

# Position of the Academy of Nutrition and Dietetics: Nutritional Genomics

## ABSTRACT

It is the position of the Academy of Nutrition and Dietetics that nutritional genomics provides insight into how diet and genotype interactions affect phenotype. The practical application of nutritional genomics for complex chronic disease is an emerging science and the use of nutrigenetic testing to provide dietary advice is not ready for routine dietetics practice. Registered dietitian nutritionists need basic competency in genetics as a foundation for understanding nutritional genomics; proficiency requires advanced knowledge and skills. Unlike single-gene defects in which a mutation in a single gene results in a specific disorder, most chronic diseases, such as cardiovascular disease, diabetes, and cancer are multigenetic and multifactorial and therefore genetic mutations are only partially predictive of disease risk. Family history, biochemical parameters, and the presence of risk factors in individuals are relevant tools for personalizing dietary interventions. Direct-to-consumer genetic testing is not closely regulated in the United States and may not be accompanied by access to health care practitioners. 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. The practical application of nutritional genomics in dietetics practice will require an evidence-based approach to validate that personalized recommendations result in health benefits to individuals and do not cause harm.

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## POSITION STATEMENT

It is the position of the Academy of Nutrition and Dietetics that nutritional genomics provides insight into how diet and genotype interactions affect phenotype. The practical application of nutritional genomics for complex chronic disease is an emerging science and the use of nutrigenetic testing to provide dietary advice is not ready for routine dietetics practice. Registered dietitian nutritionists need basic competency in genetics as a foundation for understanding nutritional genomics; proficiency requires advanced knowledge and skills.

**T**HE SCIENCE OF GENETICS AND genomics is moving at an accelerated pace. New technologies and scientific discoveries are deepening our understanding of how nutrients and dietary patterns affect health maintenance and disease development. Advances in epigenetics and the influence of the microbiome on health and disease also are contributing to the understanding of nutrition and health. Many omic approaches—transcriptomics, proteomics, and metabolomics—will help us understand nutrient–genome interactions. Genotyping alone will not be sufficient to personalize diet for improved health.<sup>1</sup> Understanding and manipulating how diet affects the phenotype of an individual will require technologies that can reveal the processes of what happens from the genetic blueprint through transcription and synthesis of proteins to identification of metabolites that will tell us what has

happened, both abnormal and normal. Whereas new scientific discoveries and technologies continually inform the science of nutritional genomics, translating these scientific discoveries into practical clinical application requires obtaining the same rigorous evidence that is the backbone of dietetics practice.

## SEQUENCING THE HUMAN GENOME

The first draft of the human genome was published in 2001 through an international effort called the Human Genome Project that took 20 years from inception to completion and cost \$3 billion. This incredible accomplishment was a mere 150 years after Mendel manipulated the colors of peas leading to his discovery of autosomal recessive inheritance, 100 years after chromosomes were identified as bearing inherited traits, 50 years after Watson and Crick described the molecular structure of genetic material as the double helix, and 30 years after the first DNA sequencing technology was invented. The full sequence of the human genome was completed and

published in 2003.<sup>2</sup> Perhaps the most startling discovery was that the number of human genes was estimated to be significantly fewer than early estimates. Since the completion of the Human Genome Project, hundreds of genomes have been sequenced from the tiniest bacteria to the largest mammal.<sup>3</sup> Technological advances have dramatically dropped the cost of sequencing a human genome from \$95 million in 2001 to <\$6,000 in 2013.<sup>4</sup> However, these costs do not reflect the costs associated with the development of bioinformatics, computational tools, equipment, and the analysis and interpretation of the data.<sup>5</sup> As the time and cost to sequence a human genome continues to drop, the expectation that it will become an integrated part of medical practice becomes more of a reality. However, translating whole genome sequencing into therapies that will benefit an individual will require strategies to handle large amounts of biological and medical data and the ability to identify significant and clinically meaningful results.<sup>6</sup>

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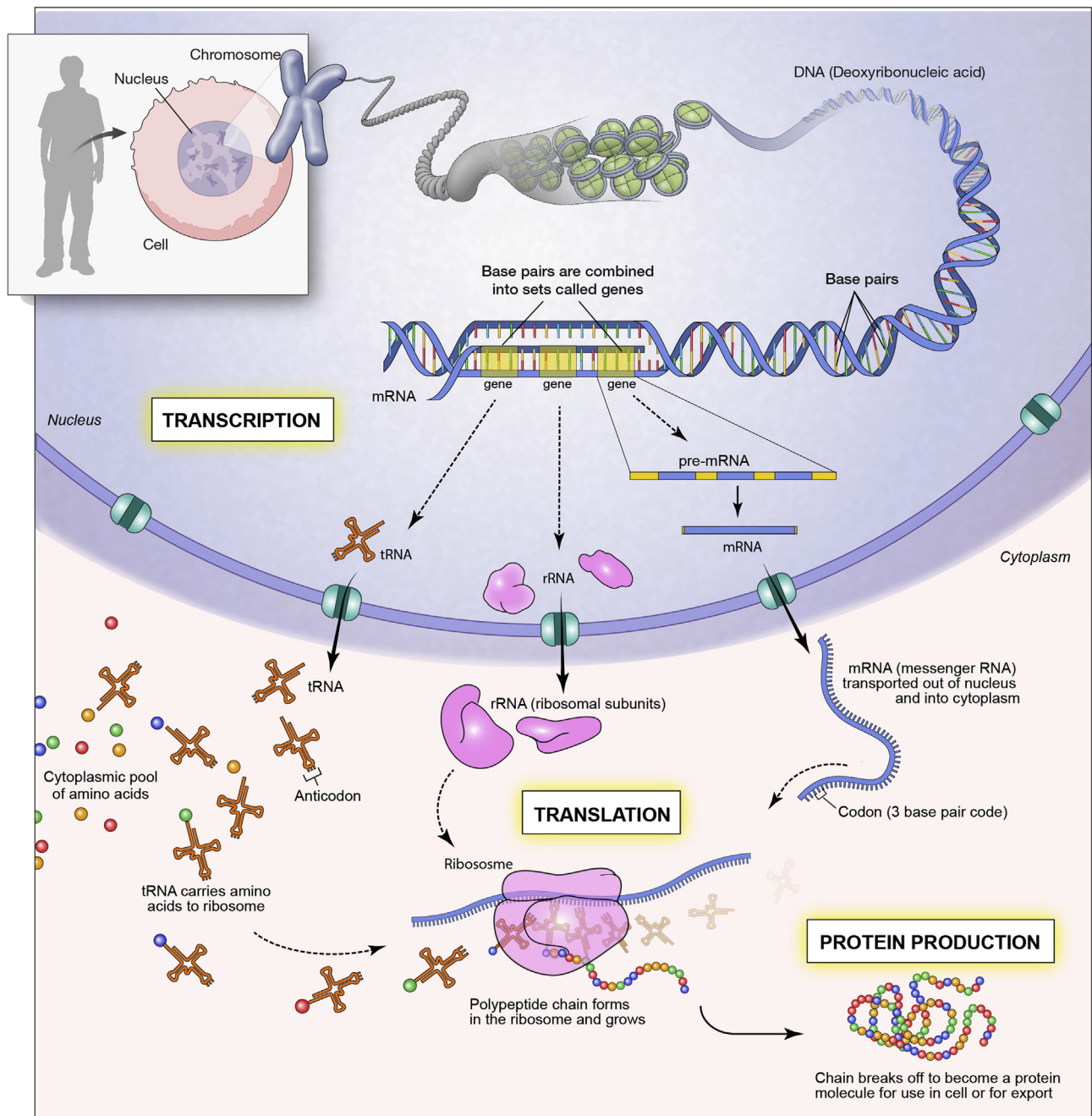
## GENETICS

Genes contain all of the biological information needed to build and maintain a living organism (see [Figure 1](#)). Genes are responsible for protein

formation and, ultimately, metabolic function. Genes are turned on and off in response to metabolic signals that the nucleus receives from internal factors, such as hormones and enzymes,

and external/environmental factors, such as diet.

Genes vary in size from a few hundred DNA bases to >2 million bases. Human beings have between 20,000



**Figure 1.** Within the nucleus of cells throughout our body are 23 pairs of chromosomes; within each chromosome is the genetic material organized into sequences known as genes. During the processes of transcription and translation, proteins are formed. In transcription, the information stored in a gene's DNA is transferred to RNA in the cell nucleus. Messenger RNA (mRNA) carries the message from the DNA out of the nucleus into the cytoplasm. In translation, mRNA interacts with ribosomes to read the sequence of mRNA bases. Each sequence of three bases, called a codon, usually codes for one particular amino acid. Each amino acid is brought to the ribosome by transfer RNA (tRNA). These tRNAs are specific for the particular amino acid they carry and recognize the codons along the mRNA.

and 25,000 genes. Most genes are the same from person to person, but <1% of genes are slightly different between people, which translates to a difference of 3 million bases. Natural variations in a gene, DNA sequence, or chromosome that occur with fairly high frequency in the general population are known as polymorphisms.<sup>7</sup> The most common type of polymorphism involves variation at a single base pair and are known as single nucleotide polymorphisms (SNPs), also referred to simply as polymorphisms (see Figure 2).

SNPs are the most common type of genetic variation in human beings. Each SNP represents a difference in a nucleotide. For example, an SNP may replace cytosine with thymine in a specific stretch of DNA. SNPs are considered a normal variation in the DNA; they account for the differences in human eye color, hair color, and blood type. Some SNPs may influence the risk of developing certain diseases or disorders.<sup>7</sup> A glossary that defines

some terms used in this article is found in Figure 3.

### Gene Expression

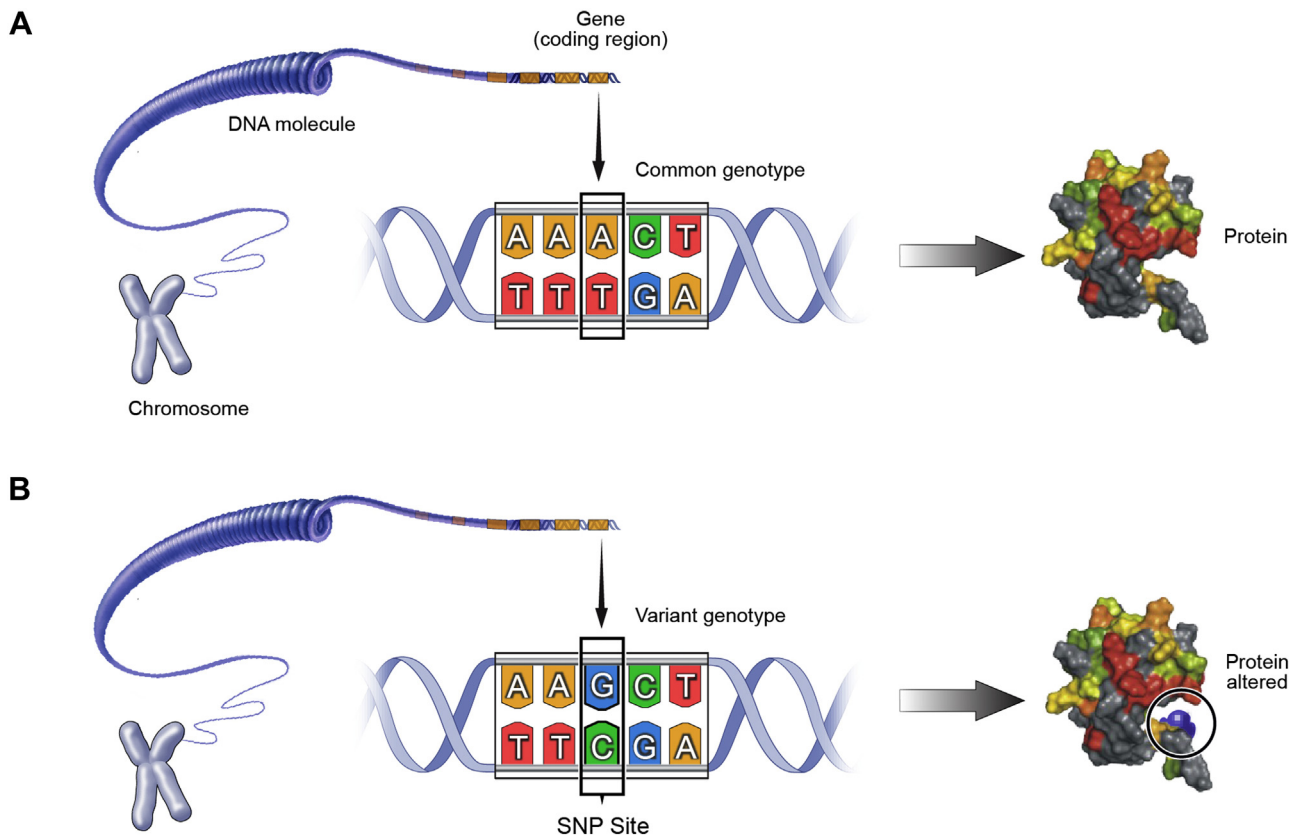
The central dogma of molecular biology is the flow of information from DNA to RNA. In a tightly controlled process of transcription and translation, proteins are formed. The first step, transcription, occurs when the information stored in a gene's DNA is transferred to RNA in the cell nucleus. Messenger RNA (mRNA) carries the message from the DNA out of the nucleus into the cytoplasm. The second step, translation, occurs when mRNA interacts with ribosomes, which read the sequence of mRNA bases. Each sequence of three bases, called a codon, usually codes for one particular amino acid. Proteins are formed in a process of gene expression (see Figure 1).<sup>8</sup>

### Nutritional Genomics

The genome is the entire DNA sequence of an organism; the genome

contains all of the biological information needed to build and maintain a living organism. *Omics* refers to the entire complement of a given category of biological molecules and information being studied, measured, or described.<sup>9</sup>

*Nutritional genomics* is the broad term encompassing nutrigenetics, nutrigenomics, and nutritional epigenomics, all of which involve how nutrients and genes interact and are expressed to reveal phenotypic outcomes, including disease risk. *Nutrigenetics* is the influence of genetic variability between individuals accounting for the variations in health status and disease risk despite similarities in dietary intake.<sup>10</sup> *Nutrigenomics* encompasses the interactions between dietary components and the genome and the resulting changes in proteins and other metabolites that affect gene expression.<sup>11</sup> Despite these delineations, nutrigenomics is often used synonymously with nutritional genomics. *Nutritional epigenomics* refers to



**Figure 2.** Single nucleotide polymorphisms (SNPs) are small sequence differences within genes where the DNA sequences of many individuals vary by a single base; not all SNPs result in structural protein changes. For example, some people may have a chromosome with an A at a particular site where others have a chromosome with a G. SNPs occur in about 1% of the population.

Term	Definition
Allele	An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene, one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous. <sup>82</sup>
Chromosomes	Structure found in the nucleus of a cell, which contains the genes. Chromosomes come in pairs, and a normal human cell contains 46 chromosomes. <sup>82</sup>
Codon	In DNA or RNA, a sequence of three nucleotides that codes for a certain amino acid or signals the termination of translation (stop or termination codon). <sup>82</sup>
DNA	Deoxyribonucleic acid. The molecules inside cells that carry genetic information and pass it from one generation to the next.
DNA methylation	The degree to which methyl groups are present or absent from certain regions of genes. <sup>35</sup>
Epigenetics	Changes in the regulation of the expression of gene activity without alteration of genetic structure. <sup>82</sup>
Gene silencing	Interruption or suppression of the expression of a gene at transcriptional or translational levels. <sup>82</sup>
Genome	The entire set of genetic instructions found in a cell. In human beings, the genome consists of 23 pairs of chromosomes found in the nucleus, as well as a small chromosome found in the cells' mitochondria. These chromosomes, taken together, contain approximately 3.1 billion bases of DNA sequence. <sup>82</sup>
Genome wide association studies (GWAS)	GWAS searches the genome for small variations or SNPs that occur more frequently in people with a particular disease than in people without the disease. Each study can look at hundreds or thousands of SNPs at the same time. These studies identify genes that may contribute the risk of developing a certain disease. <sup>82</sup>
Genotyping	Testing that reveals the specific alleles inherited by an individual; particularly useful when more than one genotypic combination can produce the same clinical presentation, as in the ABO blood group, where both the AO and AA genotypes yield type A blood. <sup>82</sup>
Histone	A protein that provides structural support to a chromosome. For very long DNA molecules to fit into the cell nucleus, they wrap around complexes of histone proteins, giving the chromosome a more compact shape. Some variants of histones are associated with the regulation of gene expression. <sup>82</sup>
Human Genome Project	An international research effort to determine the sequence of the human genome and identify the genes that it contains. <sup>83</sup>
messenger RNA (mRNA)	A single-stranded RNA molecule that is complementary to one of the DNA strands of a gene. The mRNA is an RNA version of the gene that leaves the cell nucleus and moves to the cytoplasm where proteins are made. During protein synthesis, the ribosome moves along the mRNA, reads its base sequence, and uses the genetic code to translate each three-base triplet, or codon, into its corresponding amino acid. <sup>82</sup>
Methylenetetrahydrofolate reductase (MTHFR)	This enzyme converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. This reaction is required for the multistep process that converts homocysteine to methionine. <sup>84</sup>
Microbiome	The collective genomes of the microbes (composed of bacteria, bacteriophage, fungi, protozoa and viruses) that live inside and on the human body. <sup>85</sup>
Multigenetic	The combined contribution of one or more often unspecified genes and environmental factors, often also unknown, which cause a particular trait or disease. <sup>82</sup>

(continued on next page)

**Figure 3.** Glossary of terms used in the Academy of Nutrition and Dietetics position paper on nutritional genomics. The terms in this glossary are related to genetics, genomics, and epigenetics.

Term	Definition
Nutrigenetics	Impact of genetic differences between individuals on the response to dietary intake and the ultimate influence on health status and disease risk. <sup>10</sup>
Nutrigenomics	The interactions between dietary components and the genome and the resulting changes in proteins and other metabolites that affect gene expression. <sup>11</sup>
Phenotype	Observable characteristics of an organism produced by the organism's genotype interacting with the environment. <sup>82</sup>
Polygenic	Genetic disorder resulting from the combined action of alleles of more than one gene (eg, heart disease, diabetes, and some cancers). Although such disorders are inherited, they depend on the simultaneous presence of several alleles; thus, the hereditary patterns usually are more complex than those of single-gene disorders. <sup>82</sup>
Proteomics	The study of protein expression and function. <sup>82</sup>
Ribonucleic acid (RNA)	A single-stranded molecule similar to DNA. An RNA strand has a backbone made of alternating sugar (ribose) and phosphate groups. Attached to each sugar is one of four bases: adenine (A), uracil (U), cytosine (C), or guanine (G). Different types of RNA exist in the cell: mRNA, ribosomal RNA, and transfer RNA. Some small RNAs have been found to be involved in regulating gene expression. <sup>82</sup>
Ribosome	A cellular particle made of RNA and protein that serves as the site for protein synthesis in the cell. <sup>82</sup>
Ribosomal RNA (rRNA)	The most abundant form of RNA. Together with proteins, rRNA form the ribosomes and play a structural role and also a role in ribosomal binding of mRNA and tRNAs. <sup>82</sup>
Single nucleotide polymorphisms (SNPs)	A type of polymorphism involving variation of a single base pair. <sup>82</sup>
transferRNA (tRNA)	A class of RNA that recognizes the triplet nucleotide coding sequences of mRNA and carries the appropriate amino acid to the ribosomes, where proteins are assembled according to the genetic code carried by mRNA. <sup>82</sup>

**Figure 3.** (continued) Glossary of terms used in the Academy of Nutrition and Dietetics position paper on nutritional genomics. The terms in this glossary are related to genetics, genomics, and epigenetics.

the influence of diet on changes in gene expression without changing the DNA sequence. Other omic areas are modified in response to diet. These include transcriptomics (the study of the transcriptome, the complete set of RNA transcripts produced by the genome at any one time), proteomics (the study of protein expression and function), and metabolomics (the study of low-molecular-weight molecules found within cells and biological systems).

### Nutrigenetics

The best-known example of nutrigenetics is classic phenylketonuria (PKU) caused by mutations in the phenylalanine hydroxylase gene. The primary treatment is a low phenylalanine diet. PKU is among a small group of rare, autosomal recessive metabolic

disorders of nutrient metabolism in which dietary treatment that is implemented shortly after birth ameliorates the phenotype of severe cognitive impairment and a host of medical problems. Unlike PKU, most chronic disorders, such as cardiovascular disease (CVD), hypertension, diabetes, and cancer, are multigenetic and multifactorial.<sup>12</sup> In these chronic diseases, a genetic variant, or SNP, does not necessarily translate into a greater risk of developing disease. Environmental factors, such as smoking, physical activity, and diet modify genetic expression and influence disease outcome.<sup>13</sup>

A nutritionally relevant SNP or polymorphism involves folate and homocysteine status, and potentially CVD, neural tube defects, and other disease risks. The C677T polymorphism is a common SNP of the methylenetetrahydrofolate reductase (*MTHFR*) gene,

which encodes the 5,10-MTHFR enzyme and uses folate to metabolize and thereby remove homocysteine. The C677T polymorphism in the *MTHFR* gene reduces enzyme efficiency, so in many populations without folic acid fortification, individuals with TT genotype have a lower blood folate levels and about a 20% higher homocysteine level than those with the more common CC genotype.<sup>14</sup> The C677T polymorphism in the *MTHFR* gene has been associated with a moderately increased risk of CVD occurrence in some genotyping studies in countries that do not fortify foods with folic acid, but overall the CVD risk of individuals with the TT genotype is unclear. Interestingly, folic acid fortification, which occurred in the United States in 1998, may be lessening the CVD risk in individuals with this genotype. An inverse relationship of the TT variant and CVD mortality was

found in a cohort in the period following folic acid fortification.<sup>15</sup> It is possible that the additional folic acid in the diet is protecting those susceptible individuals, although multiple pathways are involved in folate metabolism, which makes interpretation of folic acid status complex. There is insufficient evidence regarding C677T polymorphism in the *MTHFR* gene to modify current folate recommendations from those provided in the Dietary Reference Intakes.

Folate, methionine, and choline are intricately involved in the methylation of DNA, RNA, and proteins; disturbing the metabolism of one results in compensatory changes in the others.<sup>16</sup> The importance of their interactions is evident in the example of choline status in premenopausal women. Providing a choline-deficient diet to human beings results in reversible fatty liver with liver and muscle damage.<sup>17</sup> Premenopausal women are somewhat resistant to these deleterious outcomes because they have an estrogen-enhanced capacity for producing choline through the phosphatidylethanolamine N-methyltransferase (*PEMT*) gene.<sup>17</sup> The *PEMT* gene is induced by estrogen and codes for an enzyme that catalyzes the endogenous synthesis of choline. However, premenopausal women who have an SNP in *PEMT* may have an increased risk for developing liver and muscle dysfunction when fed a low-choline diet. In addition, premenopausal women with an SNP in the methylenetetrahydrofolate dehydrogenase 1 (*MTHFD1*) gene, which codes for another folate enzyme, were 15 times more likely to develop signs of choline deficiency on the low-choline diet than those without the SNP.<sup>17</sup> These SNPs may provide insight as to the interindividual variation in choline and folate requirements. However, more research is needed before clinical application of genetic testing of the *PEMT* gene is available and adequate intake values for choline are adjusted.

The most widely investigated common SNP–disease association is the relationship between the apolipoprotein E (apoE) genotype and coronary heart disease (CHD) risk. ApoE is a protein involved in cholesterol and triglyceride metabolism and clearance. ApoE has three isoforms (E2, E3, and E4) that equate to three gene alleles; E3 is normal whereas E2 and E4 are dysfunctional.

Generally, individuals with the E4 allele have higher low-density lipoprotein (LDL) cholesterol levels and those with the E2 allele have lower LDL cholesterol levels than individuals with the common E3/E3 genotype.<sup>18</sup> However, the consistency in phenotypic outcome from gene variants is not always what is expected. In the case of apoE, numerous studies have investigated the effect of the apoE genetic variant on CHD risk, including three meta-analyses.<sup>18–20</sup> Two of the analyses found that individuals with the E4 allele had an increased risk of CHD and those with the E2 allele showed no difference in CHD compared with the common allele<sup>19,20</sup>; the third analysis showed less of an effect in individuals with the E4 allele and a stronger protective effect of the E2 allele.<sup>18</sup> These analyses did not consider dietary influence, which may have contributed to the inconsistent results. Other potential variables contributing to the inconsistencies are the lack of statistical power, confusion by other gene variants, dietary interactions, and the lack of accurate measurements of dietary fat.<sup>13</sup> Early studies indicate that the apoE genotype interacts with dietary saturated fat, increasing LDL cholesterol concentrations and CHD risk, more in E4 carriers than the other alleles.<sup>13</sup> Insufficient evidence, study limitations, and other risk factors for CHD preclude making dietary fat recommendations based on apoE genotype testing.

A similar scenario exists with the cholesteryl ester transfer protein genotype. Initial research indicates an interaction between cholesteryl ester transfer protein SNP and alcohol consumption in determining high-density lipoprotein cholesterol concentrations and CVD risk. However, it has been difficult to replicate these results.<sup>13</sup> Another CVD risk-related gene variant is the apolipoprotein A5. In this case, the SNP is associated with higher triglyceride concentrations and n-6 polyunsaturated fatty acid dietary intake increases triglyceride levels.<sup>21</sup> Although this finding is promising, more studies are required before practitioners can provide dietary guidance based on apolipoprotein A5 genotype.

Genetic variations that predispose individuals to obesity, inflammation, dyslipidemia, and oxidative stress may interact with environmental exposures, including diet, to alter an individual's risk for developing these conditions.<sup>22</sup>

Several single gene mutations have been linked to severe obesity; however, they represent only a small fraction of population-level obesity. Like most chronic disease, obesity is polygenic, involving complex gene–gene and gene–environment interactions.<sup>23</sup> More than 20 genes are associated with obesity-related anthropometric measures, including body mass index (BMI), waist circumference, and waist-to-hip ratio.<sup>24</sup> Gene variants relating to the regulation of energy intake and expenditure include the adrenergic receptors, uncoupling proteins, peroxisome proliferator-activated receptor, proopiomelanocortin, melanocortin 4 receptor, and fat mass and obesity associated (*FTO*) genes.<sup>23</sup>

Variation in the *FTO* gene has been associated with obesity in genome-wide association studies. Adults with the *FTO* SNP genotype are likely to be more obese than those who do not carry the risk allele.<sup>25</sup> Energy intake is higher in children with the *FTO* risk allele, independent of body weight.<sup>26</sup> Carrying the A allele of the *FTO* gene increases the risk of obesity but the risk can be modified by either physical activity or by reducing energy intake.<sup>23</sup> The genetic vulnerability to obesity may be expressed in specific eating and activity patterns that are heritable, but only expressed when the environmental exposures permit them to be expressed.

The established obesity-associated genes together explain <2% of the interindividual BMI variation, which falls well below the estimated heritability for obesity. The heritability of BMI and waist circumference of 40% to 70% indicates there may be much more genetic variation left to uncover.<sup>24,27</sup> Additional genetic factors, such as rare and low-frequency variants, copy number variants, noncoding RNA (ie, microRNAs that regulate gene expression after transcription), and epigenetic modifications may be involved.<sup>24</sup> When additional functional genetic variants and further molecular and physiologic characterizations of the genes and pathways are uncovered, therapeutic guidelines for obesity intervention based on genotype variance may become a viable approach.

## Nutrigenomics

Energy restriction and dietary modification in obese individuals are

providing insights into how nutrients affect gene expression. Studies are finding that when overweight and obese individuals modify their diet, genes related to metabolism and insulin-like growth factor are decreased or down-regulated.<sup>28,29</sup>

Future nutrigenomic studies, which examine how diet and dietary patterns affect gene expression, may help guide clinicians in classifying obese patients into subtypes and identify different phases of weight loss, such as acute or long-term weight loss.<sup>30</sup> Although nutrigenomic and gene profiling tests are not validated for clinical practice, future testing may allow for more targeted therapy to subclasses of obese patients and aid in the development of obesity treatment strategies.

The effects of diet intervention on gene expression is beginning to emerge in other diseases, including cancer. Nutrigenomic testing was used in a pilot study of low-risk prostate cancer patients who declined traditional treatment and participated in an intensive nutrition and lifestyle intervention.<sup>31</sup> After 3 months, the men were consuming about 12% energy from fat, exercising >3.6 hours per week, and practicing stress management for 4.5 hours per week. CVD risk factors were improved, including reductions in BMI, waist circumference, blood pressure, and lipid levels. Gene expression analysis detected 48 up-regulated and 453 down-regulated transcripts after the intervention. In particular, a set of RAS family oncogenes were down-regulated, which may function as an androgen receptor coactivator, and for which expression is increased in tumor tissues.<sup>31</sup> A double-blind placebo-controlled randomized clinical trial, the Molecular Effects of Nutrition Supplements, also looked at nutrient intervention and gene expression in low-risk cancer patients and found no effects of diet on gene expression. Men with low-risk prostate cancer were stratified based on self-reported dietary consumption of fish and tomatoes and then randomized to receive supplemental lycopene, fish oil, or placebo. After 3 months, gene expression analysis revealed no significant individual genes that were associated with high intake of fish or tomato.<sup>32</sup> Limitations of this study include not controlling the patients' dietary intake and the multiple lifestyle

variables that could confound the results.

### EPIGENOMICS

Epigenetics are the heritable changes not encoded in the DNA sequence itself, but that play an important role in the control of gene expression.<sup>33</sup> Epigenetics is the process that regulates how and when genes are silenced and activated; epigenomics refers to the analysis of epigenetic changes in a cell.<sup>34</sup> Diet can cause epigenetic changes that may turn certain genes on or off, ultimately affecting cellular function and metabolism.<sup>34</sup> One epigenetic mechanism is DNA methylation, which refers to the degree to which methyl groups are present or absent from certain regions of genes. Generally, hypomethylation allows gene expression to be activated; hypermethylation interferes with gene expression. Both hypomethylation or hypermethylation describe an aberrant scenario and the influence on a gene will depend on the specific genes, the time point, and the tissues.<sup>35</sup>

### Nutritional Epigenomics

The nutrients folate, methionine, choline, vitamin B-12, and vitamin B-6 are involved in one-carbon metabolism and play a critical role in maintaining DNA methylation. The intake of too much or too little of any of these nutrients affects one-carbon metabolism and has the potential to disrupt DNA and histone methylation patterns.<sup>36</sup> In animal studies, diets deficient in methionine, choline, vitamin B-12, or folate induce global hypomethylation and site-specific hypermethylation and have been linked to increased cancer development.<sup>36</sup>

Some of the strongest evidence that diet plays a role in epigenetics, through methylation, was done in the agouti mouse model. The wild type agouti mice have a yellow coat color and are genetically prone to obesity. The addition of folic acid, vitamin B-12, choline, and betaine to the maternal diet of pregnant mice altered the wild type phenotype of yellow coat and obesity to a phenotype characterized by a less yellow coat color; pseudo-agouti; and lower prevalence of cancer, diabetes, and obesity.<sup>37</sup> Adding genistein at levels comparable with human beings

consuming high-soy diets to the maternal diet led to similar outcomes.<sup>38</sup>

Dietary factors can act via epigenetic mechanisms throughout the lifespan, and also may extend across generations. Individuals exposed to famine provide evidence that early-life environmental conditions can cause epigenetic changes in human beings that persist through generations. Six decades after individuals were prenatally exposed to famine during the Dutch Hunger Winter in 1944-1945, they had less DNA methylation of the maternally imprinted insulin-like growth factor 2 gene, which is a key factor in human growth and development, compared with their unexposed, same-sex siblings.<sup>39</sup> The association occurred in the periconceptional period, reinforcing that very early mammalian development is a crucial period for establishing and maintaining epigenetic marks.<sup>39</sup> The individuals exposed to famine periconceptionally have had a higher incidence of chronic diseases, including a doubling in the incidence of schizophrenia, type 2 diabetes, CHD, hypercholesterolemia, and some cancers.<sup>40</sup> This concept of early programming mechanisms in human adaptation to the social environment can have generational effects.

The chronic low-grade inflammatory state that is associated with obesity, insulin resistance, CVD, and metabolic syndrome may also be under epigenetic regulation.<sup>41</sup> Human trials are looking at DNA methylation patterns before and after dietary interventions. In a small study of obese men on a weight loss regimen, hypocaloric diets induced changes in the DNA methylation pattern. There were noted differences in methylation between those men considered to be high responders (lost >5% body weight) compared with the low responders (lost ≤5% body weight). After the weight loss intervention, methylation changes from baseline were apparent, leading to the premise that some of the markers affected could be used as early indicators of response to the metabolic effects of a weight-loss program.<sup>42</sup> Future epigenetic research will likely focus on quantifying the importance of epigenetic regulation in the etiology and development of obesity and the characterization of the genes involved in the processes.<sup>41</sup>

Other epigenetic mechanisms include histone modifications, gene silencing by microRNA, and chromosome stability. DNA is tightly coiled around proteins known as histones; histone modification refers to how tightly the DNA strand is wrapped around the histones. Histone modifications are known to influence protein transcription, DNA repair processes, DNA replication, and chromatin condensation. Promising evidence in human beings suggests that diet and environmental factors directly influence these epigenetic mechanisms.<sup>33</sup>

Genomic imprinting, which can occur through DNA methylation or histone modification, is another mechanism that allows for gene expression. In genomic imprinting, only the paternally or maternally inherited allele is expressed. For example, Prader-Willi syndrome that leads to severe obesity arises from imprinted gene mutations.<sup>35</sup> Interestingly, loss of expression on the paternally inherited allele causes Prader-Willi syndrome, whereas absence of expression of the maternal allele results in Angelman syndrome,<sup>43</sup> a neurodevelopmental disorder characterized by severe mental retardation and not associated with obesity.<sup>44</sup>

Although there is promising evidence that diet can influence epigenetic mechanisms, there are still many unanswered questions that need to be addressed. Such questions include whether the nutritional influences on epigenetic modifications observed in animal and cell models correlate with manifestations in human beings, and further, what is the optimal type, dose, duration, and timing of the nutritional intervention and the potential transgenerational influence.<sup>35</sup>

### APPLICATION OF NUTRITIONAL GENOMICS TO DIETETICS PRACTICE

The practical application of nutritional genomics on a personalized level requires knowledge of an individual's potential susceptibility to disease. This information may be obtained in several different ways. Family history; biochemical parameters; the presence of risk factors for disease such as obesity, hypertension, or hyperlipidemia; and results from genetic testing may provide useful information about an

individual's risk of developing disease or maintaining health.

### Family History

Family history is an important screening tool to determine risk of inherited diseases. Family history provides information on the genes, behaviors, and environmental exposures that relatives share in common. However, a state-of-the-science conference convened by the National Institutes of Health found that the usefulness of family history in assessing the risk and targeting interventions for chronic disease is limited.<sup>45</sup> A complete family history can take 15 to 20 minutes to record, and its accuracy is influenced by factors such as patient uncertainties regarding the details of their relatives' health or a poor understanding of the medical terms. Generally, health care practitioners are not obtaining family histories and, if they are, the family history is not being done thoroughly.<sup>46</sup>

The utility of the family history is still relevant. In the case of type 2 diabetes mellitus, in which more than 40 loci have been associated with the disease, a positive family history of diabetes predicts risk and genetic variation.<sup>46</sup> People with a family history of colorectal cancer are at increased risk of developing this disease.<sup>47</sup> Family history also may help guide decisions regarding the use of genetic testing in at-risk individuals. For example, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommends that all individuals with a new diagnosis of colorectal cancer be offered genetic testing for hereditary nonpolyposis colorectal cancer or Lynch syndrome, to help prevent cancer in their close relatives.<sup>48</sup> For CVD, traditional risk factors, such as lipid levels, blood pressure, and the use of family history, are beneficial for assessing disease risk. However, for persons with CVD, there is insufficient evidence to recommend genomic profiling testing because the health benefit from the testing is negligible.<sup>49</sup>

### Genetic Testing

During the past decade, the availability of genetic tests has increased markedly. Historically, genetic tests were used within a traditional medical setting to confirm a suspected diagnosis, screen

for heritable disorders in at-risk populations, and conduct population-wide newborn screening. Currently, there are about 2,000 genetic tests available for use in clinical settings,<sup>50</sup> most of which test for rare single-gene disorders. In single-gene disorders, a defective gene may confer as high as 100% probability of the disorder, such as in Huntington's disease. In regard to breast cancer genes—*BRCA1* and *BRCA2*—there is a significant increase in probability of developing breast cancer associated with these genes. Testing for single-gene disorders occurs primarily within the traditional medical testing.<sup>51</sup>

Complex disorders, such as cancer, CVD, and diabetes, are caused by genetic and environmental factors and genetic mutations are only partially predictive of risk. Because of the large number of possible gene–environment interactions, the interplay among environment, genes, and disease is poorly understood.<sup>6</sup> Tests for some complex disorders are commercially available to the public primarily through direct-to-consumer (DTC) genetic testing companies. Unlike genetic tests for single-gene disorders, tests for complex disorders, which look for mutations in SNPs, are only predictive of an altered risk associated with disease development. Because not all SNP associations and other factors that contribute to the development of a particular disease are known, the absolute risks from SNP association tests are low and they are not of significant utility to alter the standard of care at this time.<sup>51</sup>

The need to define the validity and usefulness of genetic tests offered in medical settings and directly to consumers in predicting disease and to determine whether identifying mutations improve patient outcomes prompted the Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics to develop the ACCE model. The ACCE model defines analytical validity, clinical validity, and clinical utility and ethical considerations of genetic tests as follows:

- Analytic validity refers to how accurately and reliably the test detects whether a specific genetic variant is present or absent. For example, a test that might be used in the diagnosis of



familial hypercholesterolemia (FH) would accurately and consistently determine the presence of mutations in the *LDLR*, *APOB*, or *PCSK9* genes.<sup>52</sup>

- Clinical validity refers to whether the test accurately detects or predicts the presence of a disorder or disease. Using the FH example, if specific mutations are present in the *LDLR*, *APOB*, or *PCSK9* genes, the test would confirm a diagnosis of FH.
- Clinical utility refers to how likely it is that the test will improve patient outcomes. In the FH example, the test results allow for meaningful clinical decision making for the individual.
- Ethical, legal, and social implications that may be associated with use of the test.

The CDC categorized genetic tests and their application in practice by level of evidence.<sup>53</sup> This categorization assists clinicians in the application of genomic tests.<sup>49</sup> Currently, the CDC Office of Public Health Genomics provides evidence-based recommendations for the following genomic tests that can be recommended for clinical use, having achieved analytic validity, clinical validity, and clinical utility:

- newborn screening panel of 31 core conditions for all newborns;
- *BRCA1/2* analysis for women with specific history of breast or ovarian cancer;
- Lynch syndrome screening;
- FH among relatives of persons with FH;
- human leukocyte antigen testing for abacavir sensitivity for patients with human immunodeficiency virus; and
- human epidermal growth factor receptor 2 mutation testing in breast cancer in patients with invasive breast cancer.

According to the CDC, the genomic applications that have demonstrated analytic and clinical validity but have insufficient evidence for clinical utility include:

- breast cancer gene expression profiles to estimate risk of recurrence and target therapy;
- family history for common diseases;

- pharmacogenomic testing to inform safety and effectiveness of medications; and
- single-gene disorders and chromosomal abnormalities for diagnosis, management, and carrier testing for these disorders.

The CDC determined the following genomic applications are not ready for routine practice because they lack analytic validity, clinical validity, and clinical utility:

- genetic risk factors for common diseases;
- >400 emerging genomic tests for various intended uses; and
- next-generation sequencing/whole genome sequencing to assess risk for common diseases.

Genetic tests are added or re-categorized as their status changes, depending on the outcome of several evidence-based evaluation mechanisms, including from the Evaluation of Genomic Applications in Practice and Prevention Working Group and the US Preventive Services Taskforce<sup>54</sup>; the CDC website is periodically updated.

### Regulation and Oversight of Genetic Tests

Multiple federal and state governmental entities share responsibility for the oversight of genetic tests. A comprehensive review is available in *US System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*.<sup>55</sup>

There are two categories of genetic tests used in clinical practice. In vitro diagnostic tests are manufactured to be distributed to multiple laboratories. Laboratory-developed tests are solely used in the test developer's laboratory. New technologies and testing platforms, such as gene panels and whole-genome tests that analyze many variants and DTC genomic testing, are challenging conventional regulatory paradigms. DTC genetic tests are considered laboratory-developed tests but their classification is unclear because they often use a gene chip, a tool that identifies variations in genes, bought from a third party.<sup>56</sup>

### DTC Genetic Testing and Nutrigenetic Testing

DTC genetic testing refers to genetic tests that are marketed directly to

consumers; DTC genetic testing has become increasingly available online during the past 10 years due to declining costs, improved testing technologies,<sup>57</sup> and lack of regulation.<sup>58</sup> Typically, a customer sends a DNA sample, such as a cheek swab, through the mail and results are returned by mail, over the telephone, or posted online.<sup>59</sup> A health care provider is typically not involved in either ordering the test or interpreting the results,<sup>60</sup> although some DTC genetic testing companies do provide access to a health care practitioner.

Currently available DTC genetic tests include >100 disease susceptibility markers, a number of traits (eg, eye color), carrier and diagnostic testing, drug response, and ancestry and kinship testing.<sup>51</sup> Despite claims by DTC testing companies that the information provided allows consumers to make more informed health care decisions, the health value of this testing remains questionable.<sup>57</sup> Moreover, the results that are returned to consumers is an interpretation of risk, and the accuracy of the interpretation is dependent on many factors, including the particular panel of risk SNPs used by the company and the other environmental factors that contribute to the risk of developing disease.<sup>61</sup>

DTC nutrigenetic testing companies that offer tailored diets and advice regarding the use of dietary supplements based on SNP analysis proliferated during the early 2000s. The concern about the lack of regulation of DTC nutrigenetic tests was brought to wide attention during 2006 with the publication of a US Government Accountability Office report<sup>62</sup> that found selected tests misled consumers and provided nutrition advice based primarily on medical and family history. The Federal Trade Commission notified several companies that their advertising claims mislead consumers because their tests had not demonstrated clinical validity or utility. Most of these companies went out of business or changed their business model.<sup>63</sup> Other DTC companies market their tests as lifestyle behavior approaches rather than disease diagnosis<sup>59</sup> and have been able to avoid the regulatory red flags of selling medical devices. Regulatory agencies, such as the Federal Trade Commission and the Food and Drug Administration,

Agency	Genetic testing activities	Comments	Website
Food and Drug Administration (FDA)	<ul style="list-style-type: none"> <li>Regulates genetic tests as medical devices if they provide medical information used to diagnose, treat, or prevent disease<sup>61</sup></li> <li>Regulates IVD<sup>a</sup> genetic tests that are made by one company then sold as a kit to a laboratory</li> <li>Regulates genetic tests based on risk/degree of harm of inaccurate test results, not dependent on type of test or who makes the test</li> <li>FDA has authority over LDTs<sup>b</sup>, but has limited its regulation because historically LDTs were low-risk diagnostic tools interpreted by experts in test developer's laboratory</li> </ul>	<ul style="list-style-type: none"> <li>FDA has exercised its regulatory authority over IVDs and approved several tests for specific genetic factors</li> <li>LDTs have been increasingly used to assess high-risk common conditions often with minimal or no findings to support their clinical usefulness</li> </ul>	<a href="http://www.fda.gov/MedicalDevices/default.htm">www.fda.gov/MedicalDevices/default.htm</a> <a href="http://www.fda.gov/NewsEvents/Testimony/ucm219925.htm">www.fda.gov/NewsEvents/Testimony/ucm219925.htm</a>
Centers for Medicare & Medicaid Services (CMS)	<ul style="list-style-type: none"> <li>Regulates clinical laboratory testing in the United States through CLIA<sup>c</sup></li> <li>Ensures analytical validity of genetic tests</li> </ul>	<ul style="list-style-type: none"> <li>Does not address the clinical validity or utility of tests<sup>64</sup></li> </ul>	<a href="http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/">www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/</a>
Federal Trade Commission (FTC)	<ul style="list-style-type: none"> <li>Administers consumer protection laws, especially related to unfair or deceptive trade practices, such as misleading advertising claims</li> </ul>	<ul style="list-style-type: none"> <li>Relevant for DTC<sup>d</sup> genetic testing because companies market products directly to consumers rather than to physicians or health care companies</li> <li>FTC can enforce action to prohibit DTC companies' claims of clinical validity if there is inadequate scientific evidence for such claims</li> </ul>	<a href="http://www.consumer.ftc.gov/articles/0166-home-genetic-tests">www.consumer.ftc.gov/articles/0166-home-genetic-tests</a>
National Institutes of Health (NIH) Genetic Testing Registry (GTR)	<ul style="list-style-type: none"> <li>Central location for voluntary submission of genetic test information by CLIA-certified laboratories</li> </ul>	<ul style="list-style-type: none"> <li>Does not independently verify information submitted</li> <li>Does not endorse tests or laboratories listed</li> </ul>	<a href="http://www.ncbi.nlm.nih.gov/gtr/docs/code/">www.ncbi.nlm.nih.gov/gtr/docs/code/</a>

(continued on next page)

**Figure 4.** Regulation and oversight of genetic tests and personal genetic information.

Agency	Genetic testing activities	Comments	Website
	<ul style="list-style-type: none"> <li>Information included is the test's purpose, methodology, validity, evidence of test usefulness, and laboratory contacts and credentials</li> </ul>	<ul style="list-style-type: none"> <li>Submitters must abide by Code of Conduct that forbids them to make claims that NIH approves or endorses tests or information submitted</li> </ul>	
Consumer Protection	Description	Comments	Website
Genetic Information Nondiscrimination Act of 2008 (GINA)	<ul style="list-style-type: none"> <li>Prohibits discrimination by health insurance companies and employers on the basis of genetic information</li> </ul>	<ul style="list-style-type: none"> <li>Genetic information is defined as information about an individual's genetic tests, genetic tests of family members, and manifestation of a disease or disorder in family members</li> <li>Does not cover life, disability, and long-term care insurance</li> </ul>	<a href="http://www.genome.gov/24519851">www.genome.gov/24519851</a>

<sup>a</sup>IVD=in vitro diagnostic.  
<sup>b</sup>LDT=laboratory-developed tests.  
<sup>c</sup>CLIA=Clinical Laboratory Improvement Amendment.  
<sup>d</sup>DTC=direct to consumers.

**Figure 4.** (continued) Regulation and oversight of genetic tests and personal genetic information.

monitor the industry (see Figure 4).<sup>61,64</sup> A recent Food and Drug Administration panel recommended that some DTC genetic tests sold online no longer be readily available to consumers and that pre-symptomatic, high predictor tests that are available for at-home use without a prescription should not be used without the involvement of a physician or genetic specialist.<sup>65</sup>

**Ethical, Legal, and Social Issues**

Ethical issues associated with nutritional genomics relate to research, genetic testing, and clinical practice. The same regulations that apply to using human subjects in research<sup>66</sup> apply to nutritional genomic research. Nutritional genomics research ethics challenges traditional human research ethics because genetic information is often generated through large-scale population studies.<sup>67</sup> The generation of genetic information raises issues of whether or not genetic data per se should be treated differently from

other health-related information and genetic exceptionalism. Genetic exceptionalism refers to information that identifies family relationships, can predict future health events, may be of interest to third parties such as insurers and employers, and can be recovered from stored biological specimens in the future.<sup>68</sup> There are protections in place arising from the Genetic Information Nondiscrimination Act of 2008, which prohibits discrimination by health insurance companies and employers on the basis of genetic information (see Figure 4). Ethical questions arise regarding the obligation of informing nutrigenomic study participants of results of genotypic tests in which the consequences of particular genotypes may be unknown.<sup>67</sup>

Whether or not registered dietitian nutritionists (RDNs) inform clients about genetic test results is an ethical issue and the course of action is not well defined. Although it has been suggested that RDNs inform clients of genetic test results that might include

unrelated or incidental findings,<sup>69</sup> informing clients about results that are not in their purview may have serious ramifications depending on the specific findings. Disclosure of the presence of a gene variant from SNP analysis to a relative may pose undue burden and should also be handled by geneticists or genetic counselors. In the case of genetic variants, it is difficult to predict disease risk in an individual; to extrapolate results to family members would be questionable. As an integral part of a team approach to patient care, an RDN may collaborate with a primary care physician and/or genetics professional in the interpretation of genetic testing results and development of a care plan. However, disclosure of genetic test results should be the responsibility of primary care physicians in conjunction with geneticists or genetics counselors. As genetic testing expands to genome sequencing and the potential to detect the presence of genetic mutations of unknown significance, recessive disease carrier status,

and genes that predict adult-onset conditions in children, interpretation and decisions regarding disclosure of results to clients and patients should be handled by genetics professionals.

### RDNs' Knowledge of Genetics and Nutritional Genomics

The application of nutritional genomics in clinical practice requires that health care professionals understand, interpret, and communicate complex test results in which the actual risk of developing a disease may or may not be known.<sup>70</sup> Yet most health care providers are not trained in clinical genetics and molecular testing and have limited ability to discuss probability and risk.<sup>70</sup>

For more than a decade, surveys of RDNs in the United States, Canada, and the United Kingdom have found low knowledge of nutritional genomics and poor confidence in incorporating this science into practice.<sup>71-74</sup> Genetics course content is required in undergraduate dietetics programs and internships; however, stand-alone genetics courses are not required and the degree of proficiency in genetic knowledge has not been delineated. As would be expected, those who had exposure to genetics through university education and continuing professional education reported greater knowledge about the relationship between genetics and diet.<sup>74</sup> A plan to introduce nutritional genomics education in undergraduate dietetics curricula has been reported.<sup>75</sup>

### The Future of Nutritional Genomics

Models being developed for personalized medicine may be applicable to nutritional genomics in the future. A recently described model, the Integrative Personal Omics Profile, combines genomic data with transcriptomic, proteomic, and metabolomic profiles and other biochemical data to understand healthy states and monitor the onset and progression of disease states.<sup>76</sup> In a case that used this integrative model, Chen and colleagues<sup>76</sup> sequenced the genome of a normal weight, healthy man and discovered risk alleles for type 2 diabetes. During a 14-month period, blood tests were drawn every 2 months and the man was monitored. Based on increasing

blood glucose and glycosylated hemoglobin levels, the man was diagnosed with type 2 diabetes triggered by a viral infection. The implementation of dietary changes and increased exercise normalized this man's biochemical parameters without the use of medications. Although this was a single subject, the case highlights several important aspects of the application of nutritional genomics to dietary practice. The use of multiple technologies combined in ways that identify medical risk and monitor physiologic states is a model that will link associated disease risk alleles with the development of actual disease or maintenance of health. This model provides an opportunity to positively change outcomes and influence standards of care. In addition, RDNs as integral members of health care teams will have the advantage of intervening early in chronic disease progression with the aim of prevention.

The 2012-2022 Dietetics Workforce Supply and Demand Future Scan identified the evolution of personalized nutrition as a "change driver."<sup>77</sup> Whereas "new personal health testing and monitoring technologies will create opportunities for dietetics practitioners," specialized knowledge and/or experience will be required.<sup>77</sup> According to the scan, RDNs with expertise in managing genetic metabolic disorders through nutrition intervention and counseling will lead the way.<sup>77</sup> Standards of Professional Practice for genetic metabolic dietitians were published in 2008<sup>78</sup> and their role as advanced practitioners in genetics and nutritional genomics has been characterized.<sup>79</sup> Although these RDNs have focused their clinical and academic expertise primarily on single-gene disorders, they are well trained for complex, multifactorial disorders. RDNs in integrative and functional medicine have developed standards of practice that include the use of genetics and genomics in clinical care.<sup>80</sup> RDN researchers, academicians, and clinical practitioners with expertise in systems biology, outcomes research, and those with academic coursework in genetics and genomics are needed to move the discipline of nutritional genomics forward in the future.

Food consumption is driven by culture, economics, availability, and knowledge. Some people eat for pleasure, some eat what is available, others

eat with concern for specific health effects, and many fall somewhere between those. Current public health messages provide important nutrition guidance for the general population. Nutritional genomics may help RDNs bridge the gap from overarching public health messages to more individualized dietary guidance. 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. The knowledge gained from nutritional genomics requires an evidence-based approach to validate that personalized recommendations result in health benefits to individuals<sup>34</sup> and do not cause harm.<sup>79</sup> Whether or not the knowledge gained from nutritional genomics can be integrated into the everyday lives of consumers is yet unknown.<sup>81</sup>

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