requires considering biomarkers of aging and how they interact with biomarkers of nutrition. As a final challenge, he mentioned that the above report (NASEM, 2017a) recommends use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group’s standards of evidence. But, he pointed out, this is a field that is driven primarily by observational data, most of which are not at the GRADE level of evidence needed to set chronic disease endpoints. He added that, given that half of the adult population in the United States is under the care of a physician for some sort of chronic disease, combined with the fact that the DRIs are intended for healthy people and therefore may not apply directly to what is essentially half of the population, the National
Academies convened a separate committee to plan a public workshop to examine nutritional requirements in disease states.  

Stover continued by arguing that, while the DRIs are highly focused on the nutritional needs of healthy individuals, nutritionists need to start thinking about the totality of nutritional requirements and how to classify and evaluate human nutrient needs from health, through disease prevention, to disease management. Acknowledging that there are many markers available that can be used in attempting to understand the nutrient needs for health and disease prevention, he asserted that other types of indicators will need to be considered as nutrition scientists work to understand the connection between food and disease management (see Figure 4-1). These include indicators of tissue-specific nutritional status, because chronic disease often exhibits tissue-specific effects that may not relate to whole-body effects; restoration of function, as addressed by Claudia Morris in her presentation on conditionally essential amino acids (as summarized in Chapter 3); and tissue regeneration (i.e., the unique nutritional needs of stem cells as they repair damaged tissue). Stover suggested that in thinking about the connection between food and disease management, one can begin to think about distinct nutritional requirements (DNRs) instead of DRIs. He noted that these requirements would include medical foods, which provide nutrients that may not be accessible from the food supply in the quantity or quality one needs.

**Dietary Requirements as Complex Traits**

Like previous speakers, Stover described dietary requirements as complex traits. That is, many physiological processes inform the nutrient needs of an individual (i.e., absorption, catabolism, excretion, metabolism, stability, transport, bioactivation, energetic state, nutrient storage), all of which interact with each other as well. He added that nutrient requirements also are affected by a number of modifiers and sensitizers, including disease, but also epigenetics, the food matrix, genetics, nutrient–nutrient interactions, pharmaceuticals, toxins, age and physiological decay, the microbiome, pregnancy, and sex. He noted that although the topic of the workshop was genetics, it does not make sense to consider any one of these modifier or sensitizer variables in the absence of the others, given that nutrient requirements are what he described as “true complex traits.” Of course, he continued, this has been recognized for many years, as indicated by the American Society for Nutrition’s 2013 research agenda, on which one of

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1 For information on this April 2–3, 2018, workshop, see http://www.nationalacademies.org/hmd/Activities/Nutrition/ExaminingSpecialNutritionalRequirementsinDiseaseStatesWorkshop.aspx (accessed April 23, 2018).
the top priorities is to understand variability among individuals in response to diet and food (Olhorst et al., 2013). More recently, he added, the U.S. federal government released the National Nutrition Research Roadmap, 2016–2021, which also focuses not just on the connection between nutrition and disease prevention, but on the importance of understanding individual differences in nutritional status as well (Interagency Committee on Human Nutrition Research, 2016).

Genetics as a Modifier of Nutritional Status

Stover went on to emphasize the importance of remembering, when thinking about the effects of genetics on nutrition, that the purpose of the Human Genome Project was not only to inventory all of the genes in the human genome, as well as variations in these genes, but also to assemble and understand cellular networks, or circuits; variation in these circuits; and how they can be manipulated by inputs, whether these be drugs or nutrients. The impact of genetics on diet is rooted in evolutionary biology, he observed. He showed the cover of a 2002 issue of Scientific American with the headline “Food for Thought.” The article is about dietary change as a driving force in human evolution (Leonard, 2002). Stover explained that the molecular basis of the evolution of a species is the evolution of genes, but not all genes evolve, or change over time, at the same rate. Genes that evolve quickly are those that enable adaptation to a local environment, he noted, adding that upon examination, it appears that one of the most powerful selective pressures in genome evolution is diet. Thus, he argued, today’s human genome—not just its primary sequence, but also genome programming and gene expression—is suited to a particular,
historical nutrient environment. When the genome is exposed to a changed
nutrient environment, he said, people experience food intolerances, special
dietary requirements, and susceptibility to disease.

Stover explained that there are two major contributors to all of the
variation in today’s human genome. First is the introduction of the genome
of archaic humans into that of what are now modern humans. More spe­
cifically, with the recent sequencing of the Neanderthal genome, it appears
that about 500,000 to 1 million years ago, probably through the male
germline, Neanderthal DNA was integrated into the human genome. He
added that, based on identification of the Denisovan archaic humans, it is
now known that Denisovan DNA also became integrated into the modern
human genome. Further, he said, it is likely that a third, unknown hominid
also contributed DNA to the current human genome. He suggested that, in
addition to contributing to understanding of why humans across the planet
are so genetically variable, knowing which Neanderthal and Denisovan
genes became integrated into the modern human genome and how they
affect human traits is of interest to consumers. He cited as an example
23andMe, which offers a genetic test whereby consumers can learn not
just about their ancestry but also what percentage of their genome is
Neanderthal or Denisovan.

Stover identified as a second major source of human genetic variation
mutation events that subsequently extended though a population via either
selection or drift. He explained how computers can identify genes or regions
in the genome in which what he called a “selective sweep” occurred—that
is, where a mutation enabled some sort of selective advantage that displaced
all of the preexisting variation. Many of the genes that show evidence of
selective sweep are related to nutrition, metabolism, or immunity, he noted,
which he interprets as good evidence that nutrition has played an active role
in much of the variation that exists today.

Importantly, however, in Stover’s opinion, the relationship between
nutrition-related genetic variation and phenotype is not a one-to-one cor­
respondence. The one gene in the human genome that shows the strongest
evidence for this type of selection, he observed, is the lactose tolerance gene,
with a mutation in the promoter allowing the gene to be expressed through
adulthood, and therefore allowing a source of nourishment inaccessible to
the rest of the population. However, he noted, when the geographic distri­
bution of this gene is overlaid on a map of the phenotype of lactose intoler­
ance, the two overlap fairly well but not completely (Itan et al., 2010). “No
one gene variant completely determines what the phenotypic expression is
going to be,” he said.

Stover added that there is also evidence of evolution of nutrition-related
copy number variants (CNVs), such as amylase CNVs. Across human
populations, he elaborated, individuals have between one and nine copies
of the gene. Those with high copy numbers are from populations with a history of an agrarian lifestyle (for improved digestion of starch), he explained, whereas those with low copy numbers are from populations with a history as hunter-gatherers. Stover pointed to this as another example of an adaptation that has been driven by the food supply.

Stover went on to observe that many other diet-related genes, such as the calcium transporter gene, have similarly displayed genomic signatures of adaptive evolution by selection (Stover, 2007). He finds it interesting that selection for the lactose tolerance gene appears to have occurred before selection for the calcium transporter gene. That is, only after the lactose tolerance gene arose and expanded and enabled milk consumption did the calcium transporter mutation arise and expand.

Stover suggested that while all of this evidence provides a strong biological premise for the link between nutrients and health, one rooted in evolutionary biology, “what we are not so sure about” is the strength, or penetrance, of the effect. Again, he stressed, dietary requirements are complex traits, and genetics is only one of many factors that determine the relationship among food, nutrition, and health. For Stover, this uncertainty raises the question of whether all of this genetic variation really matters in public health. He went on to describe an example in which, in fact, it does.

The MTHFR polymorphism is a fairly common variant in human populations, Stover explained, with about 80 percent of individuals having a C allele, which codes for alanine, and the other 20 percent having a T allele, which codes for valine. The T allele protein is less stable and less active, and individuals carrying that variant have a lower folate status and, all other things being equal, a higher folate requirement and greater risk for birth defects and miscarriage. However, Stover observed, if individuals with the T allele survive to adulthood, their risk of colon cancer is reduced by 70 to 80 percent if they maintain adequate folate status (Ma et al., 1999). He noted that this finding has been replicated in several cohorts. “This is a very powerful effect from a single nucleotide polymorphism,” he said.

The C and T allele frequencies at the MTHFR polymorphism vary across the globe, Stover added. He explained that the polymorphism clearly arose after migration out of Africa, but it does not show a signature of selection, so it either accumulated through drift or entered the human genome from another archaic human.

Stover stated that there is also good evidence from controlled feeding trials that the variant can affect nutrient requirements for folate. When Solis and colleagues (2008) fed adult Mexican men the recommended daily allowance (RDA) for folate, they found that initially, serum folate levels dropped for both CC and TT individuals, but by the end of 12 weeks, the CC individuals had significantly higher levels of serum folate relative to the CC individuals. In addition, homocysteine level, which is a functional
biomarker of folate metabolism, did not change over time among CC individuals but rose markedly among TT individuals. According to Stover, “This is an example of one single polymorphism that definitely affects nutrient requirements.” In fact, he suggested that the RDA is probably not adequate for Mexican American men who harbor the TT genotype. But again, he asked, whether these findings have affected policy. The answer, he said, is yes.

In 2015, the World Health Organization (WHO) published a guideline for optimal serum and red blood cell folate levels to prevent birth defects (WHO, 2015). Stover explained that this action was taken in response to member states approaching WHO and asking how much folate they should be adding to their food supplies. He described the WHO (2015) committee’s work as remarkable because it represented the first time a chronic disease endpoint was being used to help establish a nutrition reference value, and because big data integration was used to reach this conclusion. Regarding the latter point, he explained that there was a paucity of data linking folic acid intake to risk of neural tube defects and that what data did exist were of low quality. However, there were data linking folic acid intake to folate concentration in red blood cells. So through Bayesian modeling, Stover explained, the WHO (2015) committee was able to derive a computed dose-response curve predicting estimated risk of neural tube defects as a function of folate concentration in red blood cells (Crider et al., 2014). He added that, although the curve was computer generated, data from the one empirical study that does exist, a small study in an Irish population, align with the big data curve of Crider et al. (2014) and the WHO (2015) committee. He highlighted this as a case in which evidence of a single polymorphism was used to generate a guideline, in this instance on what the optimal level of folate should be to prevent neural tube defects.

Genetic Testing: What Consumers Will Need to Know

Stover pointed out next that consumers have available to them a range of genetic tests that are providing not only ancestry information but also, increasingly, health information. He raised the question of what consumers really need to know to use this information.

It has been suggested, Stover observed, that individuals be classified into subgroups for diets, which he noted had already been discussed earlier in the workshop. He referenced the recently released National Academies report on redesigning the process for the Dietary Guidelines for Americans (DGA), which emphasizes not only the prevention of chronic disease but also the need to take into account a range of individual factors, including age, gender, and metabolic health (NASEM, 2017b). He identified as a challenge to this approach, however, that although there have been many
studies on various types of diets and how they affect health in human populations, most of those studies are based on observational data, and very few are long-term.

Stover cited a recent long-term study in inbred mice, in which Barrington and colleagues (2018) fed the mice one of four diets—American, Mediterranean, ketogenic/Maasai, or Japanese—for much of their lifetime and compared the diets’ effects on metabolic health. Additionally, they measured certain health-related metabolic and epigenetic markers over time. Stover reported that the study showed that the best diet for maintaining health varied depending on both the health outcome of interest and the genetic background of the mouse. So, for instance, among mice fed the Mediterranean diet, HDL cholesterol levels were at very healthy levels in one strain but not another (see Figure 4-2). In Stover’s opinion, these findings provide a good biological premise for matching diet to genotype. “Of course,” he said, “the challenge is, how are we going to classify people? Because we can’t classify them based on inbred strain, if you will.”

**FIGURE 4-2** (a) Diet ingredient profiles and geographic origins for the four diets fed to the mice in the Barrington et al. (2018) study; (b) comparison of metabolic phenotypes in each strain of mice fed the Mediterranean, Japanese, and ketogenic/Maasai mouse diets relative to the American mouse diet.

NOTE: A = A/J strain mice; ALT = alanine aminotransferase; B6 = C57BL/6J strain mice; Chol. = cholesterol; FVB = FVB/NJ strain mice; GTT = glucose tolerance test; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NOD = NOD/ShiLtJ strain mice; TG = triglyceride.

SOURCES: Presented by Patrick Stover on December 5, 2017, from Barrington et al., 2018. Reprinted with permission from the Genetics Society of America.
Instead of classifying subgroups of people by diet, Stover continued, it has been suggested that subgroups be classified by nutrients. This approach, he explained, is based on the precision medicine model, in which a prognostic test related to a risk for some chronic disease predicts whether a drug will work or which drug will work, as well as how to dose the drug. According to Stover, however, this approach has been somewhat problematic for nutrition thus far. He cited the example of diabetes, which is such a complex trait affected by so many nutrition-related variables that it has made classifying individuals difficult. He asked, “Does it really make sense to split the pie up in so many pieces?”

In fact, in Stover’s opinion, it may not even matter. Instead of classifying subgroups by either diet or nutrient, he elaborated, the trend toward real-time personal readout has created a third possibility. He pointed out that people are collecting a tremendous amount of data on themselves, with apps available to record how many steps they have taken, what their blood pressure is, and so on. Increasingly, he added, high-resolution biomarker data are being collected and will be available to almost everyone. Still, he suggested, the questions are what guidance will be provided to individuals and whether systems/network biology can be applied. He then cited one example of point-of-care measurement of nutrition-related biomarkers, explaining that his colleagues at Cornell University have developed what they call the Nutriphone, a smartphone-based microfluidic device. He described this device as much like a pregnancy test, except that it provides a real-time readout of 8–10 nutrient status markers, functional biomarkers, chronic disease markers, and infectious disease markers (Lee et al., 2016). According to Stover, the price of the device will eventually fall to a few dollars, but again, he raised the question of what consumers will do with the information collected.

In an attempt to understand how best to help consumers with the genetic and other information now emerging, Stover and his group have been working with researchers at the University of Toronto to develop a stochastic model for understanding metabolism networks. They have recreated the entire folate network, running the simulation for hours or days at a time, with different inputs, until the system reaches equilibrium, and they are using the model to conduct sensitivity analyses for changes in gene expression and enzyme levels (Misselbeck et al., 2017). Stover described this as the type of algorithm that will be needed to manage all of the data coming from cell phone apps. He envisions plugging one’s phone into some sort of computational model and then receiving guidance on how to optimize the function of one’s own network.

In closing, Stover mentioned that he was helping to organize the First International Conference on Precision Nutrition and Metabolism in Public Health and Medicine (September 21–26, 2018, in Crete, Greece), with the
goal of bringing together people in the fields of nutrition, engineering, and computer science to address how a systems-level understanding of nutrition can be used to provide better guidance to consumers.

**GENE-GUIDED NUTRITION INTERVENTIONS**

Steven Zeisel, University of North Carolina at Chapel Hill, began by saying that he would be sharing his thoughts on how to develop a nutrigenomic application in industry based on his work with a number of companies that are doing just that. Additionally, he himself was involved in the early startup phase of Zthera, a gene-guided medical foods company.

“We’ve heard over and over again how metabolically different we are,” Zeisel said, noting that each individual has about 50,000 common, inherited single nucleotide polymorphisms (SNPs) out of the millions that exist. Because people have inherited these SNPs from their ancestors, he explained, the distributions of many of them differ among populations. As an example, he cited the distributions of the GG, GC, and CC genotypes of the \( \text{PEMT} \) rs12325817 polymorphism. These genotypes vary worldwide, with their proportions differing among populations in Africa, Asia, Europe, and America. Zeisel noted that the C allele is associated with inefficient choline production.

But because so much is already known about metabolism, Zeisel continued, there is no need to be overwhelmed by such complexity. Scientists understand the metabolic pathways, he elaborated; they know that nutrients have to transit these pathways; they know that each of these pathways depends on a number of genes; they know what these genes are; they know how the different pathways interact with each other; and they know that the polymorphisms that affect the function of a gene in a specific pathway will have a metabolic marker, such as buildup of a precursor or less final product. “So we can cut down on the complexity of what we look at,” he said, “and increase the power by having pre hoc hypotheses based on our understanding of metabolism.”

Zeisel pointed out that some polymorphisms that are functionally active will create “roadblocks” in metabolism—for example, by changing the affinity site of the enzyme or by changing the regulator of a gene, thereby making metabolism inefficient. “If we know this,” he said, “we can ask, how do we step around this? . . . How could you develop nutritional solutions or medical foods, if they meet all the other Food and Drug Administration (FDA) criteria, that are specifically designed to bypass each of the roadblocks that you identify as being associated with a health condition related to nutrition?”

Zeisel went on to observe that not all SNPs cause functional change. For example, more than 1,000 polymorphisms for the gene \( \text{PEMT} \) have
been identified in humans, but only a selected subset—about 10 thus far that have been identified—are functionally important (i.e., because they change, for example, the binding site or a response element). But if one of those SNPs that are functionally active causes a roadblock, Zeisel explained, it creates a bottleneck such that less metabolite is being produced and more precursor is building up, unless diet hides this fact. That is, if someone has a metabolic inefficiency because of one of these SNPs but is eating enough of the relevant nutrient to push through the bottleneck, the SNP will not manifest as functionally important (see Figure 4-3). It is only when one is challenged by having low amounts of the nutrient in one’s diet that an inefficiency becomes important. Zeisel said he would be giving an example of this from his research with choline (see the following section), but first he argued that this is why genome-wide association studies (GWASs) have been “so abysmal” at identifying nutritionally relevant SNPs. By failing to consider dietary intake, he elaborated, GWASs combine people who are consuming large amounts of a nutrient with people who are challenged for the nutrient, thus canceling out any significant effect among those who are challenged.

FIGURE 4-3 By delivering large amounts of a metabolite, diet can bypass, and “hide,” a metabolic roadblock caused by a single nucleotide polymorphism (SNP). SOURCE: Presented by Steven Zeisel on December 5, 2017.
Gene-Guided Nutritional Intervention: Choline as an Example

Zeisel began his discussion of choline by remarking that anyone can do with another nutrient what he and his colleagues have done with choline—that is, identify genetic polymorphisms that explain the difference between responders and nonresponders to a nutritional intervention. He then mentioned that in addition to an adequate intake (AI) recommendation set by the Institute of Medicine (IOM, 1998), choline has had approved FDA labeling since 2016. He also explained that choline is important for both the liver and muscle. It can be made in the liver through the enzyme coded by *PEMT*, and it is contained in such foods as liver and eggs, as well as other high-cholesterol foods. But Zeisel cited National Health and Nutrition Examination Survey (NHANES) data (2009–2014) showing that most Americans are not meeting the recommended AI for choline, which is about half a gram per day for adults, a finding with especially important implications for pregnancy and lactation, as he would explain later. He noted that only small children, who drink a great deal of milk, come close to achieving their recommended AI, making choline what he called a “problem nutrient.”

In one of his first choline studies, Zeisel and his team questioned whether the half a gram per day requirement was really necessary. To explore this question, they removed the nutrient from their study participants’ diets to see if they would develop fatty liver or liver or muscle damage caused by apoptosis. In the process, they noticed that young women needed less choline relative to both men and postmenopausal women (Fischer et al., 2007). After 42 days without choline, only 44 percent of the young women got sick. In contrast, most men (77 percent) and post-menopausal women (80 percent) got sick. Most of the participants who fell ill presented with fatty liver and liver damage, and only about 10 percent presented with muscle damage.

So Zeisel and his collaborators asked the question of what is different about young women. Why is it, they asked, that 56 percent of young women do not need choline? Estrogen appeared to be an obvious answer, Zeisel recalled. Indeed, the researchers found that *PEMT* is induced by estrogen and is turned on at exactly the concentrations of estrogen that are achieved during pregnancy (Resseguie et al., 2007). But if that is the case, Zeisel’s team asked—that is, if women can turn on *PEMT* to make their own choline when estrogen is present—why do 44 percent still get sick when deprived of choline? According to Zeisel, it turns out that there is a polymorphism, or set of polymorphisms, in the estrogen response element for *PEMT* that prevents *PEMT* from responding to estrogen even if a woman’s estrogen level is high (Resseguie et al., 2011). Women who are homozygous for the C allele at *PEMT*rs12325817 do not respond to
estrogen at all, he reported, in contrast to women who are homozygous for the G allele, who do respond, and heterozygotes, who respond somewhat. Because women who are CC at this polymorphism cannot increase their production of choline during the high-demand period of pregnancy and lactation, he added, they need to ingest choline. Zeisel explained that it was because of this kind of data—that a polymorphism can help predict which women will need choline in their prenatal diet—that the American Medical Association (AMA) voted for the first time in 2017 to recommend that prenatal vitamins contain choline.

As Zeisel had mentioned earlier in his presentation, the different genotypes at the PEMTrs12325817 polymorphism are distributed differently around the world. In Europe and America, 72 percent of women have one or more alleles of the C allele, and 22 percent are homozygous for it. In contrast, very few women in The Gambia have the C allele. Zeisel explained that the indigenous diet in The Gambia is very low in choline, which he said is an indication that the C allele was selected against. Among the Maasai in Kenya, by contrast, where the diet is higher in choline, the C allele is as common as it is in Europe, where there was enough choline in the diet (e.g., in eggs) so that presumably there was no such selection (Silver et al., 2015).

Regarding the effects of low choline on the fetus, Zeisel shared results from a mouse study showing that when pregnant mice were fed a low-choline diet, their offspring had significantly fewer neural progenitor cells relative to the offspring of control mice (Wang et al., 2016). This phenotype, he explained, has a lifelong effect on memory in mice and probably occurs in humans as well. It has been shown, he reported, that maternal choline intake during the first and second trimesters of pregnancy is correlated with performance at age 7 years on a cognitive test known as the Wide Range Assessment of Memory and Learning, 2nd Edition (WRAML2), with an apparent dose-response (Boeke et al., 2013).

Based on this cumulative evidence, Zeisel envisioned a company forming around this scenario: a gene test (for the PEMT SNP), an obvious intervention (dietary choline), and a common mutation (72 percent of women in the United States having at least one allele for this gene).

Recognizing the Involvement of Multiple SNPs

While single SNP analysis is useful, Zeisel continued, as the field of nutrigenomics evolves, companies will need to start recognizing the complexity of metabolic pathways and the involvement of both multiple pathways and multiple “hits” within pathways. He explained that with choline, for example, other SNPs besides the PEMT SNP can alter sensitivity to low choline and put people at greater risk of becoming depleted and developing liver or muscle problems. In addition to this observation having been
demonstrated in his own work with multiple SNPs (da Costa et al., 2006, 2014; Kohlmeier et al., 2005), Caudill and colleagues (2009) showed that MTHFR alters sensitivity to low choline and increases one’s choline requirement. According to Zeisel, these other SNPs can be found at almost every step of the choline pathway.

Another question that has interested Zeisel is why choline deficiency presents differently, with 90 percent of individuals developing fatty liver and the other 10 percent developing muscle damage. So again, he and his research team examined the responders and nonresponders to see what was different about them and found that people who are choline deficient cannot export fat from the liver as very low-density lipoprotein and thus develop fatty liver (Corbin et al., 2013). He explained that this is because choline is needed to export fat from the liver. That is, the liver makes a “wrapper” out of phosphatidylcholine to export the fat, and without this wrapper, the fat remains in the cytosol. But given that a number of pathways affect how fast the liver can package fat and how much choline is needed, Zeisel and his team genotyped the liver tissues of a population of individuals who had provided liver biopsies, for various reasons. They found a number of SNPs in other pathways (e.g., genes related to choline metabolism, folate metabolism, fatty acid transport, and bile synthesis) that were also associated with fatty liver (Corbin et al., 2013). When they included these genes from the other pathways in their prediction model, they were able to predict susceptibility to liver disease with 95 percent accuracy, compared with 70 percent when they included only the choline polymorphisms. Additionally, however, they found that the predictive power of these polymorphisms was what Zeisel termed “totally useless” in lean people, because lean people are not making a large amount of fat in their liver and can afford to be inefficient at exporting it. Thus it is only individuals with a high body mass index (BMI) for whom export of fat from the liver is important because their liver produces much more fat from the excess calories they consume, and for whom these polymorphisms predict the development of fatty liver.

As a result of this research, Zeisel’s team now has a gene test for 19 SNPs in women and 21 in men that predict susceptibility to developing fatty liver with 90 percent accuracy among people gaining weight. According to Zeisel, a nutritional intervention that bypassed the choline-related SNPs probably would be about 70 percent effective, while an intervention that bypassed all of the roadblocks probably would be about 90 percent effective. In his opinion, given the difficulty of delivering all of these metabolites with a normal diet, the best intervention likely will be a medical food. The idea, he reiterated, is that by giving people whatever metabolite they are unable to make because of a metabolic roadblock, the problem is solved theoretically. And in fact, he asserted, in the case of choline it works: when
people who are choline deficient and who have developed fatty liver are given choline, their fatty liver resolves.

Zeisel then turned to the 10 percent of people who are choline deficient and have developed muscle defects. It turned out, he reported, that everyone in his team’s study who developed muscle damage (rhabdomyolysis) had SNPs that resulted in a problem in the transport of choline into the muscle cells and in phosphorylating choline once it had entered the muscle cells. He explained that, as with glucose, choline metabolism entails phosphorylating the choline to give it a charge so that it cannot leak out of the cell. In addition to the choline polymorphisms he had discussed, the MTHFD1 polymorphism also appears to predict who is going to develop rhabdomyolysis, as measured by leakage of creatine kinase from muscle cells (da Costa et al., 2014). More specifically, he continued, during exercise, people break down their muscles more if they have these polymorphisms and are eating a diet lower in choline. So again, he predicted the opportunity for another medical food as a solution to a blocked metabolic pathway, or pathways—in this case the SNPs responsible for muscle breakdown during exercise.

SNPs and Sperm Dysfunction: Another Example of Gene-Guided Intervention

Zeisel went on to explain that when a study is conducted in humans and polymorphisms are identified that appear to be important, as was the case with choline deficiency, those polymorphisms can be knocked out in mice and other effects examined. So he and his team knocked out the choline dehydrogenase gene, Chdh, in mice because it was one of the genes that affected the choline requirement in humans, and they found that the mice developed what he characterized as horrible-looking mitochondria in their sperm (Johnson et al., 2010). The sperm were infertile, unable to swim, and unable to make adenosine triphosphate (ATP). The researchers then found that they could restore sperm function in the mice by giving them the metabolite (betaine) that was being blocked from production. Although Chdh is a nuclear gene, Zeisel noted, the protein resides in the mitochondria.

Zeisel’s team next examined this same polymorphism in men (Johnson et al., 2012). It is a common polymorphism, he observed, existing in about 5–9 percent of men, depending on lineage. The researchers found that men who are homozygous for the T allele make little ATP in their sperm, and heterozygotes can make only half as much ATP as GG homozygotes. Although the sperm in the men with the T allele “look terrible,” as they did in mice, Zeisel and his team have yet to test whether they are less fertile.

2 Rhabdomyolysis is a condition in which damaged skeletal muscle breaks down.
He suspects that they are, as their sperm do not swim well. “So again,” he said, “you can imagine if you were trying to think of a company, you could genotype men who are unable to have a baby, predict poor sperm function using ATP in sperm as a biomarker, and conduct a clinical trial to see if their low sperm ATP is reversible by delivering the metabolite that bypasses the genetic roadblock.” And again, he emphasized his underlying thought process: “Take what you know about metabolism and use that to predict what nutrigenetic test and treatment should work.”

**Future Developments: Medical Foods as a Starting Point for Developing Nutrigenomic Products**

To move forward, Zeisel called for better methods for working with complex metabolic pathways involving multiple SNPs. He remarked that he had been focusing on choline because that is his area of expertise. But he argued that the same approach could be used to study vitamin D, for example, to design interventions that would bypass specific inefficiencies in metabolism that contribute to the problems people have with vitamin D.

Additionally, Zeisel called for a better way to include diet information in GWASs. He remarked that, as part of many precision medicine initiatives, researchers are going to be measuring genes and metabolome, but, he said, “they are not thinking of collecting nutritional data.” Yet without those data, he asserted, it will be impossible to know who is being challenged by low or high intake. If people with a polymorphism are not being challenged, he added, they will look the same as people without the polymorphism.

Finally, Zeisel encouraged the workshop participants to think about medical foods, as defined by FDA, as a potentially good starting point for developing nutrigenomic products. He referred to José Ordovás’s description of what Zeisel called the “prototype medical food”—a food for rare mutations that cause aminoacidopathies, such as phenylketonuria. He argued that the same strategy could be used for metabolic roadblocks, except that instead of bypassing a rare mutation, the medical food would be bypassing a common polymorphism. In his opinion, an intervention that specifically bypasses a multitude of blocked pathways would not be easily deliverable in a normal diet; indeed, it would not even necessarily be easy to calculate, he opined. Therefore, he said, “it is the perfect fit to the FDA’s current definition of what a medical food should be.”

**DISCUSSION**

Following Zeisel’s presentation, he and Stover participated in an open discussion with the audience, summarized here.
Questions About the Potential Role of Medical Foods in Nutrigenomics

Much of the discussion revolved around the potential role of medical foods in nutrigenomics, beginning with a question from an audience member about Zeisel’s rationale for working toward developing choline as a medical food when it could be a dietary supplement. Zeisel agreed that if choline alone were the issue, a dietary supplement would be a good nutritional solution, but he argued that when multiple pathways are involved, a medical food makes more sense. The advantage of a medical food, he asserted, is that a physician or other health professional would be overseeing the interpretation of the gene test for its need. Additionally, he observed, physicians understand prescription medicine, and a gene test tells them what to prescribe. The test, he elaborated, validates that there is a problem and that they are really treating something, providing both physician and consumer with more confidence. He added that, because developing this type of nutritional intervention will require research and investment, it would be beneficial to make it something (i.e., a medical food) that brings slightly higher returns to account for that extra cost.

Another audience member, noting that “Food Product Development” was in the title of this session, questioned how nutrigenomics tools will impact what kinds of food products become available, how widely used these products will be, and what the regulations around them will be. She pointed to gluten-free foods as an example of a class of food products that has become very mainstream and is related to a medical condition that she presumed could be predicted with nutrigenomics tools.

“I would say we are at a frontier,” Zeisel replied. He predicted that someday, it will be obvious how to develop foods that are not commodities, that is, foods that have a little extra value because they are designed specifically to deal with a health problem. They may or may not be based on genetics, he added. “We’re going to have a lot of snake oil,” he acknowledged, “but we have a lot of snake oil diets with regular foods.” He emphasized that he liked the idea of medical foods as a starting point because FDA has already set some ground rules in this area. The agency has not fully defined the problem, he remarked, but with what it has defined, there is at least some oversight. At the same time, he characterized the development of a medical food as “kludgy,” requiring a much greater financial investment and being more difficult relative to developing a dietary supplement. Yet, he said, using the term “medical foods” is a way to differentiate these products from those developed by what he called “mom and pop operations” that sell products that do not work. Once it can be shown that a nutrition intervention works as a medical food, he suggested, one can work backward and consider how to make it an over-the-counter intervention and distribute it to the public at large.
Douglas Wallace remarked that one of the goals of nutrigenomics is to minimize chronic disease. “The pharmaceutical industry would love to develop drugs that have the same effect,” he said. He asked how these conflicting perspectives on how to deal with chronic disease are going to be managed when an estimated 50 to 60 percent of the population is being prescribed pharmaceuticals to minimize a chronic disease.

Stover replied that FDA is very clear about the effect of chronic disease treatment on nutrition; that is, if a pharmaceutical changes one’s requirement for a nutrient, the change must become part of the formulation for the drug. He suggested that perhaps this rationale needs to be revisited given how widespread use of these drugs is today, but that is how it currently stands. With respect to which is going to play the bigger role in lowering rates of chronic disease—food or drugs—Stover expressed the view that both need to move forward, but, he said, “I think a lot of the evidence is that these are diet-driven, and in the long run, the diet-driven approaches are going to be the best approaches in terms of lowering rates of chronic disease without side effects and without the added health care cost.” At the same time, he added, those are decisions made by politicians, not scientists.

Tim Morck agreed with Zeisel that medical food appears to be an appropriate category for nutrigenomics products. However, he observed, not everyone is familiar with what he described as “all the narrowness” that this characterization entails from a regulatory standpoint. Choline is a nutrient, he said, “so at least it gets that part of the box checked.” But he argued that many people are trying to make medical foods out of things that are not actually nutrients. He identified as a second challenge with the medical food category that although medical foods require medical supervision, which he agrees is an appropriate approach, it is important to emphasize that these products are for nutritional management. One would not be able to say, he elaborated, that they are being used to treat a disease because that characterization is allowed only for drugs; instead, one would have to say that they are being used to address the nutritional imbalance a patient has by virtue of a genetic condition, or in some cases, a disease impact. He argued that this then calls into question how to talk about nutritional balance, or normalization—in other words, the restoration of normal metabolism—rather than about a pathological condition. Keeping this in mind, he said, medical foods are the only categorization that would allow for a nutritional treatment for patients with disease, as dietary supplements can only help support normal function.

Zeisel clarified that he was not suggesting a medical food is the only way to start implementing nutrigenomics; rather, he was suggesting that it might be the best way to get the field started. It is credible, he argued, because it has science behind it. Moreover, he suggested, given the complexity of nutrigenomics, developing a medical food rather than focusing
on dietary advice is a way to simplify and focus on a small problem with a well-understood outcome. He predicted that eventually, products will be developed that address multiple problems, and the idea that nutritional intervention works will begin to permeate medicine. At that point, physicians will be able to tell their patients, “Go out and eat more eggs.” (During his presentation, he had mentioned eggs as a dietary source of choline.) But at present, in his opinion, most physicians would not be comfortable telling their patients, “Go out and eat more eggs”; they would be more comfortable with conducting a genetic test and then prescribing a nutritional intervention on the basis of its results.

The audience member observed that, given the direction this field appears to be going, it eventually will require the involvement of both clinical nutrition and clinical genetics, as well as medical supervision. Yet, she asserted, even adults who have inborn errors of metabolism caused by single gene defects are not well handled right now in what she described as “the great hospitals of America.” She acknowledged that perhaps children with these disorders are being well handled, but argued that their adult counterparts are not being integrated into internal medicine, adding that she was unaware of the situation with surgery. She asked, “How is this all going to be handled, this brave new world?”

Medical foods fit the precision medicine model, Zeisel replied. He described precision medicine as a powerful movement at present, with the support of both federal researchers and many large medical schools, and as a subject being taught to every medical student today. “I think everybody will be practicing that way,” he said, so “this will just look the same to them.”

Stover suggested that the formulated medical foods being used to treat loss of function in individuals with inborn errors of metabolism also serve as a model. In the case of inborn errors of metabolism, he noted, the loss of function is due to a single-gene defect, and many chronic diseases are similarly due to a loss of function, not in a single gene, but across multiple genes, and other factors, such as inflammation. Thus, he argued, just as medical foods are used to restore function in individuals with single-gene inborn errors of metabolism, they could also be used to restore function in people with chronic disease.

**Foods: From Wellness to Therapeutics**

Naomi Fukagawa called attention to what she called a “spectrum” of classifications for food, from wellness to therapeutics, and asked how categories of food along this spectrum will be differentiated from each other and from supplements.

Stover clarified that some chronic disease can be initiated prior to
conception. It is a trajectory over time, he said, and nutrition can change or modify that trajectory. He suggested that complete prevention may not be possible in all cases, and the idea of the food supply and wellness does not always align well with the idea that chronic disease manifests over a lifetime as the result of multiple factors, including genetics and others, in addition to diet. For Stover, the question to ask is when the requirements of an individual fall outside the realm of what can be achieved through a natural, food-based diet because of genetic or other age-related factors. For example, he observed, depending on one’s genetic makeup, one may not be able to get enough folate from the food supply without fortification or supplementation to prevent the risk of neural tube defects.

Zeisel suggested that another way to think about Fukagawa’s question is that without a challenge, a person may be phenotypically healthy, but when challenged, that person’s genetic or other limitations are revealed, and they get sick. For example, he noted, there is no need to worry about fatty liver in someone who is not consuming excess calories or is not making a large amount of lipid in the liver. In that case, he said, transport of fat out of the liver does not matter; it becomes important only when a person is challenged. Thus, he observed, one could anticipate the fatty liver phenotype appearing as a person moves toward becoming overweight, which is when the need to transport fat out of the liver increases. So the question for Zeisel is, What is the challenge that is going to reveal someone’s metabolic inefficiency? The limitation of this approach, he added, is that it misses things that were never conceived as being likely. The other approach, which will reveal things not anticipated to be present, is to measure everything and see what is correlated with health outcomes. But this approach, Zeisel argued, is limited by the fact that the results will be associational and not based on an understanding of the person’s biochemistry and metabolism.

**Nutrigenomics in the Context of Preexisting Conditions**

An audience member asked about the future of genomics, metabolomics, and proteomics given that preexisting conditions may cause a problem with insurance for today’s children. Stover responded that insurance coverage is one of the greatest challenges with medical foods—for example, for children with inflammatory bowel disease who are dependent on a liquid diet for their survival. It is very difficult, he observed, for those families to get insurance to pay for these products. He stated that political interest in this issue is currently growing, and a bill now pending, the Medical Nutrition Equity Act of 2017, would address the problem. The question is, he suggested, What will be the standard of evidence that justifies this huge expansion in reimbursement, that demonstrates these products actually work and are meaningful for
managing disease? “That is something that this community is going to have to wrestle with,” he said.

In Zeisel’s opinion, if someone already has a problem, such as fatty liver or rhabdomyolysis, his or her physician is already looking for the optimal treatment at the lowest cost. He argued that testing is standard for physicians, and if a test comes back positive, the physician feels confident prescribing a treatment. If a test shows that someone has a specific metabolic effect, for example, and there is a medical food designed to treat that effect, Zeisel would argue that prescribing that medical food as an intervention poses no greater risk than would be the case if there were no such option.

Zeisel suggested that eventually, babies will be genotyped at birth. Thus, for example, if a person were prescribed warfarin later in life, that person would not need to be genetically tested because his or her genotype would be on file. Zeisel cautioned, however, that legislation will be necessary to ensure that this type of screening does not place people at a disadvantage. He mentioned a study in which he was involved with the National Aeronautics and Space Administration (NASA), in which 16 of 32 astronauts who spent more than 16 months in space were found to have permanently lost visual acuity by the time they returned. It is not clear why, he said, but the best clue is that they have higher homocysteine levels, not out of the normal range, but still higher than those of the other astronauts who did not lose visual acuity. They have some polymorphisms as well, he added. Once NASA knows the genotype associated with lost vision, he observed, it will not want to send those astronauts to Mars. So again, he added, there is a risk to genetic testing, and there must be either legislation or a treatment. He mentioned a similar situation with the U.S. Army Special Forces, among whom a significant percentage have developed rhabdomyolysis and had to be sent home from the field. Again, he noted, the army would like to avoid rhabdomyolysis in those people, so soldiers are not going to want to be genotyped. On the other hand, he said, if there is a solution related to the genotype that cures the problem such that muscle breakdown does not develop, it will be worth being genotyped.

Implications for Dietary Guidelines

Wendy Johnson posed the question of what understanding of genetic variation and how the environment impacts gene expression means for dietary guidance. Will dietary guidelines still exist in “this new world,” she asked, or are they to be abandoned altogether and replaced with something more progressive?

For Stover, the question is whether the focus will be on clinical nutrition in a patient or in a population. “I think the answer is both,” he said.
He referred to the description in his presentation of the WHO recommendation for fortifying the food supply to prevent neural tube defects, and how the WHO committee included in its model the effects of the \textit{MTHFR} polymorphism on folate status and the prevalence of the polymorphism in the population. He explained that the question will always be the degree to which any sort of modifier or sensitizer (e.g., the \textit{MTHFR} polymorphism) affects the requirement for a given nutrient. If there is an identifiable group that falls outside of the normal population distribution, he observed, then either the value for the nutrient will need to be changed to accommodate that minority group, or the group will need to be considered a separate subgroup with separate nutritional requirements. Then the question becomes, he suggested, how many subgroups there can be. “But there is no way I think we are going to be able to walk away from having population-based nutritional requirements,” he asserted, “because that’s the basis of the food supply. The question is, how do we deal with people who fall outside the distribution?”

In Zeisel’s view, a polymorphism found in 72 percent of U.S. women (i.e., those with at least one \textit{PEMT} C allele), represents a large enough identifiable group to be accommodated. On the other hand, he suggested, a polymorphism that occurs in only 1 percent of the population may be too infrequent to accommodate. As far as what accommodation entails, he said it could involve a genetic test indicating whether someone needs, for example, more of a particular nutrient, or it could involve extending the upper limit of the nutrient to meet that higher nutritional requirement. He cautioned that the latter approach would be pushing toward toxicity.

With respect to the number of identifiable groups, Zeisel suggested that the next step for the dietary guidelines may be to base recommendations on haplotypes. He described a haplotype as a “lumping of genes that tend to travel together with an ancestry,” and remarked that there are many fewer of them than SNPs.

Stover urged the workshop participants to keep in mind, especially when thinking about chronic disease endpoints for either dietary or nutrient guidelines, that the risk factors for chronic disease include genetics, but they also include age and diet and the interactions among genetics, age, and diet. “The aging genome has just as much effect on a chronic disease, and maybe even on nutritional requirements, as genetics,” he asserted.

**Consolidation and Collaboration**

Nathan Price remarked that both Stover and Zeisel had addressed the notion of “genetics under challenge,” which he subscribes to as well. He noted that for GWASs, a 1 percent effect is considered large, yet speakers in this session had presented examples of much larger effects under challenge.
He asked about the degree to which this information has been catalogued or consolidated such that other people can learn from it. Additionally, he asked how the field can move beyond a few examples to begin studying genetics under challenge on a large scale.

Stover replied that many databases are available to aid in developing the architecture of a metabolic network, such as those for gene expression, SNPs, the proteome, and the transcriptome, any of which can be used to set a range for or circumscribe the magnitude of an effect at any one node. Yet, he added, although the information is available, one must have some familiarity with the field to understand it. Once the dynamic range of an effect is known, he observed, one can perform a sensitivity analysis to determine how different inputs of nutrients affect the range of responsiveness. But, he added, there has been no coordinated effort to examine and determine, node by node, the degree of stochasticity of expression that is associated with each node, something he believes is clearly needed.

Zeisel called for greater collaboration between experts who know how to measure the genome or metabolome but do not really understand metabolism and experts in nutrition and other fields who understand metabolism and know the inputs, outputs, and challenges along a pathway. He stressed that most GWASs are focused only on statistical association, without accounting for the fact that both challenged and unchallenged individuals are involved.
Nutrigenomics: Regulatory, Ethical, and Science Policy Considerations

In session 3, moderated by Patsy Brannon, speakers considered a range of policy and ethical issues in personalized nutrition. Their presentations took a close look at the nature and strength of nutrigenomic evidence in terms of both what it needs to be and what it is, and at consumer perspectives, behaviors, and ethics. This chapter summarizes the session 3 presentations and discussion, with highlights provided in Box 5-1.

Scientific Basis of Genetically Personalized Nutrition: Ethical Implications of Methodological Limitations

To begin her discussion of the ethical implications of the methodological limitations of the scientific evidence for personalized medicine, Cecile Janssens, Emory University, remarked that she had presented a similar lecture at the 2008 Evaluation of Genomic Applications in Practice and Prevention (EGAPP) meeting in Atlanta, Georgia. The title of that talk was “A Critical Appraisal of the Scientific Basis of Commercial Genomic Profiles Used to Assess Health Risks and Personalize Diet and Lifestyle Interventions.” At the time, she recalled, there were many companies selling personalized diet DNA tests via the Internet, with many people believing what Janssens referred to as the “myths about weight loss.” For example, Genotrim was among the first companies to introduce a DNA-customized “solution” for weight, telling consumers that the advice being provided would last a lifetime because, the company claimed, “your genes are not a
BOX 5-1
Overview of Points Presented by Individual Speakers*

- A 10-year-old critical appraisal of the scientific evidence behind seven different companies’ dietary recommendations concerning the health risks associated with certain genes found, for example, that almost half of the 56 genes tested by these companies were not supported by robust evidence. Because such a comprehensive review of the evidence has not been conducted for the genetic tests currently being offered, the field, while promising, is not ready for prime time. (Janssens)
- There is a discrepancy between what genetic testing companies’ advertisements claim and what their disclaimers reveal. Companies need to communicate more respectfully with consumers regarding the prematurity of genetically personalized nutrition recommendations. (Janssens)
- In the future, the nutrition community will be using a stratified approach to develop nutrition recommendations—that is, with individuals being clustered into groups based on how they respond to particular dietary interventions (as opposed to personalized, or individual, nutrition). This approach has an analogy in cancer treatment. (Schork)
- One can envision greater leverage of N = 1 and other emerging trial designs that collect an individual’s phenotypic information over time to establish personal, as opposed to population, thresholds for change in health status. (Schork)
- In the context of nutrigenomics, there are differences among the Clinical Laboratory Improvement Amendments (CLIA) standards; the U.S. Food and Drug Administration’s (FDA’s) authority under the medical device provisions of the Federal Food, Drug and Cosmetic Act, as well as FDA’s regulation of the safety and labeling of food; and the Federal Trade Commission’s (FTC’s) authority. (Roller)
- Key regulatory issues that merit further consideration as nutrigenomics moves forward in a commercial context include the adequacy of the existing FDA regulatory framework to accommodate nutrigenomics claims for foods without triggering “drug” status. (Roller)

* This list is the rapporteur’s summary of the main points made by individual speakers (noted in parentheses). The statements have not been endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they are not intended to reflect a consensus among workshop participants.

fad.” Some of the genomic profiles being sold by those companies, Janssens noted, focused on specific diseases or disease categories, such as heart health, bone health, or inflammation health, while others were what she characterized as a potpourri of gene variants supposedly statistically associated with some kind of health outcome. She added that the companies would then provide dietary recommendations based on having detected, for
example, an increased risk for heart disease. Her presentation began with a
review of the evidence behind these claims.

**Reviewing the Evidence Behind Company Claims That
Gene Variants Are Associated with Disease Risk**

In an article published in the *American Journal of Human Genetics*,
Janssens and colleagues (2008) review the scientific literature for evidence of
any association between the gene variants being tested by those early com-
panies and disease risk. Janssens explained that she and her colleagues did
not limit the outcomes of their search to certain classifications of disease.
For example, if a company was using a gene to provide consumers with
information about heart health, they searched for evidence of an association
between that gene and any disease, not just heart disease. Additionally, they
required that the evidence be robust, so they reviewed only meta-analyses,
not single studies. Specifically, they investigated the claims of seven differ-
et companies, pooling all patients tested for a total of 69 polymorphisms
in 56 genes. Of those 56 genes, they found no evidence at all for almost
half (24); that is, none of those genes had been included in a meta-analysis.
Another 7 of the 56 genes had been analyzed in meta-analyses but showed
no statistically significant association with any disease. The remaining 25
genes also had been included in meta-analyses and had been shown to be
significantly associated with disease, but with 28 different diseases, and
most of the reported effects were small. What Janssens characterized as the
two most amazing findings of this review were, first, that the genes being
used to construct consumers’ cardiogenomic profiles were more frequently
associated with noncardiovascular than with cardiovascular diseases; and,
second, that two of the five genes used to construct consumers’ osteo-
genomic profiles (i.e., risk for bone diseases) were associated not with bone
disease but with Alzheimer’s disease, asthma, non-Hodgkin’s lymphoma,
obesity, psoriasis, and systemic lupus erythematosus.

While this review was conducted 10 years ago, Janssens continued,
“I’m not really very positive that the situation at this moment is very much
different.” In a recent commentary, Janssens and colleagues (2017) describe
their observation of two nutrigenomic studies in which the investigators
had tested all participants for the *APOE* gene in order to tailor recom-
mendations on saturated fat intake, but without telling them that one
of the *APOE* alleles is a major risk factor for Alzheimer’s disease. Thus
now, she explained, all of the people tested in one of these studies know
whether they carry either one or two copies of the risk allele, and all of the
people tested in the other study know whether they carry at least one copy.
And, she added, as soon as they search for and read about *APOE* on the
Internet, they will know they carry an allele that is associated with a risk
for Alzheimer’s. For Janssens, that they were not told about this risk is an indication that too few clinical genetics experts were involved in the studies. In her opinion, even a clinical geneticist in training would have recognized the association between APOE and an increased risk for Alzheimer’s disease. She believes this example of the APOE allele illustrates many ethical issues, such as those of informed consent, privacy, data sharing, and return of results.

Janssens went on to describe another study similar to Janssens et al. (2008), conducted by a team of researchers in Greece (Pavlidis et al., 2015). She explained how they identified several nutrigenomics companies, examined whether the genes included in the companies’ profiles were associated with any disease or pathological condition, and found no single statistically significant association for any of the 38 genes of interest. In cases in which a weak association was demonstrated, she noted, the evidence was based on only a limited number of studies. These authors concluded, “As solid scientific evidence is lacking, commercially available nutrigenomics tests cannot be presently recommended.”

Janssens remarked that, as a critical reviewer of scientific literature, she is always aware of confirmation bias. She acknowledged that the results of the Pavlidis et al. (2015) review accord with her skepticism about nutrigenomics, but she also expressed the view that the review was not very well conducted. The investigators conducted their search of the literature using the following combination of terms: “nutrigenomics,” “[gene name],” and “[disease name].” Thus, the only articles that appeared in their search results were articles with “nutrigenomics” in their title or abstract. But Janssens pointed out that many of the possible associations of relevance to the 38 genes of interest could have been studied by researchers who were not interested in nutrigenomics, in which case that term probably would not have appeared anywhere in their papers. She said she was unsure whether the results of the Pavlidis et al. (2015) meta-analysis would have been any different if the investigators had conducted a more thorough search.

Regarding what is argued by researchers working in the field, Janssens quoted the Academy of Nutrition and Dietetics’ position paper on nutritional genomics (Camp and Trujillo, 2014): “Although the discipline of nutritional genomics holds promise for tailoring diet to a person’s genotype and influencing chronic disease development, the science is still developing.” She noted that this paper was being updated with new evidence, but did not know whether the updates would alter this conclusion. She also cited another paper, written by Görman and colleagues (2013), the principal investigators of the Food4Me study, a large nutrigenomic trial in Europe, who concluded “There is convincing evidence that common diet-related diseases are influenced by genetic factors, but knowledge in this area is fragmentary and few relationships have been tested for causality.
The evidence that genotype-based dietary advice will motivate appropriate behavior changes is also limited.” Janssens interpreted these papers to mean that the field is “not ready for prime time” yet. “It was premature in 2008,” she said, and “it’s still premature in 2017.”

Company Claims Versus Disclaimers

Despite this lack of what she characterizes as robust evidence, Janssens continued, companies advertising genetic testing for consumers continue to claim that insights from their DNA can help them eat a healthy diet best suited to their genetic makeup, metabolism, and lifestyle, or simplify dieting with a personalized nutrition plan based on their DNA. One company claims that people’s DNA plays a large role in determining how their body interacts with food, affecting preferences, sensitivities, and metabolism. But does DNA really play such a large role?, Janssens asked. Her answer was no. These companies, she asserted, are not providing recommendations—they are promising genetically personalized eating plans. In her opinion, their claims are too optimistic and can be misleading.

In contrast to their claims, Janssens continued, these companies’ disclaimers are very transparent with regard to the limitations of the testing they provide and the marginal role of genetics in how the body responds to diet. As an example she cited Helix, an online marketplace that sells nutrition-related DNA testing applications, whose disclaimer states, “Genetic variants related to nutrition are connected by the way that your body processes food, but they do not guarantee that you will or will not be successful with any given diet plan. Your DNA may help you narrow in on new diet plans that you might prefer or find more successful than others, or even just a better understanding of your existing preferences. Everyone, regardless of their genetics, will benefit from a well-balanced diet.”

Janssens went on to point out that all of these companies provide legal disclaimers, although consumers must scroll down to the bottom of their terms of service pages to find this information, and when they do, the information is in legal language. To illustrate, she showed a screenshot of a disclaimer that reads,

This site and the information, services and materials contained on this site are provided on an “as is” basis and your use of this site is at your own risk. . . . Neither Vitagene nor its affiliates warrant that the information on this site is accurate, reliable or current. . . . Neither Vitagene nor its affiliates nor any third party supplier can be assured that the user, in using this site, has selected an appropriate service provider. Again, you should

1 See https://www.helix.com/shop/dnafit-mealplanner (accessed April 17, 2018).
The point is, Janssens said, “if you put this on the bottom of your site, you can get away with any test.”

For Janssens, the content of these claims and the way these disclaimers are being communicated is where ethical principles come into play. The ethical norms of both medicine and marketing, she stressed, basically say the same thing: do good with the best intentions, and treat your patient or customer with honesty, responsibility, and transparency. In her opinion, the companies whose claims and disclaimers she had described are not meeting these criteria. She elaborated on two ethical principles in particular, as summarized below: doing good (beneficence) and autonomy.

**Beneficence**

Janssens explained that beneficence, which is the intent of doing good, involves, first, developing and maintaining skills and knowledge and continuously updating them to reflect the best of what is available; and, second, considering the individual circumstances of all patients. She expressed uncertainty as to how the latter criterion should be applied on the Internet, but asserted that at least the first criterion can be met. But an important question for her is whether, given that nutrigenomics research is still so young, the commercial offers of these companies are in the best interest of customers or the best interest of the companies. She highlighted as another important question whether there is any evidence on how to “compensate” genetic effects with diet, to which, in her opinion, the answer is no. “The knowledge that we have does not provide enough evidence for those kinds of tests,” she argued.

To explore further the concept of beneficence in personalized nutrition, Janssens described the analytic framework used by the U.S. Preventive Services Task Force (USPSTF) to investigate whether a screening program provides a benefit to persons at risk—for example, whether a glucose test used to screen obese individuals for prediabetes results in improved health after a dietary or exercise intervention (Melnyk et al., 2012) (see Figure 5-1a). She remarked that, while many studies link diet and genes to final outcomes—which in the glucose/prediabetes example include reduced diabetes, cardiovascular disease, and mortality—clear evidence linking diet and genes to an intermediate outcome—which in the glucose/prediabetes example would be weight loss—should be adequate for personalized nutrition (see Figure 5-1b). The problem, she emphasized, is that there is no

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FIGURE 5-1 Analytic framework used by the U.S. Preventive Services Task Force (USPSTF) to investigate (a) whether a screening program (e.g., glucose test) provides a benefit to a person at risk (e.g., an obese individual); and (b) whether DNA testing (combined with a survey and other lab tests) provides a benefit to healthy consumers.

NOTE: CVD = cardiovascular disease.

SOURCES: Presented by Cecile Janssens on December 5, 2017, adapted from USPSTF, 2017.
evidence showing that a genetic disadvantage can be compensated by changing one’s diet. In other words, as represented by the question marks in Figure 5-1b, there is no evidence showing that personalized nutrition is associated with any beneficial intermediate outcomes, let alone final outcomes. “I think that’s where the science is lacking,” Janssens asserted—not with gene–disease associations, but with the solution that is being offered by these companies to break these associations.

Janssens reiterated, “I think there is not enough evidence yet to offer those tests online.” She believes that if people want to purchase these tests, they should be able to do so, but they should also be provided with the information necessary to make informed decisions about whether to make such a purchase.

**Autonomy**

In addition to beneficence, Janssens views autonomy as an ethical problem with current nutrigenomics companies. She explained that many websites use proprietary algorithms that provide consumers with no insight into how the company makes its recommendations based on a consumer’s DNA profile. This means, she stated, that neither consumers nor scientists can verify whether the information being provided makes sense, nor can anyone verify what the company is doing with the algorithm. For Janssens, this raises the question of whether a company is using an advanced algorithm to develop a personalized diet based on multiple SNPs with small effects, or using a simple list of specific recommendations, or rules (e.g., the rule for one SNP might be “eat more broccoli,” and for another, “consume more vitamin D”), and then combining them into a personalized combination of recommendations. Janssens argued that to build trust, it is essential to provide some insight into how advanced a company’s algorithm is.

If the companies are not using advanced algorithms, Janssens continued, they are providing essentially the same services that were offered 10 years ago, when, for example, it was recommended that an individual with variation in *MTHFR, MTRR, MTR*, or *CBS* add a supplement containing 800 mcg folic acid, 15 mg vitamin B6, and 20 mcg B12 (Arkadianos et al., 2007). Basically, she elaborated, there was a specific recommendation for every gene, and one’s personalized diet was the combination of all of these specific recommendations. “But that was 2008,” she said, adding that, by 2017, one would have expected the field to have advanced further.

Janssens called for companies to be straightforward when evidence is lacking, as she said 23andMe has been. She described how she had her DNA tested by 23andMe in 2009 and how the information she received from the company indicated that, while her risk for diabetes, for example, was what it was at the time of the testing, evidence was accumulating
that could alter her risk. Additionally, the company provided her with exact information about the volume of patients used to predict her risk for diabetes and how her risk would increase or decrease if she had other genotypes. In her opinion, that was enough information to verify what the company was doing and to draw a conclusion about whether the information being provided made sense.

Final Remarks

In closing, Janssens called for better and more relevant scientific studies, especially those showing whether personalized nutrition improves intermediate outcomes. Additionally and more important, in her opinion, she called for companies to show more respect to consumers. She cautioned against “spoiling the field” before personalized nutrition matures, noting that it is lacking an appropriate scientific basis.

VETTING PERSONALIZED AND GENOMICALLY GUIDED NUTRITION: ISSUES AND STRATEGIES

Delving more deeply into the vetting of personalized, genomically guided nutrition, Nicholas Schork, J. Craig Venter Institute,3 began by listing the three themes he would be covering during his presentation: (1) how to leverage trends in the biomedical sciences in nutrition-based health care, touching on themes addressed by previous speakers; (2) how to identify, verify, and vet nutrition strategies for individuals, borrowing strategies used in cancer and chronic disease management; and (3) how to apply N-of-1, aggregated N-of-1, and personal threshold–based trials.

Leveraging Trends in Biomedical Science in Nutrition-Based Health Care

Schork identified four trends in today’s biomedical science that he believes could be leveraged in nutrition-based health care: (1) personalized health care; (2) a number of emerging technologies that could facilitate personalized health care, such as DNA sequencing, proteomics, wireless technologies, and novel imaging technologies; (3) big data and the use of information technology to identify patterns in the massive amounts of data that are being collected at the population level; and (4) emerging strategies in artificial intelligence. He identified as the goal for nutrition-based health

3 Schork was chair of the planning committee for the 2006 National Academies workshop on nutrigenomics (IOM, 2007). The workshop summary is available at https://www.nap.edu/catalog/11845 (accessed March 23, 2018).
care combining these trends such that something compelling can be said about the nutritional needs of individuals.

However, Schork continued, these trends also raise some questions, beginning with what he termed the “garbage in, garbage out principle”: that unless data are of sufficient quality, an analysis of those data will not yield reliable results. In the context of vetting nutritional strategies, he elaborated, a number of questions need to be addressed, including how to develop these strategies in the first place, how to test them in humans, and how to deploy them at the population level. Additionally, he raised the question of what these nutritional strategies are trying to optimize—individual outcomes; cost savings for the community as a whole, such as by reducing the incidence of disease in the population at large; or quality of life. He encouraged the workshop participants to keep these questions mind as he proceeded and suggested that they could shed light on some of the controversies he would be describing.

In addition to these emerging trends in biomedical science, Schork mentioned recent, relevant changes at the U.S. Food and Drug Administration (FDA). He predicted that some of these changes will bear on the claims one can make in the future about nutritional interventions. Specifically, he was referring to the 21st Century Cures Act, signed into law by President Obama in December 2016, which under certain conditions allows companies to provide “data summaries” and “real-world evidence,” such as results of observational studies, insurance claims data, patient input, and anecdotal data, rather than full clinical trial results (FDA, 2017a). The data must be compelling and collected in a sophisticated way, although definitions of “compelling” have yet to be proposed. Nonetheless, Schork characterized this as “a complete game changer.” He noted that FDA has issued a number of white papers on various aspects of this new legislation that he thinks may be worthy of consideration by nutritional scientists.

Identifying, Verifying, and Vetting Nutrition Strategies for Individuals

For Schork, a key question to consider when thinking about how to leverage this new legislation and new technologies to identify, verify, and vet nutrition strategies for individuals is what is actually being tailored to what. Is a gross diet, such as the Atkins or Mediterranean diet, being tailored to an individual’s genetics? Or are refined nutrient recommendations being tailored to an individual based on the collection of many different types of data?

Schork described four levels of nutrition strategies for individuals. First is the traditional, one-size-fits-all strategy, which involves simply providing everyone with the same diet. Second is stratified nutrition, which may involve using a couple of biomarkers of relevance to nutritional response
to place people in homogeneous categories and then providing each category, or subgroup, with a specific diet. Third, taking that strategy one step further, multiple biomarkers could be used to refine the subgroups, an approach Schork referred to as “precision nutrition.” Finally, at the individualized, or personalized, nutrition level, every individual is provided a uniquely nuanced diet based on his or her genetic or biochemical profile. But, again, Schork suggested, these possibilities raise questions: Which of these four levels works best? How does one define “best” (e.g., economics, patient benefit, scientific understanding)? And how does one prove that one or another approach is best?

As an example of work in this area, Schork referenced a study by Zeevi and colleagues (2015), who developed a strategy for collecting a large amount of data on a group of individuals and then matching those profiles to certain dietary recommendations in an attempt to identify subgroups of individuals who would respond best, or optimally, to particular dietary interventions. Additionally, the authors took their study one step further to pursue what Schork said amounted to a small randomized controlled trial that showed that in fact, the strategy had value.

Schork went on to state that this stratified approach has an analogy in the cancer space. The cancer community knows, he explained, that certain drugs can overcome the defects induced by certain genetic perturbations (i.e., mutations) often found in tumors (Simon and Roychowdhury, 2013). But to test, or vet, each drug–perturbation match would require what Schork described as “a zillion small clinical trials,” which no one is likely to pay for or pursue. So, he said, the cancer community has developed a few strategies for vetting drug–mutation matches. As an example, he cited the “basket trial,” whereby patients who are enrolled in a trial are steered toward whatever treatment “basket” is most relevant, or most likely to counteract the defect(s) caused by their mutation profile, based on an a priori scheme, or algorithm, for matching patients to drugs. He emphasized that it is not the individual drugs that are being tested in these basket trials, but the a priori scheme for matching a drug to a mutation. Based on his conversations with FDA, he remarked that this same vetting strategy is applicable not just to cancer but to all diseases, and that people can be profiled not just at the genomic level but on the transcriptomic and proteomic levels as well. He predicted that in the future of nutrition, it will be these algorithms that will be tested, not individual nutrients versus individual profile characteristics.

Schork noted that in his discussions with FDA, another issue that arose was that this type of study often does not take into account insights derived outside of a trial. According to historical FDA standards, he elaborated, someone initiating a trial to test a particular matching scheme would not be able to incorporate any new information with bearing on the drug or
nutrient being tested that emerged over the course of the trial. According to Schork, this potentially could result in a disservice to the individuals participating in the trial. In the future, he argued, some discussion will need to take place around how to make these trials more adaptive such that they can incorporate data external to a trial into whatever strategy is being vetted.

Schork stated that in his opinion, it should not be obligatory to test the algorithms being used to develop nutrition strategies for individuals (e.g., via legislation or regulatory oversight at some level)—that is, to show that people who are provided therapies based on an algorithm have better outcomes than those resulting from the standard of care or experienced by some comparator group. However, he suggested further that if a company is not curious enough about or confident enough in its technologies to want to see if its algorithm works, that company should probably be approached “with major caution.”

**N-of-1, Aggregated N-of-1, and Personal Threshold–Based Trials**

Finally, Schork considered several emerging trial designs that focus on the well-being of an individual rather than that of the population at large (Schork, 2015). He characterized the basic idea behind these trials as fairly simple. He explained that one may want to measure an individual’s phenotype and then modify it through intervention, but not know what intervention would be useful. So one could measure the phenotype; subject the individual to a particular intervention, or diet; take the individual off the diet; then subject him or her to a comparator diet; and finally measure the phenotype over the course of these alternating applications. Then on this basis, Schork stated, objective claims could be made about which intervention worked best for that particular individual. He added that the same N-of-1 study on a different individual might yield a different result; that is, the second individual might respond better to a different intervention.

Schork noted that although N-of-1 studies have been pursued in the literature (Lillie et al., 2011), only some have dealt with dietary manipulations. But he envisioned the approach being used more in nutrition in the future, leveraging wireless technology to collect phenotypic information continuously.

There are several different N-of-1 study designs, Schork continued, including the sequential design (i.e., making decisions in real time), as well as aggregated N-of-1 studies (Schork and Goetz, 2017). He explained that the latter design involves aggregating results from multiple N-of-1 studies so that patterns can be detected, and subsets of individuals with the same kind of response can be identified. Then the next question would be, he said,
What is it about one subset that differentiates it from another? It could be, for example, that individuals in that subset possess a particular genotype, or perhaps they were exposed to something that was not accounted for when the study was started. Schork suggested thinking about N-of-1 studies as a way to identify phenotypes for later detailed study.

Schork cited as an example of an N-of-1 study the work of David and colleagues (2014), who collected information on one of the investigator's own microbiomes, as well as information on his diet, every day for more than 1 year. At the end of the study, they found a number of compelling associations—such as that between fiber in the diet and changes in the microbiome—that they believed might provide insights into how one can optimize one's diet. Schork himself conducted an N-of-1 study on the effects of interventions on blood pressure. In this study, he and his colleagues found that one of two drugs had a greater effect, but they were unable to discern whether the individual's drop in blood pressure was due to the effect of that one drug or to weight loss, because over the course of the study, the individual had become more health conscious and had lost 10 pounds. Schork also was involved in another N-of-1 study that helped identify an optimal strategy for treating a genetically mediated sleep disorder.

In closing, Schork differentiated between population and personal thresholds. He defined population thresholds are those defined on the basis of epidemiological studies; if a person's biomarker level exceeds the population threshold, he or she is at risk. Personal thresholds, in contrast, are based on an individual's personal average (with error bars), obtained from historical or legacy measures of the biomarker in that individual, with any deviation over time being an indication of a health status change even if the person's biomarker level remains below the population threshold. Schork concluded by observing that, as demonstrated by Drescher and colleagues (2013), using a personal as opposed to a population threshold can minimize the amount of time a person might have latent disease.

POTENTIAL REGULATORY POLICY CONSIDERATIONS PRESENTED BY NUTRIGENOMICS IN THE COMMERCIAL CONTEXT

The third and final speaker of this session, Sarah Roller, Kelly Drye & Warren, LLP, shared her thoughts on key regulatory issues she believes merit further consideration as nutrigenomics moves forward commercially. She began by providing an outline of her talk. First, she would provide an overview of the current federal legal framework that governs genetic testing and health benefit claims for the types of foods that might be used in the context of nutrigenomics. She noted that she would not have time to cover state law, but emphasized that states have regulatory authority that is
comparable to federal law and in some cases is even more stringent. Next, she would be highlighting recent legal developments related to commercial direct-to-consumer genetic testing. Finally, she would be highlighting some key regulatory considerations for the commercialization of nutrigenomics moving forward.

Federal Legal Framework for Health-Related Genetic Testing

Roller explained that all laboratories that perform health-related testing, including genetic testing, are subject to federal regulatory standards administered by the Centers for Medicare & Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). These standards, she noted, govern how tests are performed, the qualification of laboratory personnel, and quality control procedures for each laboratory. She added that they are designed to ensure the analytical validity, but not the clinical validity, of genetic testing in laboratories that perform health-related testing.

In contrast, Roller continued, FDA regulates genetic testing kits and components that are sold to clinical laboratories or other persons under the Federal Food, Drug and Cosmetic Act (FDCA), which requires that products be cleared by FDA before marketing. In accordance with the definition of “device” in the statute, FDA’s authority to regulate medical devices covers in vitro reagents and any genetic testing kit or related article that is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease. Roller noted that, while there is some controversy concerning the precise scope of FDA’s authority to regulate tests that are developed in house by laboratories (i.e., laboratory-developed tests, or LDTs), FDA has taken the legal position that laboratories offering LDTs are subject to both the CLIA and the FDCA, yet FDA has generally exercised enforcement discretion and refrained from enforcing the pre-market clearance requirements for LDTs.

Roller went on to point out that in 2015, FDA issued a report on its findings from an evaluation of 20 publicly available case studies involving what it called “problematic LDTs,” including some genetic tests (FDA, 2015). According to Roller, none of the problematic LDTs appeared to have been related to nutrigenomics, but among those 20 cases, FDA identified a number of critical issues posed by LDTs that had not been cleared by the agency, including lack of evidence supporting clinical validity, lack of pre-market review of performance data, and unsubstantiated product claims. In the specific context of genetic tests, she reported, FDA found that some tests yielded too many false positives and others too many false negatives, some detected factors that had no clear relevance to the disease at issue, some linked to treatments that were based on disproven scientific
concepts, and others had problems with lack of validation. She pointed out that all of these 20 problematic LDTs had met the minimum CLIA standards.

Roller emphasized that only health-related genetic tests qualify as medical devices. So, for example, Helix’s many applications, which she noted that Janssens had also mentioned during her presentation (in the context of her discussion of the contrast between companies’ claims and disclaimers about the genetic tests they are selling), are classified as entertainment applications of genetic testing. To illustrate this point, Roller observed that through Helix, one can order genetic testing to gain insight into the types of wine one is likely to prefer based on taste preference, how much “the Neanderthal genome” is reflected in one’s own genome, or whether one’s metabolism is more farmer or hunter based. She added that consumers can even purchase socks, scarves, or tartans that are color-coded to reflect their personal genetic profile. Because these are not health applications, she reiterated, they do not qualify as medical devices, so FDA does not have jurisdiction to regulate the tests involved under the medical device provisions of the FDCA.

Direct-to-Consumer (DTC) Genetic Testing

Roller went on to point out that, while a number of personal test kits have been cleared by FDA for DTC marketing, the very first DTC genetic test—23andMe’s Genetic Health Risks (GHR) test(s)—was not cleared until early 2017. She noted that the initial set of approved GHR tests was intended for use in determining an individual’s genetic predisposition to 10 diseases, and as far as she was aware, that initial set had already been expanded by the time of the workshop. She explained that the tests analyze DNA from a saliva sample and provide results intended to help individuals make decisions about lifestyle choices or inform discussions with their health care providers.

FDA cleared the 23andMe tests through the de novo premarket review pathway, which Roller explained is available for devices that are novel, that is, not substantially equivalent to an already legally marketed device, and that present low to moderate risk. The conditions of approval were designed to provide reasonable assurance of the safety and effectiveness of both the initially approved and similar GHR tests produced by 23andMe. According to Roller, the agency intends to exempt additional 23andMe GHR tests from pre-market review and may also exempt GHR tests of other makers after they submit their first pre-market notification. Because of the higher risks associated with diagnostic tests, she added, FDA approval excluded diagnostic tests from its scope.
Regulatory Considerations for the Commercialization of Nutrigenomics: Health Benefit Claims for Foods

Under the FDCA, FDA also regulates the safety and labeling of food, Roller continued. “Food” is a broad category, she noted, defined as “articles used for food or drink,” “chewing gum,” and “components” of these articles. “Food” encompasses conventional foods and beverages, including nutritionally fortified and enriched foods; dietary supplements, which are foods that are not in conventional food form and are consumed to supplement the diet with an essential nutrient or other dietary ingredient; foods for special dietary use, which Roller noted is a very old category, one that includes foods designed to serve particular dietary needs due to a physical, physiological, pathological, or other condition, such as disease convalescence, pregnancy, lactation, food allergy, underweight, or overweight; and medical foods, which are foods that are formulated to be consumed or administered orally under the supervision of a physician and are intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements have been established that cannot be satisfied by dietary modification alone (FDA, 2017b). Roller cited Lofenalac4 for people with phenylketonuria as an example of a medical food.

Roller stressed that, regardless of category, a food may also be a drug because the FDCA defines a drug as “(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals [excludes FDA-cleared ‘health claim’].” Thus, she elaborated, if a vendor makes a claim for a food product suggesting that the food has benefits with respect to diagnosing, curing, mitigating, treating, or preventing a disease, FDA may regulate that product as a drug unless the particular claim has been cleared by the agency as a health claim. If the product is approved on the basis of a health claim instead—that is, if the claim suggests that a food has health maintenance or health promotion benefits rather than disease prevention benefits—the marketer must instead substantiate the claim under what Roller described as the structure/function claim carve-out from the drug definition.

According to Roller, while FDA historically has interpreted the drug provisions of the FDCA very broadly so as to limit the range of disease-related claims that can be made for food products without triggering drug status, the agency also has broad authority to interpret and enforce the statute and regulations flexibly. She offered a few examples in which FDA has relied on this authority to exercise enforcement discretion and refrain from enforcing the letter of the statute or agency rules. She cited as a

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4 Lofenalac is an oral powder prescribed to replace milk in the diets of infants and children with phenylketonuria; it has been regulated as a food since 1972.
recent example FDA’s guidance allowing “healthy” claims for higher-fat foods that contain a healthy balance of fatty acids, even though the rule in the Code of Federal Regulations (CFR) does not include this provision, adding that this guidance was partly in response to the most recent dietary guidelines. She referred to qualified “health claims”—truthful health claims substantiated by credible evidence that does not meet the “significant scientific agreement” evidence standard—as a second example. Finally, as a third example she pointed to FDA currently allowing medical device data systems (MDDSs) and many medical apps to be marketed without meeting the requirements for medical devices, even though their makers call their products medical devices. This latter policy, she remarked, is intended to avoid overregulation of promising lower-risk health information technology (HIT) applications.

Regulatory Considerations for the Commercialization of Nutrigenomics: Federal Trade Commission (FTC) Authority

Finally, in addition to CLIA and FDA standards and regulations, Roller discussed FTC’s broad authority under the Federal Trade Commission Act (FTCA) to prohibit unfair and deceptive acts and practices, including false advertising. In contrast with FDA, she elaborated, the scope of FTC’s authority does not cover products, only acts and practices. In the context of nutrigenomics, she explained, FTC authority encompasses advertising claims for genetic testing and food products and services, as well as data security practices of companies that produce and store personal consumer information (e.g., social security numbers and personal genetic test results).

Roller went on to point out that based on a large body of FTC false advertising case law, FTC has developed detailed policies and guidance under the FTCA concerning requirements for claim substantiation. She then highlighted a few of these policies.

First, Roller noted, both expressed and implied claims must be accurate and substantiated before they are used. Second, Roller continued, a claim must be supported by evidence that provides a reasonable basis for the claim. The basis need not be complete, she clarified, just reasonable, and the reasonable basis standard is flexible. She explained that FTC takes several factors into account when determining the nature and amount of evidence required, including the type of product and claim, the benefits of a truthful claim, the consequences of a false claim, the cost and feasibility of developing claim substantiation, and the nature and amount of evidence that experts in the relevant field believe is reasonable to support this kind of claim. For Roller, the last criterion is especially important. “It’s what people like you believe would be necessary for there to be a reasonable basis,” she said.
Roller identified as a third FTC policy concerning claim substantiation that “competent and reliable scientific evidence” is generally required for health-related claims. This means, she clarified, that studies must be conducted objectively by qualified persons using investigative procedures generally accepted in the relevant scientific community, such as randomized controlled trials. She added that even in the context of this “competent and reliable scientific evidence” standard, there is flexibility regarding the amount and type of evidence, quoting FTC guidance (FTC, 2001):

A guiding principle for determining the amount and type of evidence that will be sufficient is what experts in the relevant area of study would generally consider to be adequate. The FTC will consider all forms of competent and reliable scientific research when evaluating substantiation. As a general rule, well-controlled human clinical studies are the most reliable form of evidence. Results obtained in animal and in vitro studies will also be examined, particularly where they are widely considered to be acceptable substitutes for human research, or where human research is infeasible. . . . Although there is no requirement that a . . . claim be supported by a specific number of studies, the replication of results in an independently conducted study adds to the weight of the evidence. In most situations, the quality of studies will be more important than quantity. When a clinical trial is not possible (e.g., in the case of a relationship between a nutrient and a condition that may take decades to develop), epidemiologic evidence may be an acceptable substitute for clinical data, especially when supported by other evidence.

As an example of recent FTC enforcement, Roller reported that in 2013, FTC took an enforcement action against Genelink, Inc., and foruTM International Corporation, alleging that both companies had violated the FTCA by making false and unsubstantiated health benefit claims about their genetic tests and genetically customized dietary supplements, and by using inadequate data security practices, putting consumers at risk of identity theft. Roller did not delve into the details of the allegations, but pointed out that they addressed both the claims and the characterizations of the evidence, as well as the companies’ data security and data sharing practices falling short of requirements to protect private consumer information. The cases were settled in 2014.

Roller cited as another example that, although 23andMe’s GHR tests were recently cleared through FDA, it sent the company a warning letter in 2013 because 23andMe was marketing the tests without their having yet been cleared. The company successfully responded to that warning letter in 2014 following a cascade of class action litigation inspired by the letter. According to Roller, the complaints that were filed in those lawsuits (all of which were or are being settled, she noted) were similar to consumer protection issues
raised by FTC, such as misrepresentation to the consumer (e.g., the market-
ing of the product implied to consumers that it had scientific support and
FDA approval) and inadequate data security practices (e.g., consumers were
unaware that third parties would have access to their genetic information).

Summary

In closing, Roller recapped issues that she believes merit further consid-
eration as nutrigenomics moves forward, such as the adequacy of

- existing CMS and FDA frameworks for regulating genetic tests,
  including LDTs that are used in DTC products and services;
- existing FDA regulatory framework to accommodate nutrigenomics
  claims for foods without triggering “drug” status;
- existing claim substantiation guidance with respect to claims pro-
moting genetic tests and foods in the context of nutrigenomics, such
  as what “competent and reliable scientific evidence” should mean in
  this context; and
- data security and disclosure practices concerning the personal ge-
  netic information that is being collected.

DISCUSSION

Following Roller’s presentation, she, Janssens, and Schork participated
in an open discussion with the audience, summarized here.

Nutrition in the Disruptive Frontier: Innovation Versus Regulation

An audience member commented on how the “disruptive frontier”
being described at the workshop really challenges the way nutrition is under-
stood. As examples, she mentioned Steven Zeisel’s discussion of medical
food as a potential category for classification in the context of nutrigenomics
(Zeisel’s presentation is summarized in Chapter 4) and Schork’s discussion of
N-of-1 studies and real-world evidence as new ways to measure the impact
of nutritional interventions. She asked the speakers to reflect on the balance
between maintaining a long-term outlook and continuing to foster this type
of innovation so that nutrigenomics products can reach the people who
really need them, as well as the need for oversight to control these develop-
ments from food safety and communication perspectives.

Roller responded, “I think that right now is about as favorable an
environment for bringing those questions to the FDA as we have had in a
number of years.” In addition to the 23andMe clearance showing “some
creativity,” she mentioned a health claim that had been cleared earlier in
2017 concerning a food allergen, commenting on how the claim addressed the kind of health condition for which previous health claims had not been cleared. She cautioned, however, that while the environment is favorable, it is important to be very particular when requesting a response from FDA.

Schork added that relatively little time had elapsed since the 21st Century Cures Act was introduced, so the fact that there have not yet been many examples of such requests may simply reflect the fact that investigators have not had enough time to develop new study designs or ways to collect data in the real world. He agreed with Roller that currently, FDA is willing and eager to listen to the scientific community, more so than it has been in the past. As another example of a new development, he mentioned that it is now possible to register digital therapeutics (e.g., apps on smartphones) with FDA as health technologies, so that if approved, they can be prescribed by physicians instead of pills. “So there’s a lot of really forward thinking that goes on,” he said, adding that “of course the data is going to have to pass muster, but there’s a lot of receptivity for novel ideas.”

The Flexibility of the FDA Regulatory System

An audience member observed that currently, risk is structured by “put[ting] things very neatly into boxes with boundaries.” For example, there is a definition for food, a definition for dietary supplements, and so on, and FDA is structured that way as well; that is, devices and biologics and drugs are each considered separately. Yet, the audience member pointed out that the discussion at the workshop had revolved around a systems approach whereby testing “that” leads to “this” and to “this.” “But we don’t have a regulatory system that puts those puzzle pieces together,” she said, or an agency that is structured to deal with a holistic approach. She asked how, moving forward, the systems-level, or holistic, nature of nutrigenomics will be managed from a regulatory perspective when the regulatory system is not structured to handle such an approach.

Roller replied that, although FDA has customarily interpreted its statutes in particular ways, in fact this simply reflects a general principle of administrative law. That is, she explained, when an agency interprets its own statute, the courts will defer to the agency. So if the agency has been interpreting a statute in a particular way but decides that the world is changing and a different approach is needed, it can change its approach—it simply needs to justify the change. Roller again emphasized the flexibility and authority FDA has to be creative.

The audience member also commented on the fact that there is no established format for labeling medical foods, in contrast with dietary supplements and conventional foods. The term “medical food” does not appear on foods that are intended to be medical foods, she elaborated,
while many foods in the marketplace that do not meet the definition of medical food are labeled as such. Thus, she said, consumers cannot tell by looking at the package whether a food is a medical food (as defined by FDA). Roller replied that only one kind of food is required to have a label indicating what it is, and that is dietary supplements. For all the other food categories, she explained, what is important is that the product meet the requirements for that kind of food. She reiterated that FDA has flexibility, in this case with its approach to medical foods. In her opinion, something not being well defined can actually be a “good thing.”

Transparency of 23andMe

Ahmed El-Sohemy commented on Janssens’s approval of 23andMe’s handling of its DTC genetic testing. Janssens clarified that she has, in fact, criticized 23andMe many times in the past and that there are still things about the company she does not like, mainly in relation to its presentation of health risks. But she does like its transparency and how clearly it informs consumers that their risks will need to be updated as new material becomes available, and that their current risks are based only on “what the science at this moment knows about your genes.” She recalled that her own thrombosis risk “decreased” from 24 percent to 9 percent when the company refined incidence rates to be sex-specific.

The Ethics of Sharing Information with Patients

An audience member commented on the many medical centers in the United States that ask their patients to provide DNA so they can conduct whole-exome sequencing and then bank those data. He asked whether it was ethical not to give that information back to the patients. To him, it appears that information is being collected about many SNPs, or alleles, that could be of value to people’s health but is not being shared.

“That is a difficult question,” Janssens replied. After clarifying that only data are collected and that data do not become information until they are interpreted by an algorithm or specialist, she expressed uncertainty about whether it was ethical not to share that information. She posed a different question: Is it ethical to give something to the patient when the patient does not know what to do with it? “I think in health care,” she said, “doctors should give answers to questions, and not just answers, but that’s a personal opinion.”

Roller added that, based on her observations and in the context of litigation at the federal level, it appears that genetic information is being treated in much that same way as social security numbers. In other words, she clarified, disclose all the material facts and ensure that consumers know
what they are getting. But for her, the question is, Is it the same kind of information, or is it something more significant? Right now, she observed, there is no legal framework for dealing with these kinds of ethical issues. She added that in the complaints she had mentioned during her presentation, people have mentioned property rights. “It’s not settled right now,” she said, “but I do think it’s an issue that does deserve further consideration.”

Janssens added that the American College of Medical Geneticists has developed a list of variants that it calls “actionable mutations.” These are variants, she clarified, that need to be returned when people undergo sequencing, such as the BRCA mutation for breast cancer.

Is Nutrigenomics Premature or Is It Ready for Prime Time?: The Level of Evidence Needed

In response to points made by Janssens during her presentation, El-Sohemy pointed out, first, that the Academy of Nutrition and Dietetics had formally withdrawn its position on nutrigenomics and was not just updating it, as Janssens had mentioned; and, second, that some letters to the editor have asserted that the Pavlidis et al. (2015) study, which Janssens had discussed, should be retracted. Additionally, El-Sohemy pointed out that his company, Nutrigenomix, has been asked by practitioners to provide APOE testing to predict response to blood lipids, but that the company decided not to include that gene in its panel because of the potential for unintended consequences (i.e., due to its association with a risk for Alzheimer’s disease). He then asked Janssens what kind of evidence she would need to see to agree that nutrigenomics should be available and used.

Janssens replied that in her opinion, proper evidence does not stop with demonstrating a robust gene–diet outcome association. That is the start, she said, “but you need to show that changing a diet really compensates that genetic disadvantage.” So, for example, if a certain genotype has been shown to be associated with higher blood pressure, she believes it needs to be demonstrated that by changing diet, blood pressure in individuals with that genotype can be lowered to a level that is similar to that associated with other genotypes. Whether developing this evidence requires a randomized controlled trial or an observational study, she suggested starting with the latter; then, when sufficient observational evidence exists, see if a randomized controlled trial is still needed. She explained that she holds this view because the field is changing too rapidly to rely on randomized controlled trials. She emphasized that in her opinion, what is not needed is more evidence on clinical outcomes, and thus she discouraged the type of long study needed to show whether a change in diet affects clinical outcome. “If you can show that the intermediate factor changes, for me, that’s enough,” she said.
This chapter summarizes session 4 of the workshop, a panel discussion involving Cecile Janssens, Douglas Wallace, Steven Zeisel, and Tim Morck, Spectrum Nutrition, LLC. The goal of the discussion, said moderator Patrick Stover, was to address the question: Where do we go from here, in terms of both where the field is moving and new expectations for nutrition?

Before introducing the panelists, Stover summarized the workshop as “an update to where the field of nutritional genomics is, based on the last meeting we had 10 years ago.” The field has evolved rapidly in his opinion, with respect to not only new knowledge about the role of genetics in nutrition but also expectations for nutrition in terms of chronic disease outcomes. In addition to the bar being raised for outcomes, that is, moving beyond functional indicators as discussed by Patsy Brannon in her opening presentation (see Chapter 1), he called attention to the fact that the bar has also been raised with respect to the type of evidence that is needed. He noted that a recent National Academies publication on chronic disease outcomes calls for grading evidence such that nutrition recommendations would have to have at least moderate evidence (NASEM, 2017a). Although he believes that observational data, which he said drive this field, can reach that level of moderate evidence, large sample sizes and a dose dependence will be required to demonstrate any effect of an intervention. Thus, he said, “we have a lot of challenges in front of us.”
THE USEFULNESS OF THE PRECISION MEDICINE PARADigm IN NUTRITION

To initiate the discussion, Stover asked the panelists how they viewed the role of precision medicine, that is, being able to classify individuals as responders versus nonresponders (i.e., to a drug), as a paradigm for nutrition. Zeisel did not answer the question immediately but stressed that now is a critical time to introduce nutrition into precision medicine, as major medical centers are beginning to establish data collection systems upon which precision medicine will be based. Yet, he said he was unaware of anyone who was thinking seriously about the nutrition information that would be collected, adding that this information is often viewed as being too difficult to collect. “But if we don’t insert ourselves into the field so that the data is collected,” he asserted, “nutrition will never be part of precision medicine. It’s a critical time.”

Regarding the appropriateness of the precision medicine paradigm for nutrition, in Zeisel’s opinion, the field of epidemiology “is being turned on its head by recognizing that people are different.” Before today’s nutrigenomics tools were available, he observed, one would have concluded, for example, that half of young women need a particular intervention and the other half do not. He stated that this type of result cannot be used to make a recommendation. With the new technology, however, what he described as “finer cuts” can be made. Now, he elaborated, one can examine the 50 percent that respond and the 50 percent that do not and determine why different people respond differently. Doing so will “get the noise out of nutrition data,” he said. Then, he suggested, it will be possible to develop targeted interventions that work more predictively on subpopulations with unique genetic characteristics or some unique combination of genetic and other characteristics.

Janssens cautioned, however, that a challenge to classifying people on the basis of their profiles is that “we very easily become unique.” As soon as everyone becomes unique and there is no other “me” from whom to learn, she argued, it is very difficult to say what the best treatment or diet is for an individual. In other words, she said, profiling can reach a point at which “there is no one else with that profile,” and the only way to test interventions is through trial and error. She was curious as to whether anyone had any ideas on how to address this challenge, saying, “That, for me, is the limiting factor both in precision medicine and in precision nutrition.”

In contrast, Zeisel expressed optimism and the view that many of the ways in which people are unique have little to do with the profiling factors used to characterize individuals as responders or nonresponders. He explained that it is possible to identify profiling factors that make significant contributions to determining whether an individual will be a responder or a nonresponder, although a decision must be made about what constitutes
significant: Is a 1 percent contribution sufficient, or should it be 10 percent? “We arbitrarily decide how close we need to be to make a recommendation,” he noted. He referred to José Ordovás’s comment earlier in the workshop about perfection being the enemy of good. In his opinion, if enough profiling factors can be identified that predict 92 percent of responders versus nonresponders, that is probably good enough, whereas if the prediction rate is only 32 percent, more work should probably be done to characterize response.

Janssens stated that she was not convinced the question is that simple. When a large amount of data is collected, she said, the data reflect many different profiles that distinguish “me” from others. In her opinion, it is very difficult to identify what accounts for why different people respond to different treatments.

Wallace suggested that there may be a continuum of variants, with different variants (i.e., what Zeisel termed profiling factors) having different impacts. Some act like single genes, he elaborated, which is the basis for newborn screening whereby a particular variant is identified, and a specific nutrient is given to compensate for that variant. In contrast, he continued, mitochondrial medicine, a field in which physiological processes are affected by broad groups of related genes, requires a more general approach. Depending on the pathway that is affected, he explained, certain kinds of defects may require a more glucose-rich diet, for example, while others may require more fatty acids in the diet. The more interesting challenge, in his opinion, is the percentage of variance that can actually be controlled with diet. He wondered whether there may be too much noise, or too much variation, to control a risk for a disease such as Alzheimer’s or diabetes.

Zeisel pointed out that even in medicine, efficacy is quite low. If 30 percent of people who receive a drug treatment benefit, he argued, “we’ve done well.” He cautioned against holding nutrition up to a more stringent standard. Given that the goal of precision medicine is to try to do better than this 30 percent, he asserted that if personalized nutrition guidelines could be developed for a reasonably sized subpopulation with the understanding that the guidelines could be wrong for any given individual, “you’d be doing really well.”

In that respect, Janssens said, the term “precision nutrition” is misleading. She suggested instead “stratified nutrition,” which she believes presents a more realistic picture of what can be expected.

Zeisel argued that adopting the same terminology used by the medical community will be necessary to ensure that nutrition is actually used by that community. If “precision medicine” is the term medical professionals recognize, he stated, then only by using the term “precision nutrition” will nutrition be recognized as “every bit as important as knowing what dose of a drug to give.”
BEHAVIORAL ASPECTS OF NUTRIGENOMICS

Stover observed that the discussion to this point had focused on the classification of nutrition at a clinical level. He asked Morck about the impact of nutrigenomics on population as opposed to clinical nutrition.

“My bias is that the field of nutrition encompasses a pretty broad spectrum of health,” Morck replied. Nutrition is not just about food, he stated—it includes absorption, digestion, and all the other kinetic and dynamic processes that Patsy Brannon had laid out in her opening presentation. It also includes education (knowing what good nutrition looks like) and selection (actually making good food choices), he added. Even with all the genetic information and medical advice available, he said, “If we are not motivated to take that advice, it is worthless.” He emphasized the behavioral aspects of nutrigenomics that Brannon, Ahmed El-Sohemy, and Nathan Price had all touched on in their talks. For nutrigenomics to be successful, he asserted, the field needs to find a way to convince people that it is not just beneficial but may be imperative to change their diet should something be discovered about their genes that indicates risk. Without that motivation, he claimed, change will not happen. He pointed to smoking as an example of something that is known to be “bad,” but that people still do. Lifestyle factors need to be taken into account as well, he cautioned. With respect to precision nutrition, he imagined someone having a recommended precision diet based on genetic information, but then attending a family Thanksgiving dinner. He reminded the audience that people eat food in social settings, and suggested that precision nutrition could inadvertently impose a level of social isolation by not taking that fact into account.

For Morck, the personalization of nutrition is the personalization of one’s approach to incorporating nutrition into one’s lifestyle and as an important part of one’s future. He noted, for example, that the Mediterranean and Paleo diets provide guidelines, but posed the question of what will guide people to making better choices on an incrementally more frequent basis. Additionally, he stressed the importance of having validated biomarkers that are sensitive enough to show a metabolic or physiologic benefit when people make the effort to change their diet. At present, he asserted, the tools available are too crude to provide that type of reinforcement, and body weight, blood pressure, and cholesterol levels, for example, are not specific enough. He believes that metabolomic markers hold promise for providing patterns specific enough that people will be able to see changes within a few months and perceive the value of continuing the new dietary trends they began. He expressed the view that “the feedback is really critical . . . in making significant, long-term nutritional changes that are expected to produce real benefits.”
Zeisel suggested that there may be a biological component that helps explain why some individuals are willing to change their diet while others are not. Moreover, he suggested that this component may not be just genetic. For example, he observed, when the feces of a person with anorexia are transferred into another person, the other person starts behaving as though anorexic.

Wendy Johnson, session 2 moderator, agreed with Morck, saying, “We definitely have to have a behavioral piece . . . so that we can have the benefit of these new discoveries.” She referred to Zeisel’s earlier remark that nutrition needs to be included in precision medicine studies, or it will be left behind. She posited that the same is true of behavior—it needs to be included as well. She emphasized the importance of behavioral phenotyping and of understanding what causes people to adhere, whether that cause is genetic or something else.

**WHY THE FOCUS ON GENETICS IN THIS ERA OF DATA INTEGRATION?**

Stover pointed out that, in addition to genetics, several speakers had discussed epigenetics (Ordovás), the microbiome (Price), and other measurable features. He asked whether it made sense to continue the focus on nutrigenetics in this era of data integration.

Zeisel remarked that the nutrigenetics toolset is 5 years ahead of other toolsets, which in his opinion is the only reason it has become the priority. The microbiome is much further behind, he added, given that it attracted little attention until about 10 years ago, and the problem with epigenetics is that target tissues cannot be collected, only blood samples. “I think it is a mistake,” he argued, “to try to push too hard when you don’t have the toolset yet.”

Wallace wondered how metabolomic biomarkers in particular will be found in the future, given the inherent variability of humans. In his own research, he works with inbred mice and therefore is able to remove most of the variance so that significant chemical signatures can be identified. With that knowledge, he asserted, one should then be able to study that same chemical signature in humans and identify which groups of individuals show variation and which do not. “We have to go back and define . . . what the real markers of relevance are,” he said, “then go back to the [human] population and stratify the population.”

Zeisel added that in his opinion, the “challenge test” will be an important tool for nutrition metabolomics. He suggested that it may be the only way to see metabolic variation because unless a system is challenged, the body’s homeostatic mechanisms are capable of managing any variation in metabolism. A challenge test pushes the system and reveals weaknesses, he added.
Wallace agreed that in mitochondrial medicine, when a nutritionist believes it is appropriate, administering a challenge test such as the glucose challenge can help identify which part of the metabolic pathway is most impaired. With that knowledge, he explained, dietary recommendations can be tailored to meet that need. “That’s a really important tool for us,” he said.

**THE RELEVANCE OF NUTRIGENOMICS TO LOW-INCOME POPULATIONS**

Stover commented on how it has been estimated that nutrition-related chronic diseases cost the U.S. economy about $1 trillion annually. Thus, he asserted, one of the goals in nutrition is to lower rates of chronic disease, with much of the discussion at the workshop being relevant to those efforts. Yet, he observed, chronic disease is present mainly in low-income communities that are least likely to benefit from nutrigenomics and have bigger problems to deal with. He asked, “How do we deal with the equity issue as we begin to think about advancing the science toward reducing chronic disease when the target population that is driving the chronic disease may be the least receptive to what we have to offer?”

Wallace commented on the importance and difficulty of studying different ethnic groups. He mentioned that he and his team have been conducting fairly large studies on macular degeneration and glaucoma, which he characterized as having very different risk states in African Americans, Asian Americans, Native Americans, and European Americans. Thus, he stated, it is necessary to stratify by ethnicity, then substratify within each group, so that variable(s) that are contributing to the differences in disease can be identified and the percentage of variance due to those variables determined. Additionally, he and his research team have been very interested in studying Asian Americans in California, but have spent almost all of their budget just assembling a population that would be representative of both first- and second-generation Asian Americans. “I think this is important,” he said, “but there are also constraints, and I don’t know how we are going to manage that.”

Another point to be made, Wallace continued, is that there is an inherent assumption that a person of lower socioeconomic status has a clinical problem because of his or her socioeconomic status. He views that assumption as a sociologist’s perspective, and as a geneticist, he disagrees. He cited as an example the assumption that African Americans have a higher rate of preterm birth because they do not receive good health care. But a study in Chicago stratified African Americans by socioeconomic status and showed that preterm birth was the same regardless (Collins et al., 2007). Wallace interpreted those results to mean that in fact, there may be much more going on genetically than has been assumed in the past.
Zeisel mentioned studies conducted in Great Britain showing that socioeconomic status in early life modifies epigenetic markers and expressed concern that corporate databases are being built from people who can afford to buy genetic tests, so that the data will be heavily biased toward rich people. He suggested that because health care systems have proposed collecting data on all patients, perhaps the collection and analysis of those data could be funded in a way that would allow for the data to be correlated not only with outcomes but also with socioeconomic status. He mentioned the National Institutes of Health as a possible source of such funding.

For Janssens, the question of equality is so important that she feels uncomfortable discussing nutrigenomics and puzzling over such detailed tweaking of diet when there is an enormous nutrition problem in society that will likely require completely different types of solutions. “I’m sure that when I walk out of the building here later, and I see the people on the street,” she said, “that I’ll question myself, ‘What have I been doing this entire day? Why have I not tried to solve a bigger problem for them, instead of trying to find a little benefit in nutrigenomics?’”

Ordovás asserted that “most of the time, the people who are missing from this discussion are the policy makers.” He mentioned how the policy of subsidizing meat, for example, is known to have affected the nutritional health of certain neighborhoods. Additionally, he observed, it is known from human breastfeeding data that the quality of milk varies among neighborhoods depending on socioeconomic status. Given these circumstances, the component that is missing from the nutrigenomics discussion, in his opinion, is public policy making.

Janssens agreed with Ordovás, but only partly. “I think also,” she said, “to find a solution for the people who need it, we have to first ask ourselves whether the solution for them is in nutrigenomics.” In her opinion, this is not likely.

Zeisel disagreed. He characterized data studies as noisy, generating a great deal of variability. Results of one study will come out and lead to a new policy, for example, to recommend eating more cocoa; then another study will lead to a different policy because it was based on a different population. These discrepancies, Zeisel argued, turn people away from nutrition and from using it in policy at all. In his opinion, imprecise, noisy data lead to bad policy. Thus, he said, “I think everything we can do to refine our ability to explain the noise and to understand why some people respond and others do not is useful.” “Sure,” he added, “the big problems are going to be solved by policy, but [policy makers] won’t come up with the right answers unless our research techniques are refined.”

Johnson wondered whether a cost-effectiveness or cost-utility analysis of some sort could be carried out and the results used to talk with policy
makers about whether genetic testing is a good investment in populations that cannot otherwise afford it.

TRUST—AND DISTRUST—IN NUTRIGENOMICS

An audience member described how a genetics lab in Texas used DNA to perform facial reconstruction and how law enforcement officials, in turn, used the facial reconstruction to arrest a suspect for a crime. Historically, she pointed out, communities such as the black community have experienced what she called “medical malfeasance.” “So there’s a lot of distrust in wanting to give genetic information,” she said, even if it is for science. She asked the panelists how this distrust would impact nutrigenomics.

In Zeisel’s opinion, the use of DNA in facial reconstruction is the same as asking a witness to describe a suspect. The only difference, in his view, is that instead of being obtained from an observer, information is being sought from DNA based on what is known about genetic differences among, for example, different ancestries. Regarding medical malfeasance, he mentioned the Tuskegee study, in which black people were infected with syphilis to study its effects, greatly harming credibility. Today, by contrast, there is an expectation and a requirement that researchers consider a community’s interests. He cited the example of his own research team, which, especially with studies pertaining to genetic testing, solicits input from a community advisory board. He described the members of the board as members of the local community who can provide perspectives that the researcher may not be able to perceive. He also emphasized the importance of good communication and the sharing of benefits with respect to the knowledge generated by a study. He stated that participants should be told about the uses of the data, and they must give permission for the data to be used for other research purposes.

“But in the end, you are taking a risk when you give your genetic data,” Zeisel continued. For example, he noted, concern has been raised that if an investigator were to be subpoenaed by the U.S. court system, he or she would have to release study data even if the research subjects had been promised that their data would be confidential. He stated that for this reason, some investigators have been storing their genetic data on servers outside of the United States. He emphasized the importance of investigators informing individuals of the risks of their participation in a study and what is going to be done to mitigate those risks. Then, he said, individuals can decide whether they want to participate.
THE RELEVANCE OF AGRICULTURE TO NUTRIGENOMICS

An audience member asked about the potential impact of the consumption of genetically modified foods on a person’s long-term genetics. Zeisel replied that the genetics used to modify a plant has little to do with nutrigenomics, except for the fact that better data on people’s nutritional needs could be used to try to design better foods. He added that traditional breeding is a form of genetic manipulation. In the past, farmers chose plants with the largest fruits, for example, and bred those plants, whereas with the new techniques available today, they are making plants artificially instead of breeding. But he said that in terms of the genes being inserted into those plants, other than the effect of any food on one’s genetics, he was unaware of any inserted gene that could also enter the human genome upon consumption.

While the discussion was on the topic of agriculture, Naomi Fukagawa pointed out that much of the genetic variation in humans also exists in plants, animals, and the food that is produced from those plants and animals. In her opinion, agricultural production goes hand in hand with efforts in medicine aimed at wellness and the prevention of disease. She noted that even Hippocrates, who is credited with the precept “first do no harm,” also stated, “food is thy medicine.”


REFERENCES


REFERENCES


REFERENCES


REFERENCES


Workshop Agenda

Nutrigenomics and the Future of Nutrition
Food Forum Meeting
December 5, 2017

National Academy of Sciences Building
2101 Constitution Avenue, NW, Washington, DC
Lecture Room

8:30 AM  Welcome and Food Forum Member Recognition
          Sylvia Rowe, M.A., Food Forum Chair

8:40 AM  Setting the Stage: Introduction and Overview
          Patsy Brannon, Ph.D., R.D., Cornell University

SESSION 1:  Nutrigenomics and Chronic Disease Endpoints
            Moderator: Naomi Fukagawa, M.D., Ph.D.,
            U.S. Department of Agriculture

9:00 AM  Genotypes and Disease Risk: What Do We Currently Know
          About Nutrition and Epigenetics?
          José Ordovás, Ph.D., Tufts University
9:30 AM  Mitochondrial Genetics and Disease Risk: What Is the Current Evidence?
Douglas Wallace, Ph.D., University of Pennsylvania
Perelman Medical School

10:00 AM  BREAK

*Personalized Nutrition in the Real World*

10:15 AM  Personal, Dense, Dynamic Data Clouds and the Future of Personalized Nutrition
Nathan Price, Ph.D., Institute for Systems Biology

10:35 AM  Sickle Cell Disease: An Arginine Deficiency Syndrome with Distinctive Nutritional Requirements
Claudia R. Morris, M.D., Emory University

10:55 AM  Personalized Nutrition in the Real World: Where Do We Stand?
David Alpers, M.D., Washington University (*via WebEx*)

11:15 AM  Is Genetic Testing for Personalized Nutrition Ready for Prime Time?
Ahmed El-Sohemy, Ph.D., University of Toronto; Nutrigenomix

11:35 AM  Moderated Discussion

12:05 PM  Food and Nutrition Board Member Recognition
Bert Garza, M.D., Ph.D., Food and Nutrition Board Chair
Ann Yaktine, Ph.D., R.D., Food and Nutrition Board Director

12:15 PM  LUNCH

**SESSION 2:** Nutrigenomics Applications: Dietary Guidance and Food Product Development
Moderator: Wendy Johnson, Ph.D., M.P.H., R.D., Nestlé

1:15 PM  Nutrient Requirements as Complex Traits—What Consumers Will Need to Know
Patrick Stover, Ph.D., Cornell University
1:45 PM  Gene Guided Nutrition Interventions  
Steven Zeisel, M.D., Ph.D., University of North Carolina at Chapel Hill

2:15 PM  Moderated Discussion

2:45 PM  BREAK

SESSION 3:  Nutrigenomics: Regulatory, Ethical, and Science Policy Considerations  
Moderator: Patsy Brannon, Ph.D., R.D., Cornell University

3:00 PM  Scientific Basis of Genetically Personalized Nutrition: Ethical Implications of Methodological Limitations  
Cecile Janssens, M.Sc., Ph.D., Emory University

3:20 PM  Vetting Personalized and Genomically Guided Nutrition: Issues and Strategies  
Nicholas Schork, Ph.D., J. Craig Venter Institute; University of California, San Diego (via WebEx)

3:40 PM  Regulatory Policy Considerations Presented by Nutrigenomics in the Commercial Context  
Sarah Roller, J.D., R.D., M.P.H., Kelley Drye & Warren, LLP

4:00 PM  Moderated Discussion

SESSION 4:  Rethinking the Relationship Between Diet and Health: Can Nutrigenomics Help?: A Panel Discussion  
Moderator: Patrick Stover, Ph.D., Cornell University

4:30 PM  Panelists:  
• Cecile Janssens, Ph.D., Emory University  
• Tim Morck, Ph.D., Spectrum Nutrition, LLC  
• Douglas Wallace, Ph.D., University of Pennsylvania Perelman Medical School  
• Steven Zeisel, M.D., Ph.D., University of North Carolina at Chapel Hill

5:15 PM  ADJOURN
**About Us**

The Food Forum convenes scientists, administrators, and policy makers from academia, government, industry, and public sectors on an ongoing basis to discuss problems and issues related to food, food safety, and regulation and to identify possible approaches for addressing those problems and issues. The Forum provides a rapid way to identify areas of concordance among these diverse interest groups. It does not make recommendations, nor does it offer specific advice. It does compile information, develop options, and bring interested parties together.

The Food and Nutrition Board (FNB) established the Food Forum in 1993 to allow selected science and technology leaders in the food industry, top administrators in the federal government, representatives from consumer interest groups, and academicians to periodically discuss and debate food and food related issues openly and in a neutral setting. The Forum provides a mechanism for these diverse groups to identify possible approaches for addressing food and food safety problems and issues surrounding the often complex interactions among industry, academia, regulatory agencies, and consumers.

About the FNB: The FNB falls within the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine. The National Academies are private, nonprofit institutions that provide independent, objective analysis and advice to the nation to solve complex problems and inform public policy decisions related to science, technology, and medicine. The National Academies operate under an 1863 congressional charter to the National Academy of Sciences, signed by President Lincoln.

http://www.nationalacademies.org/foodforum
Acronyms and Abbreviations

ABCA1  ATP-binding cassette transporter
acetyl CoA  acetyl coenzyme A
ADH1B  alcohol dehydrogenase 1B
ADP  adenosine diphosphate
APOA2  apolipoprotein A-II
APOE  apolipoprotein E
ATP  adenosine triphosphate

BMI  body mass index

CFR  Code of Federal Regulations
CH  congenital hypothyroidism
CLIA  Clinical Laboratory Improvement Amendments
CMS  Centers for Medicare & Medicaid Services
COI  cytochrome c oxidase I
CoQ  coenzyme Q
CYP1A2  cytochrome P450 1A2

DRI  dietary reference intake
DTC  direct-to-consumer

EAR  estimated average requirement
EFSA  European Food Safety Authority
EGAPP  Evaluation of Genomic Applications in Practice and Prevention
EPA  eicosapentaenoic acid

FDA  U.S. Food and Drug Administration
FDCA  Federal Food, Drug and Cosmetic Act
FTC  Federal Trade Commission
FTCA  Federal Trade Commission Act
FTO  fat mass and obesity associated

GHR test  Genetic Health Risks test
GOLDN  Genetics of Lipid Lowering Drugs and Diet Network
GRS  genetic risk score

HDL  high-density lipoprotein
HIT  health information technology
HLA  human leukocyte antigen

IBD  inflammatory bowel disease
ICU  intensive care unit

LDH  lactase dehydrogenase
LDT  laboratory-developed test

M31V  methionine 31 valine
MDDS  medical device data system
miRNA  micro RNA
MTHFR  methylenetetrahydrofolate reductase

NAD  nicotinamide adenine dinucleotide
ND1  NADH-ubiquinone oxidoreductase core subunit 1
ND4  NADH-ubiquinone oxidoreductase core subunit 4
ND6  NADH-ubiquinone oxidoreductase core subunit 6
NGS  next-generation sequencing
NO  nitric oxide

PASP  pulmonary systolic pressure
PD3 clouds  personal, dense, dynamic data clouds

RCT  randomized controlled trial
RDA  recommended dietary allowance

SCD  sickle cell disease
SNP  single nucleotide polymorphism
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<tr>
<td>TCA cycle</td>
<td>tricarboxylic acid cycle</td>
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<tr>
<td>TCF7L2</td>
<td>transcription factor 7-like 2</td>
</tr>
<tr>
<td>UL</td>
<td>tolerable upper intake level</td>
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<tr>
<td>USPSTF</td>
<td>U.S. Preventive Services Task Force</td>
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Speaker and Facilitator Biographies

David H. Alpers, M.D., is a professor of medicine at Washington University. He is a graduate of Harvard College and Harvard Medical School, and received his initial medical training at the Massachusetts General Hospital (MGH), a Harvard teaching hospital. After training in molecular biology at the National Institutes of Health, he returned to the Gastroenterology Division at MGH before leaving to become chief of the Division of Gastroenterology at Washington University School of Medicine, a post he held for 28 years. He has served as editor-in-chief for the American Journal of Physiology/GI Liver Physiology and Current Opinion in Gastroenterology (Small Intestine/Nutrition); as associate editor for the Journal of Clinical Investigation and American Journal of Clinical Nutrition (2008–2017); and on the editorial board of the Journal of Biological Chemistry, the Journal of Gastroenterology, and many other journals. He is the author of 223 peer-reviewed scientific/clinical papers and is the senior author of the Manual of Nutritional Therapeutics (6th edition, 2015), and he was an associate editor of Yamada’s Textbook of Gastroenterology through its first five editions. He has served on many scientific advisory committees, including for MGH (chairman); the Bill & Melinda Gates Foundation (zinc absorption in third-world countries); and most recently the Alimentary Pharmabiotic Centre, University College Cork, Ireland, and the Sackler Center for Bio-medicine and Nutrition Research at The Rockefeller University. He has been involved for decades as a consultant in drug development on assets related to gastroenterology and nutrition, most often with GlaxoSmithKline.
Patsy M. Brannon, Ph.D., R.D., is a professor in the Division of Nutritional Sciences at Cornell University, where she has also served as dean of the College of Human Ecology. Prior to moving to Cornell University, Dr. Brannon was chair of the Department of Nutrition and Food Science at the University of Maryland. She has also served as visiting professor in the Office of Dietary Supplements at the National Institutes of Health (NIH). Her research focus includes nutritional and metabolic regulation of gene expression, especially as it relates to human development, the placenta, and exocrine pancreas. She chaired an NIH initiative to plan effective federal research related to the health effects of vitamin D, and co-chaired the NIH program “Vitamin D and Health in the 21st Century: Update Conference,” as well as the vitamin D roundtable associated with the conference. She also served on the Institute of Medicine’s Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dr. Brannon is a member of a number of professional and scientific associations and has served on the executive board of the American Society for Nutrition. She has received numerous awards, including the Pew Faculty Scholar in Nutrition award and the Centennial Laureate award from Florida State University. She received her Ph.D. from Cornell University in nutritional biochemistry. She is a registered dietitian.

Ahmed El-Sohemy, Ph.D., is a professor at the University of Toronto and has held a Canada Research Chair in Nutrigenomics. He earned his Ph.D. in nutritional sciences from the University of Toronto and completed a postdoctoral fellowship at Harvard. He returned to Toronto in 2000 to establish a research program in nutritional genomics. The goal of his research is to elucidate the genetic basis for variability in nutrient response in health and performance. Dr. El-Sohemy has published more than 130 peer-reviewed articles and has given more than 200 invited talks around the world. He is on the editorial board of 10 scientific and medical journals and served as an expert reviewer for more than 30 other journals and 12 granting agencies. He has more than 4,200 citations with an H-index of 38. Dr. El-Sohemy has served on Health Canada’s Scientific Advisory Board and several international expert advisory panels. He has made numerous appearances on television, on radio, and in print media. He was voted one of the top 10 people to watch in 2004 by the Toronto Star, Canada’s largest daily newspaper, and in 2007 was nominated for Canada’s Top 40 Under 40 award. In 2013, Dr. El-Sohemy was named one of the top 10 inventors of the year by the University of Toronto, and the following year he was awarded the Centrum Foundation New Scientist Award for Outstanding
Research by the Canadian Nutrition Society. Last year he was awarded the Mark Bieber Professional Award by the American College of Nutrition. He is the founder of Nutrigenomix and chairs the company’s International Science Advisory Board.

Naomi K. Fukagawa, M.D., Ph.D., is the director of the U.S. Department of Agriculture’s (USDA’s) Beltsville Human Nutrition Research Center in Beltsville, Maryland. She previously served as professor of medicine and acting director of the Gerontology Unit at the University of Vermont, Burlington. Dr. Fukagawa is a board-certified pediatrician and an expert in nutritional biochemistry and metabolism, including protein and energy metabolism; oxidants and antioxidants; and the role of diet in aging and chronic diseases, such as diabetes mellitus. She has served on numerous National Institutes of Health (NIH) review panels, served as chair of the NIH study section for General Clinical Research Centers, and completed a 5-year term on the NIH Integrated Physiology of Obesity and Diabetes study section. Her national/international recognition is demonstrated by her membership in the American Society for Clinical Investigation; election as president of the American Society for Clinical Nutrition (American Society for Nutrition); and service as an associate editor for the American Journal of Clinical Nutrition, as editor-in-chief of Nutrition Reviews, and as vice-chair of the 2010 Dietary Guidelines Advisory Committee of USDA and the U.S. Department of Health and Human Services. Her clinical training included residency at the Children’s Hospital of Philadelphia, University of Pennsylvania; chief residency at the University of Vermont; and nutrition/gerontology fellowships at the Children’s Hospital and Beth Israel Hospital, Harvard Medical School. Dr. Fukagawa has maintained an active research laboratory where her work ranges from cells and animals to in vivo studies in human volunteers. Her present work focuses on the impact of environmental stressors (metabolic or physical) on human health, specifically the health effects of exposure to petrodiesel and biodiesel exhaust. She received her M.D. from Northwestern University and her Ph.D. from the Massachusetts Institute of Technology in Cambridge.

A. Cecile J. W. Janssens, M.A., M.Sc., Ph.D., is a professor of epidemiology in the Department of Epidemiology of the Rollins School of Public Health, Emory University, Atlanta, Georgia. Her research concerns the translation of genomics research to applications in clinical and public health practice, and focuses on the polygenic prediction of multifactorial diseases such as diabetes, cardiovascular disease, and cancer, in particular on theoretical and methodological questions in the assessment of the predictive ability and utility of genetic testing. She regularly publishes on research methodology, research integrity, and research ethics. As the result of a serendipitous
finding, she is currently investigating a novel search method for scientific literature. Dr. Janssens has published more than 180 papers in international scientific journals. She is a lecturer in graduate and postgraduate courses in local, national, and international programs. She holds degrees in economics, psychology, and epidemiology and received her Ph.D. from Erasmus University in Rotterdam, the Netherlands.

Wendy Johnson, Ph.D., M.P.H., R.D., is the vice president of nutrition, health, and wellness at Nestlé USA; the past chair of the food and nutrition section of the American Public Health Association; and a recognized public health researcher. She is known for her focus on diverse communities and on ensuring that parents have the information and resources they need to give their children a great start. In her current role, she is charged with setting and implementing the cross-cutting Nutrition, Health and Wellness Strategy for the U.S. Nestlé businesses. Dr. Johnson is a member of the advisory board of the Newark Start Healthy Stay Healthy community program, which educates families on how to close nutrition gaps for young children. She received her Ph.D., M.P.H., and B.A. from the University of North Carolina at Chapel Hill.

Timothy A. Morck, Ph.D., is the president and founder of Spectrum Nutrition, LLC, a firm that provides expertise in nutrition-related basic/clinical research, product development, regulatory and public policy, and global scientific affairs. His career includes clinical nutrition practice, research, and medical school faculty appointments; scientific association management; entrepreneurial personalized nutrition startups; and executive and senior management positions at several global nutrition and pharmaceutical companies. His unique multidisciplinary perspective integrates science and business objectives with a passion for personalized approaches to improving health. Dr. Morck received a B.S. in animal science from The Pennsylvania State University, followed by M.S. and Ph.D. degrees in nutrition (biochemistry and physiology minors) from Cornell University.

Claudia R. Morris, M.D., FAAP, is an associate professor of pediatrics and emergency medicine at the Emory University School of Medicine. She is also a pediatric emergency medicine attending physician at Children’s Healthcare of Atlanta. Dr. Morris has been involved in sickle cell disease (SCD) research for more than 20 years; has a history of National Institutes of Health (NIH)-, U.S. Food and Drug Administration (FDA)/R01-, and industry-sponsored funding; and has led several single- and multicenter trials. She has a special interest in translational research that targets inflammation and oxidative stress. From the start of her career, Dr. Morris’s research endeavors have focused on nutritional interventions based on specific meta-
bolic pathways that cross disease disciplines, identifying alterations in the arginine metabolome in SCD, thalassemia, asthma, and pulmonary hypertension. She also published the first randomized, blinded, placebo-controlled trial of arginine therapy to treat pain in children with SCD. Dr. Morris’s efforts have always encompassed an integrative approach to the practice of medicine. She is a firm believer in nutrition as medicine, and appreciates the growing need to address distinctive nutritional requirements provoked by some acute and chronic illnesses, with SCD as an ideal paradigm.

José M. Ordovás, Ph.D., is a professor of nutrition and genetics at Tufts University and a senior scientist at the U.S. Department of Agriculture (USDA)-Human Nutrition Research Center on Aging at Tufts University in Boston, where he also is director of the Nutrition and Genomics Laboratory. He is a senior collaborating scientist at the Centro Nacional de Investigaciones Cardiovasculares and the Madrid Institute of Advanced Studies Alimentacion (Madrid, Spain). Dr. Ordovás’s research focuses on the genetic and epigenetic factors predisposing to cardiovascular disease and obesity and their interaction with environmental and behavioral factors, with an emphasis on diet. He has published more than 770 scientific articles in peer-reviewed journals and written several books on these topics. He is considered one of the most distinguished world experts in gene–diet interactions related to cardiovascular traits. Moreover, he has trained in his laboratory roughly 60 scientists from all continents. Throughout his career, Dr. Ordovás has received multiple honors for his scientific achievements, including the USDA Secretary’s Award, the Centrum American Nutrition Society Award, the Danone Foundation Award, and the Gold Medal of the Spanish Society of Cardiology. He has been awarded an honorary degree in medicine bestowed by the University of Cordoba in Spain and is a member of the Spanish Royal Academies of Sciences, Medicine, Nutrition and Pharmacy. He serves on multiple editorial, advisory, peer-review, and steering committees. Dr. Ordovás was educated in Spain at the University of Zaragoza, where he completed his undergraduate work in chemistry and his Ph.D. in biochemistry. He did postdoctoral work at the Massachusetts Institute of Technology, Harvard, and Tufts.

Nathan Price, Ph.D., is a professor and the associate director of the Institute for Systems Biology in Seattle, Washington. He is also affiliate faculty in the Departments of Bioengineering, Computer Science and Engineering, and Molecular and Cellular Biology at the University of Washington. He is the co-founder and on the board of directors of Arivale, Inc. (“Your Scientific Path to Wellness”), which was named Geekwire’s 2016 Startup of the Year. Dr. Price has won numerous awards for his scientific work, including
a National Institutes of Health Howard Temin Pathway to Independence Award, a National Science Foundation CAREER award, and a young investigator award from the Roy J. Carver Charitable Trust. He was named one of the inaugural “Tomorrow’s PIs” by Genome Technology and a Camille Dreyfus Teacher-Scholar. Most recently, he received the 2016 Grace A. Goldsmith Award from the American College of Nutrition, given each year to a researcher under the age of 50 for significant contributions to nutrition science. Dr. Price has produced more than 120 peer-reviewed scientific publications and serves on the editorial board for many leading scientific journals, including *Science Translational Medicine* and *Cell Systems*. He also serves on advisory boards for a number of companies and institutes, including Roche (personalized medicine division), Cleveland Clinic’s Center for Functional Medicine, Sera Prognostics, Inc., the Novo Nordisk Foundation Center for Biosustainability, Trelys, Inc., and the University of Washington’s Public Health Genomics. He is a fellow of the European Society of Preventive Medicine.

**Sarah Roller, J.D.**, is a partner in the Washington, DC, office of Kelley Drye & Warren, LLP, and the chair of the firm’s Food and Drug Law practice. For more than 25 years, her practice has focused on the representation of U.S. and global companies and industry trade organizations that are involved in the development, manufacture, labeling, and marketing of foods, beverages, dietary supplements, and other health products. She represents companies in proceedings before the U.S. Food and Drug Administration, the U.S. Department of Agriculture, the Federal Trade Commission, the Tax and Trade Bureau, and state governmental bodies, and serves as counsel in litigation matters involving product safety, labeling, and advertising regulation. Ms. Roller is a registered dietitian and received her B.S. from the University of Wisconsin–Madison and her M.P.H. from the University of Minnesota. She received her J.D. from The George Washington University. Ms. Roller has been recognized nationally as a leading practitioner by Chambers USA and selected as one of The Best Lawyers in America.

**Nicholas J. Schork, Ph.D.**, is a distinguished professor of quantitative medicine at the Translational Genomics Research Institute (TGen) in Phoenix, Arizona, and the co-director of the City of Hope/TGen IMPACT Center; professor and director of human biology at the J. Craig Venter Institute (JCVI) in La Jolla, California; and adjunct professor of psychiatry and family medicine and public health (Division of Biostatistics) at the University of California, San Diego. Prior to joining JCVI, Dr. Schork held faculty positions at The Scripps Research Institute, the Scripps Translational Science Institute, and Case Western Reserve University. His interests and expertise are in quantitative human biomedical science and integrated approaches
to complex biological and medical problems. He has published more than 500 scientific articles and book chapters that consider novel data analysis methodology, study designs, and applications. He also has mentored more than 75 graduate students and postdoctoral fellows, holds 8 patents, and has helped establish 10 different companies in biomedical sciences and applications. Dr. Schork is a former member of the National Academies of Sciences, Engineering, and Medicine’s Food and Nutrition Board, a member of several scientific journal editorial boards, and a frequent participant in National Institutes of Health–related steering committees and review boards. He has also served as director of the quantitative components of a number of national research consortia, including the National Institute on Aging–sponsored Longevity Consortium and the National Institute of Mental Health–sponsored Bipolar Consortium.

Patrick J. Stover, Ph.D., is a professor and the director of the Division of Nutritional Sciences at Cornell University. He teaches three classes for graduate students—Grant Writing; Translational Research and Evidence-based Policy and Practice in Nutrition; and the B-vitamin metabolism section of Micronutrients: Function, Homeostasis, and Assessment. He was elected in 2015 as a member of the National Academy of Sciences and in 2014 as a fellow of the American Association for the Advancement of Science. In 2014, he received the State University of New York Chancellor’s Award for Excellence in Scholarship and Creative Activities; the Osborne and Mendel Award for outstanding recent basic research accomplishments in nutrition from the American Society for Nutrition; and a MERIT award from National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. In 1996, Dr. Stover received the Presidential Early Career Award for Scientists and Engineers from President Clinton, the highest honor bestowed by the U.S. government on outstanding scientists and engineers beginning their independent careers. He has been selected as an Outstanding Educator four times by Cornell Merrill Presidential Scholars. He is editor of Annual Reviews of Nutrition. He graduated from Saint Joseph’s University with a B.S. in chemistry and was awarded the Molloy Chemistry Award at graduation. He received a Ph.D. in biochemistry and molecular biophysics from the Medical College of Virginia and performed his postdoctoral studies in nutritional sciences at the University of California, Berkeley.

Douglas C. Wallace, Ph.D., is the Michael and Charles Barnett endowed chair in pediatric mitochondrial medicine and metabolic disease, the director of the Center for Mitochondrial and Epigenomic Medicine at Children’s Hospital of Philadelphia, and a professor in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania. He founded the field of human mitochondrial DNA (mtDNA) genetics and demon-
strated that mtDNA variation has profound implications for human health and disease, the origins and ancient migrations of our ancestors, human and animal adaptation, and perhaps the origin of species. In recognition of his seminal contributions to human and mammalian genetics, Dr. Wallace was elected to membership in the National Academy of Sciences in 1995, the American Academy of Arts and Sciences in 2004, and the National Academy of Medicine in 2009. He received the William Allan Award from the American Society of Human Genetics in 1994, the Passano Award for Mitochondrial Genetics (with G. Attardi) in 2000, the Metropolitan Life Foundation Award for Medical Research in Alzheimer’s Disease in 2000, and the Pasarow Award for cardiovascular disease in 2006. In 2012, he received the Gruber Genetics Prize, the world’s highest genetics honor, as well as the American College of Physicians Award for “Outstanding Work in Science as Related to Medicine.” In 2015, he was awarded Doctor Honoris Causa, Université Angers, France, and was elected to the Accademia Nazionale delle Scienze detta dei XL (National Academy of Sciences of Italy). In 2017, he received the Franklin Institute’s prestigious Benjamin Franklin Medal for the Life Sciences and the Paul Janssen Award for Biomedical Research.

Steven H. Zeisel, M.D., Ph.D., is the Kenan distinguished university professor in nutrition and pediatrics; the former chairman, Department of Nutrition; director, Nutrition Research Institute; and the director, University of North Carolina at Chapel Hill (UNC) Nutrition Obesity Research Center at UNC. The Nutrition Research Institute focuses on using genetic, epigenetic, and metabolomic methods to discover why there is individual variation in responses to and requirements for nutrients. The UNC Nutrition Obesity Research Center is one of 12 centers of excellence in nutrition research funded by the National Institutes of Health. Dr. Zeisel’s research focuses on dietary requirements for the nutrient choline, genetic variation as a source of individual differences in requirements for and responses to nutrients, effects of choline and folate on stem cell proliferation and apoptosis, and resulting effects on cancer and neurogenesis. His research team works with cells, mouse models, and human clinical studies. Dr. Zeisel is the author of more than 250 peer-reviewed scientific papers. He is on the editorial board of the *FASEB Journal* and is an editor of the nutrition textbook *Present Knowledge of Nutrition*, Volume 10. He is a leader in the development of an innovative nutrition curriculum used by more than 150 medical schools. He received an M.D. from Harvard University (1975) and a Ph.D. from the Massachusetts Institute of Technology (1980).