Nutrigenomics and the Future of Nutrition: Proceedings of a Workshop in Brief

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Proceedings of a Workshop—in Brief

On December 5, 2017, the Food Forum of the National Academies of Sciences, Engineering, and Medicine hosted a public workshop in Washington, DC, to review current knowledge in the field of nutrigenomics and to explore the potential impact of personalized nutrition on health maintenance and chronic disease prevention. This Proceedings of a Workshop—in Brief highlights key points made by individual speakers during the workshop presentations and discussions and is not intended to provide a comprehensive summary of information shared during the workshop. The information summarized here reflects the knowledge and opinions of individual workshop participants and should not be seen as a consensus of the workshop participants, the Food Forum, or the National Academies of Sciences, Engineering, and Medicine.

SETTING THE STAGE

In her opening presentation, Patsy Brannon of Cornell University explained how the first two steps of the risk assessment framework are central to current, population based dietary guidance. First, a health outcome is identified from a review of the literature and a synthesis of the evidence and, second, the dose–response relationship between a nutrient, or diet, and the health outcome is characterized. Using this population-based approach, Dietary Reference Intakes (DRIs) are based on distributions of nutrient intake. In the past, Brannon continued to explain, it has been impossible to ascertain where in one of these distributions an individual’s needs fall. 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,” she said.

The fact that there is a distribution of responses to nutrient intakes, even in a healthy population, raised the question for Brannon: Why do people vary? She discussed how genetic, epigenetic, and nutrient–gene interactions drive individual variation in nutritional kinetics and dynamics, elaborated on the complexity of these interrelationships, and illustrated how this complexity is reflected in the variety of ways that different authoritative bodies have defined nutrigenomics. In her opinion, this complexity will need to be addressed as population-based nutrition guidance transitions into personalized nutrition guidance (see Figure 1).

“Adding to this complexity,” Brannon continued, “is the reality that consumer and food behavior is very, very difficult to fully elucidate and understand.” Health is not the only driving force and is likely not even the major driving force in food choices. “Taste is often the primary force,” she said, “and nutrigenomics is not going to change that reality.”

In closing, Brannon opined that, because of these complexities, rather than thinking about population-based and personalized dietary guidance as an either-or situation, the two approaches will likely need to be integrated.

1 Presentations, videos, and other materials from the workshop can be found at nationalacademies.org/foodforum (accessed January 23, 2018).
2 When people consume food, Brannon explained, there are both kinetic (e.g., digestion, bioavailability) and dynamic (e.g., temporal response) aspects of the concentration and action of a nutrient at the site of action.
In the first session, moderated by Naomi Fukagawa of the U.S. Department of Agriculture, speakers discussed the inter-relationships of diet, genomics, and health outcomes, with a focus on chronic disease endpoints.

To begin, José Ordovás of Tufts University discussed both the genome and epigenome in relation to nutrition and disease risk. According to Ordovás, the root of personalized therapies is newborn screening. In the United States, each year, more than 1,000 babies are born with congenital hypothyroidism (CH), one of several monogenic diseases that require specific treatments. According to Ordovás, the approximate cost of screening for CH is $20 million, compared to $400 million in benefits (i.e., costs avoided by having treated the disease). Costs and benefits of such screening aside, he continued, “what we know” is that the genome influences what therapies we need and how we respond to pharmacological and diet treatments. As a less extreme example than CH, he described what scientists have been learning about APOA2 and how earlier research had showed that individuals homozygous for the less common C allele (CC genotype) ate more food, specifically fatty foods, and as a result weighed more than individuals with TT and TC genotypes. Yet, in later work, scientists discovered that under low saturated fat conditions, genotype no longer mattered and that only when consuming a high saturated fat diet, which Ordovás described as a diet that stresses the physiology, do individuals with the CC genotype gain more weight than individuals with either of the other two genotypes. “This is a polymorphism that may have a significant impact in terms of personalized recommendations,” he said. He emphasized that this later finding has been replicated not only across populations worldwide, but also across ethnicities.

Although the absolute complexity of the epigenome is smaller than the genome, with its 30 million CpG dinucleotides in various states of methylation, compared to the genome’s more than 300 million base pairs, Ordovás

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1. APOA2 is a gene that is expressed primarily in the liver and that codes for apolipoprotein A-II, a protein that is present in high-density lipoprotein (HDL).
2. CpG is a coupling of a cytosine and guanine nucleotide in linear sequence; the cytosines in CpG dinucleotides can be methylated, unmethylated, or hemi-methylated, with methylation status affecting gene expression.
remarked that it is much more difficult to study in humans with respect to its importance in nutrition because of its
dynamic nature. Unlike the genome, the epigenome changes over time and across organs and cell types. Yet, evidence
in humans that nutrition-related epigenetic changes can influence adult-onset chronic diseases is beginning to emerge.
Ordovás described some of what has been learned about the consequences of fetal starvation during the Dutch famine of
1944–1945 (the “Dutch Hunger Winter”), including obesity and neurological disorders later in life and significant differ-
ces in the epigenetic profiles of individuals who experienced fetal starvation compared to those who did not. He provid-
ed additional examples as well, including cases where both genetics and epigenetics ought to be taken into consideration
when predicting the impact of diet on health. Otherwise, he said, recommending that everyone increase their intake of the
omega-3 fatty acid or EPA (eicosapentaenoic acid) for example, would result in a positive effect in some individuals with
respect to HDL cholesterol, but a negative effect in others.

In closing, Ordovás remarked that the microbiome also plays a role in nutrition and that personalized nutrition
will likely require combining not just an individual’s genomics and epigenomics, but his/her microbiome as well. “I don’t
know that we’ll ever get to perfect,” he concluded, meaning 100 percent personalized nutrition. However, paraphrasing
an old Italian proverb, he said, “perfection is the enemy of good.” There is enough known now, in Ordovás’s opinion, to
begin putting the pieces of the puzzle together in the right places and to control some of what he described as the “snake
oil” being sold by some commercial ventures.

“Why can’t we understand and cure the common metabolic and degenerative diseases?” Douglas Wallace of the
University of Pennsylvania began his presentation on mitochondrial genetics and its relationship with disease risk. He sus-
ppected that perhaps the problem is not the effort, given the trillions of dollars that have been spent trying to understand
chronic disease in humans; rather it is the basic assumptions upon which the scientific community is studying disease.
Rather than focusing on anatomy and Mendelian (i.e., nuclear) inheritance alone, Wallace suggested also thinking about
bioenergetics and non-Mendelian (i.e., mitochondrial) inheritance. He described how nuclear and mitochondrial DNA
have differentiated over evolutionary time, with today’s mitochondrial genome specializing in energy. The flow of energy
across the mitochondrial membrane is, he said, “absolutely critical” to life.

Wallace explained how the different components of the mitochondrial “wiring diagram” have co-evolved and
how maternal inheritance of mitochondrial DNA has ensured that these co-evolved components remain tightly coupled.
Through this tight coupling, energy production is more efficient than it would be otherwise. However, although
mitochondrial DNA does not undergo sexual recombination, mitochondria are constantly replicating and, as they repli-
cate, mutations accumulate. As these mutations accumulate, the different tissues in the body become mosaics of different
mitochondrial genotypes, Wallace continued to explain. And as the number of mutant mitochondrial DNA increases, en-
ergy output declines. Regardless of the type of mitochondrial mutation, when energy output crosses a minimum energy
threshold for that organ, disease begins.

“Once we begin to think energetically,” Wallace said, “then all the common diseases have the same etiology:
a bioenergetics defect.” He described results from several studies of mitochondrial mutations, as well as mitochondrial
heteroplasmy (cells with a mixed population of mutant and normal mitochondria), in relation to a wide range of disease
and behavior phenotypes.

PERSONALIZED NUTRITION IN THE REAL WORLD

Shifting the focus from research to personalized nutrition in the real world, Nathan Price of the Institute for Systems
Biology presented work under way at Arivale, a wellness and personal coaching company he co-founded. But first, he dis-
cussed the complexity of the relationship between nutrition and disease at the molecular level; the many different systems
biology inputs that contribute to this complexity (e.g., genetics, metabolic function, physical activity); and the estimated
90 percent of a person’s lifetime health that is attributed to genetics, behavior, or the environment (as opposed to health
care). He differentiated between the health care industry and the wellness industry, the latter having a mixed reputation,
in his opinion, because of the many non-scientifically-based approaches being applied. Price discussed how he and a col-
league proposed the 100K Wellness Project to increase credibility in the wellness industry. The goal of scientific wellness,
he explained, is to predict and prevent disease before it happens; the goal of the 100K Wellness Project is to collect a
dense, dynamic dataset for 100,000 individuals that can be watched over time for early warning signs of disease.

In the meantime, Price and colleagues have completed a 9-month feasibility study, the Pioneer 100 Wellness
Project, which involved 108 participants who underwent detailed laboratory tests at three different times and received
personal wellness coaching for the duration of the study. Data were collected on hundreds of metabolites and markers
and the investigators also provided participants with wellness coaching. Regarding the coaching, Price referred to other
workshop speakers’ emphases on the critical role of behavior change in personalized nutrition. Over the course of the
study, participants showed improvements in a number of clinical markers, such as a 12 percent improvement in inflammation by 6 months (i.e., inflammation was reduced). Price noted that participants who have stayed with the program, through participation in Arivale’s scientific wellness program, have shown continued improvements. In addition to mining the data and returning new health discoveries back to the study participants, Price and colleagues have also been studying the nearly 4,000 correlations detected among the different data types (e.g., associations between metabolites in the blood and genetic risk scores). “These data types had never before been measured simultaneously on a population of people,” he said.

Continuing the focus on the potential for nutrigenomics in the real world, next, Claudia Morris of Emory University shared her research on arginine deficiency syndromes, mostly in relation to sickle cell disease and trauma. She described both as having distinct nutritional requirements that develop because of metabolic abnormalities that may benefit from arginine replacement therapy. Arginine, a conditionally essential amino acid (i.e., it becomes indispensable under stress or critical illness, but is otherwise non-essential) is an obligate substrate for nitric oxide (NO) production. NO, in turn, is a potent vasodilator with multiple functions. Morris stressed that a drop in an amino acid does not necessarily translate into a clinically significant deficiency. For a nutritional deficiency to occur, a biological process that is dependent on that nutrient has to be compromised, that compromise has to lead to an abnormal physiological response that is causative of a poor outcome, and those poor outcomes need to be reversible when the nutrient is replaced. In the case of pulmonary hypertension in sickle cell disease, Morris demonstrated how low arginine bioavailability meets these criteria: it leads to endothelial dysfunction (i.e., the compromised biological process), which may lead to pulmonary hypertension (i.e., the abnormal physiological response), which is associated with increased mortality in patients with sickle cell disease (i.e., the poor outcome) and may be reversible with arginine supplementation.

Patients with sickle cell disease have also been shown to have lowered arginine-to-ornithone ratios, which, in turn, have been associated with higher risk for pulmonary hypertension. Morris and colleagues observed decreases in pulmonary hypertension among sickle cell patients treated with arginine similar to what has been reported for some of the pulmonary hypertension medications on the market. She described how arginine deficiency also has been shown to play a role in other diseases, including cardiovascular disease. In one study, the arginine-to-ornithone ratio was more predictive of cardiovascular disease than cholesterol.

Although the potential benefit of arginine therapy for sickle cell disease, as well as for trauma, has been demonstrated in mice and humans, most of these studies are limited by methodological weaknesses, according to Morris. Additionally there is a paucity of data in children. There are other therapeutic strategies to consider as well, such as arginine precursors (e.g., glutamine) and combination therapies that target multiple mechanisms. Morris concluded by calling for more research, including the identification of sub-populations that would likely benefit the most from arginine replacement therapy.

“We have heard a lot of evidence that has tremendous promise,” David Alpers of the Washington University School of Medicine in St. Louis began, but said, “we are just in the early stages of where we can utilize this information.” Nutrigenomic studies are difficult not only because they are complex, but also because proving causation from associations is especially challenging in the field of nutrition. There are many components in the diet that interact and which, together, cause multiple metabolic changes in the body. 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 and which to other factors. In the clinic, Alpers 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.” 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. For example, turmeric and garlic extracts and other nutrient components have been shown to play potent roles in preventing some cancer changes in cells or in animals. But most of these findings have not been translated to human data. Alpers further stated that the human data that do exist, for example, studies on omega-3 fatty acid supplementation, are not as suggestive as they are in animal studies. In sum, Alpers expects a long lag before strong human data are available and nutrigenomics can be commercially implemented.

Meanwhile, he continued, there are many personalized Internet services currently available to consumers that provide individuals with information based on an analysis not of their genomes, but of their dietary patterns. Many of these services are mobile phone based, which Alpers predicts will become a potent method for modifying behavior when nutrigenomics does become commercially implemented. Also available are personalized programs based on phenotypic data, for example, wrist-watch accelerometers that monitor and deliver physical activity information. Alpers acknowledged that these programs work in terms of the immediate feedback they provide, but reiterated that what is missing is whether the information provided, if used by the recipient, will actually change a disease phenotype. Finally, in fact, there are some personalized nutrition services already available that rely on genomic data; however, most of the information comes from
observational studies linking single nucleotide polymorphisms (SNPs) to dietary patterns. “That’s not really enough in itself,” Alpers said, as those links have yet to be translated into changes in disease phenotypes.

In closing, Alpers remarked, “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.”

The final speaker of this session, Ahmed El-Sohemy of the University of Toronto and founder of Nutrigenomix, Inc., remarked that, while he agreed with many of Alpers’s comments, he would also be presenting evidence to show that many of Alpers’ criticisms “are actually not true.” He acknowledged, however, that the field is not without controversy, as what is being offered is quite varied and some of what is being offered is not rooted in robust scientific evidence. But where there have been enough observational studies linking nutritional factors with health outcomes, the responses are variable. El-Sohemy emphasized the importance of understanding genetic differences that help to explain these variable responses. Without this understanding, he argued, “outlier” individuals could actually be harmed by advice that benefits others. As an example, he described coffee intake and how the risk of myocardial infarction associated with coffee intake depends on whether one is a fast metabolizer or a slow metabolizer based on the CYP1A2 genotype. The CYP1A2 genotype has also been shown to modify the association between coffee intake and several other health outcomes, El-Sohemy continued to describe. While questions remain about the economic and social aspects of genetic testing, including the cost and accessibility of such testing, in terms of the science, referring to the CYP1A2 studies, El-Sohemy said, “I think these are some really good examples of proof of concept at how an individual SNP, a single SNP, can modify the association between a dietary component and a variety of different health outcomes.”

El-Sohemy went on to describe some of the ways that nutrigenomics is portrayed in the media and what he perceived as problems in how information is communicated. He provided an example of an article where a pediatrician who was asked during an interview about the variability of diet response and he was unaware of the evidence that suggests that people respond differently to different diets. Per El-Sohemy, not only does such evidence exist, but it is “pretty robust” and has been replicated. He was referring to evidence showing that a person’s response (i.e., change in fat mass) to a low protein versus a high protein diet depends on an individual’s genotype. Specifically, people with an AA genotype lost a considerably greater amount of fat mass on a high protein diet, compared to a low protein diet. In contrast, individuals with the TT or TA genotypes showed no difference in loss of fat mass on a low protein versus a high protein diet. Bringing to mind Brannon’s prediction in her opening presentation that the future likely will bring an integration of population-based and individualized dietary guidance, as opposed to completely transitioning into individualized dietary guidance, El-Sohemy asked: How can this kind of personalized dietary advice (e.g., regarding FTO genotype) be balanced with public health recommendations for populations? He described the results of a randomized clinical trial showing that people who were provided with DNA-based dietary advice had a greater understanding of the recommendations, compared to people who did not receive the advice; were motivated to change their eating habits; and showed greater compliance 1 year later. This finding has been replicated, according to El-Sohemy, suggesting that providing people with personal information can be a very useful tool for motivating them to change their eating habits.

NUTRIGENOMICS APPLICATIONS: DIETARY GUIDANCE AND FOOD PRODUCT DEVELOPMENT

In Session 2, moderated by Wendy Johnson of Nestlé, the workshop sharpened its focus on how to move nutrigenomics forward in what Johnson described as “a way that makes a difference in people’s lives.” First, Patrick Stover of Cornell University explored what consumers of nutrigenomics will need to know given the complexity of nutrient requirement traits. Dietary requirements are influenced not just by disease, but also by genetics and a number of other modifiers and physiological processes. He discussed in detail the impact of genetics in particular and how the food environment has been one of the most powerful selective pressures in human evolution. He stressed, however, “no one gene variant completely determines what the phenotypic expression is going to be.”

Given that genetics is only one factor that determines phenotypic expression, for Stover, the question becomes: Does nutrition-related genetic variation matter in public health? Stover showed data illustrating that, in the case of an MTHFR polymorphism that affects folate status, yes, it does matter. In 2015, the World Health Organization (WHO) used these data to generate a guideline for what the optimal folate level should be to prevent neural tube defects.

Stover then asked, what do consumers need to know when provided with genetic information? In a recent study of four different diets in different strains of inbred mice, investigators found that the best diet to maintain health depends not only on an individual’s genetic background, but also on the specific health outcome. In his opinion, these findings provide a very good biological premise that diets should be matched to genotype. But then, he noted, the challenge

5 The MTHFR gene provides instructions for making an enzyme called methylenetetrahydrofolate reductase.
becomes: How should people be classified? Unlike mice, he quipped, people cannot be classified based on inbred strain.

Instead of classifying subgroups for diets (i.e., predicting which diet will work best based on genetic or other biomarkers), or for nutrients, Stover suggested that another “precision nutrition” strategy is to leverage the trend toward real-time personalized read-outs (i.e., through the use of apps or point-of-care devices). Still, questions remain regarding what guidance to provide to individuals and whether systems/network biology can be applied to the tremendous amount of data that individuals are collecting on themselves through these apps and devices.

“Putting aside how complicated and how much more work we have to do in this field, you’ve got to start somewhere,” Steven Zeisel, University of North Carolina at Chapel Hill, began his presentation on opportunities for developing nutrigenomic applications in industry. He noted that he had been working with a number of companies who were thinking of entering the nutrigenomics field, and he disclosed his own involvement with a gene-guided medical food company, Zthera.

People are metabolically different, with different populations having different distributions of metabolic polymorphisms, he emphasized. Moreover, much is known about the many metabolic pathways that nutrients must transit, the genes on which those pathways depend, and how certain variants of some of these genes (i.e. SNPs) act as “roadblocks” in metabolism, reducing the amount of metabolite produced. Zeisel suggested that one could develop nutritional solutions, or medical foods, to bypass roadblocks known to be associated with a health outcome related to nutrition. As an example, Zeisel described how premenopausal women with a PEMT SNP require more dietary choline than premenopausal women (PEMT is involved in choline production through an estrogen response element). Without additional choline, women with the SNP get sick with fatty liver, liver damage, and other outcomes. Zeisel envisioned a company forming around the scenario: a common mutation (72 percent of women in the United States are either heterozygous or homozygous for the SNP), a gene test (for the PEMT SNP), and an obvious intervention (dietary choline).

Zeisel explained how diet can “hide” roadblocks by delivering enough of the metabolite that a person is able to “push through” the metabolic roadblock. “That’s why GWAS has been abysmal at identifying nutritionally relevant SNPs,” he said. Diet intake is often missing in GWASs, and mixing responders (people whose diet is not masking a nutrition SNP) and non-responders (people who are eating enough of the SNP metabolite that their diet hides the presence of the SNP) in the same study results in a canceling out of effects.

While single SNP analysis is useful, Zeisel continued, as the field of nutrigenomics evolves, companies may need to start recognizing the complexity of metabolic pathways and the involvement of multiple SNPs. For example, there are other SNPs besides the PEMT SNP that can alter sensitivity to low choline. Again, Zeisel said, one could intervene with a medical food that delivers the nutrient(s) affected by the defective pathways. He provided a couple of additional examples illustrating the same concept: intervene with a medical food to bypass blocked metabolic pathways.

To move forward, Zeisel hoped for better methods of working with complex metabolic pathways involving multiple SNPs; the inclusion of dietary information in GWASs; and consideration that medical foods, as defined by the U.S. Food and Drug Administration (FDA), may be a good starting point for developing nutrigenomic products.

**NUTRIGENOMICS: REGULATORY, ETHICAL, AND SCIENCE POLICY CONSIDERATIONS**

In the third session, moderated by Brannon, speakers took a close look at the nature and strength of nutrigenomic evidence, both in terms of what it is and what it should be. In addition, a range of ethical and policy issues were presented and discussed.

Cecile Janssens of Emory University discussed the ethical implications of the methodological limitations in the scientific evidence for personalized medicine. She began by discussing a 10-year-old critical appraisal of the scientific evidence behind seven different companies’ dietary recommendations based on genomic profiling and health risks associated with certain genes. Among other findings, such as that almost half of the 56 genes tested by these companies had not been subject to meta-analyses of gene–disease associations, Janssens said she was most amazed, first, that profiles being tested by these companies for heart health were based on genes more frequently associated with non-cardiovascular diseases than with vascular diseases and, second, that two of the five genes being used to assess risk for bone diseases were associated not with bone disease, but with Alzheimer’s, asthma, or another outcome. “I’m not really very positive that the situation at this moment is very much different,” Janssens said. She described a more recent meta-analysis reporting a similar lack of association between 38 genes that were part of several companies’ nutrigenomic profiles and disease. She agreed with researchers working in the field, who have cautioned that, while promising, the field of nutrigenomics is “not ready for prime time yet.”

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6 **PEMT** encodes an enzyme that converts phosphatidylethanloamine into phosphatidylcholine.

7 Genome-wide association studies (GWASs) involve searching a genome for SNPs that occur more frequently in people with a particular disease than in people without the disease.
After describing a couple of the companies that advertise genetic testing to consumers and then use the genetic testing to provide consumers with personalized eating or nutrition plans, Janssens emphasized the discrepancy between what the companies’ advertisements claim and what their disclaimers reveal. Their disclaimers are very clear that genetics has only a very marginal role in how one’s body responds to diet. This discrepancy, she said, is where ethical principles play a role, particularly beneficence (i.e., the intent of doing good) and autonomy. Regarding beneficence, while Janssens agreed that there are known genetic associations between genes and diet, for many nutrients, she said, “we have no idea how much you need to eat to compensate for that genetic disadvantage.” In her opinion, there is not enough evidence yet to offer these tests online. Regarding autonomy, which Janssens explained requires that people be provided enough information so that they can make their own decisions, she pointed out that many websites of these companies do not provide any insight at all into how they derive their recommendations from consumers’ DNA. Moving forward, Janssens called for more relevant scientific studies, namely studies showing how dietary changes can improve intermediate markers (not necessarily clinical endpoints), and for companies to more respectfully communicate with consumers regarding the prematurity of genetically personalized nutrition recommendations.

Delving deeper into the vetting of personalized, genomically guided nutrition, Nicholas Schork of the J. Craig Venter Institute (and past chair of the planning committee for the 2006 National Academies workshop on nutrigenomics) began by discussing how trends in the biomedical sciences (e.g., the use of information technology to identify patterns in massive amounts of data) can be leveraged in nutrition-based health care. He further remarked on how recent changes in FDA (i.e., the 21st Century Cures Act) will bear on how one can make claims about nutritional interventions in the future (i.e., by allowing companies, under certain conditions, to provide “data summaries” and “real-world evidence” rather than full clinical trial results).

When leveraging these trends and new legislation to identify, verify, and vet nutrition strategies for individuals, key questions to consider, in Schork’s opinion, will be: What is being tailored to what? For example, is a gross diet being tailored to an individual’s genotype? Or, are more refined recommendations (e.g., nutrients, supplements) being tailored to a complex profile based on not just genetic, but also biomarker and other information about an individual? At what level should nutrition recommendations be operating? Is personalized, or individual, nutrition the best approach, or would a stratified approach be better (i.e., with individuals clustered into groups based on how they respond to particular dietary interventions)?

The stratified approach has an analogy in cancer treatment, where genetic perturbations (e.g., mutations) in an individual’s tumor are “matched” to a specific drug, using evidence from multiple sources. The problem is that vetting all of these matches, one by one, would require what Schork described as “a zillion little small clinical trials.” Instead, cancer researchers have adopted a few vetting strategies, such as the “basket trial,” whereby patients are steered toward whatever treatment “basket” is most relevant based on an a priori scheme for matching patients to drugs (i.e., based on genetic perturbations). He emphasized that, in these basket trials, it is not the individual drugs that are being tested, rather the a priori scheme, or algorithm, for matching that drug to the mutation or other genetic perturbation. In the future, Schork predicted, the nutrition community will be using a similar stratified approach, testing algorithms, not individual nutrients versus individual profile characteristics. He cautioned, however, that one challenge that will need to be addressed is how to make trials more adaptive such that they can take into account data that emerge after a trial has started.

Finally, Schork considered N=1 and other emerging trial designs that focus on an individual’s well-being, rather than the population at large. He envisioned leveraging these types of studies to collect phenotypic information for an individual over time and to establish personal, as opposed to population, thresholds that indicate a health status change.

The final speaker of this session, Sarah Roller of Kelly Drye & Warren, LLP, provided an overview of the current federal legal framework that governs genetic testing and health benefit claims for foods. Roller shared her thoughts on key regulatory issues that merit further consideration as nutrigenomics moves forward in a commercial context. She began by describing how Clinical Laboratory Improvement Amendments (CLIA) standards are designed to ensure the analytical, but not clinical, validity of genetic testing in laboratories that perform health-related testing. In contrast, under the medical device provisions of the Federal Food, Drug and Cosmetic Act (FDCA), FDA regulates genetic testing kits and components sold to laboratories or other persons. She explained that FDA’s authority covers only health-related tests considered to be medical devices, not “entertainment” applications of genetic testing (e.g., tests that provide consumers with insights into the type of wine they are likely to prefer). According to Roller, although there is some controversy around the precise scope of FDA’s authority to regulate genetic tests developed in-house (Laboratory Developed Tests, or LDTs), FDA has taken the legal position that laboratories that offer LDTs are subject to both CLIA and the FDCA. She noted that, in 2015, FDA issued a report that identified several critical issues with LDTs, such as a lack of evidence supporting clinical validity, but none of the problem LDTs appeared to be related to nutrigenomics.
While a number of personal test kits have been cleared by FDA for direct-to-consumer marketing, Roller continued, the first direct-to-consumer genetic test was not cleared until early 2017. That was 23andMe’s Genetic Health Risk test, which provides information on an individual’s predisposition to particular diseases. Roller explained that, because of the higher risks associated with diagnostic tests, the approval excludes them.

FDA also regulates the safety and labeling of food, Roller continued. She defined and described the different categories of “food,” but emphasized that, regardless of type, a food may also be a drug if a vendor makes a suggestive claim that has not been cleared by FDA as a “health claim.” However, FDA has broad authority to interpret and enforce health benefit claim regulations without triggering drug status, Roller explained.

Finally, in addition to CLIA and FDA standards and regulations, Roller discussed Federal Trade Commission (FTC) authority to prohibit false advertising claims for genetic testing products and services, such as its requirement that claims be supported by evidence that experts in the field believe is reasonable. The FTC’s authority also encompasses data security and data-sharing practices.

In her closing comments, Roller stressed the importance of considering the adequacy of all of these different components of regulation to accommodate nutrigenomic tests, claims, and personal consumer genetic information.

RETHINKING THE RELATIONSHIP BETWEEN DIET AND HEALTH: CAN NUTRIGENOMICS HELP?

The final session of the workshop, moderated by Stover, was a panel discussion with Janssens, Tim Morck, Wallace, and Zeisel of Spectrum Nutrition, LLC. This panel focused on three issues: the role of precision medicine as a paradigm for nutrition, the potential impact of precision or stratified nutrition, and equity. This brief summary provides only a snapshot of this panel discussion as a whole.

In response to Stover’s question about the role of precision medicine as a paradigm for nutrition, Zeisel opined that classifying individuals in terms of their responses will help to “get the noise out of nutrition data” and to develop targeted interventions. Janssens cautioned, however, that a challenge to classifying people on the basis of their genomic profiles is that people very easily become unique. Profiling can reach a point, she said, where “there is no one else with that profile.” She viewed this as a challenge for both precision medicine and precision nutrition. Wallace suggested that there may be a continuum of nutrition-related diseases, ranging from monogenic diseases that can be detected via newborn screening and treated by simply adding the nutrient back into the diet, to diseases like diabetes and Alzheimer’s, which may be too variable to control with diet. Zeisel pointed out that, in fact, even in medicine, efficacy is quite low, with only about 30 percent of individuals benefiting from a drug treatment. Given that the goal of precision medicine is to try to do better than this 30 percent, in his opinion, if nutrition guidelines could be developed for what he referred to as “a reasonable subpopulation,” with the understanding that the guidelines could be wrong for any given individual, “you’d be doing really well.” If that is the case, Janssens said, than the term “precision medicine” is misleading. She suggested “stratified medicine,” or “stratified nutrition.”

The potential impact of precision (or stratified) nutrition is “not just the food,” Morck remarked. He referred to Brannon’s opening presentation on the importance of nutritional kinetics and dynamic. Additionally, even with the best genetic information and nutritional advice, if someone is not motivated to take that advice, then that advice is worthless. For him, the personalization of personalized nutrition is the personalization of one’s approach to incorporating nutrition into one’s lifestyle and future. Morck called for validated biomarkers that indicate metabolic changes in response to dietary change—seeing those metabolic changes can motivate someone who has made the effort to change their diet to continue with that effort. “That feedback is really critical, I think,” he said. Right now, he said, the available biomarkers, like body weight, are too crude.

Finally, according to Stover, nutrition-related chronic diseases cost the U.S. economy about $1 trillion per year. Thus, one of the goals in nutrition, including personalized nutrition, is to lower this cost. However, most chronic disease is present in low-income communities that are probably least likely to benefit from what nutrigenomics offers. He asked the panel to consider how this equity issue should be addressed. For Janssens, the question is “so big,” that she always feels uncomfortable and puzzled when discussing nutrigenomics given the enormity of the over-nutrition problem among low-income populations. She was not convinced that nutrigenomics would serve this population. Ordovás observed that, too often, it is the public policy makers who are missing from this discussion. Without them in attendance, in his opinion, the issue cannot be addressed. Zeisel disagreed and argued, “everything we can do to refine our ability to explain the noise and to understand why some people respond and others don’t is very useful.”
DISCLAIMER: This Proceedings of a Workshop—in Brief was prepared by Leslie Pray as a factual summary of what occurred at the workshop. The statements made are those of the rapporteur or individual workshop participants and do not necessarily represent the views of all workshop participants; the planning committee; or the National Academies of Sciences, Engineering, and Medicine.

REVIEWERS: To ensure that it meets institutional standards for quality and objectivity, this Proceedings of a Workshop—in Brief was reviewed by Naomi Fukagawa, U.S. Department of Agriculture; Wendy Johnson, Nestlé Corporate Affairs; and Sylvia Rowe, SR Strategy, LLC. Lauren Shern, National Academies of Sciences, Engineering, and Medicine, served as the review coordinator.

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