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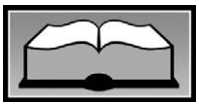

Continuing Education Questionnaire, page 666
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Nutritional Genomics in Practice: Where Do We Begin?

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Editor's note: This is the first in a series of articles on nutritional genomics. The series will appear periodically in the Journal, *and is designed to address the educational, professional, and practical needs of the dietetics professional in this rapidly changing arena. Dr DeBusk, an author of the below article, has graciously volunteered to serve as the Coordinating Editor for this series.*

ABSTRACT
Nutritional genomics, which studies the genome-wide influences of nutrition, has far-reaching potential in the prevention of diet-related disease. It is highly likely that during the next decade the nutritional supplement and functional food industries will continue robust growth in response to advances in nutritional genomics research and its applications. Parallel to this growth will be impressive progress in understanding the specific influence of certain food components on metabolic pathways and on long-term risk for disease. As genetic information about individuals becomes available, such data are likely to redefine the current concept of preventive medicine. Dietetics professionals have the potential to harness this information and influence health promotion and disease prevention on a global scale. For these reasons, the dietetics profession has an exciting opportunity that, if seized and properly executed, could enhance the scientific foundation of clinical practice, improve therapeutic outcomes, and significantly expand career and economic opportunities for practitioners. The future of dietetics is unquestionably intertwined with nutritional genomics.
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Consider the following scenario: A husband in his early 50s and a wife in her early 60s, both with strong family histories of early death from heart disease, have come to a nutritional genomics practitioner to obtain a nutrition and lifestyle prescription that will minimize their risk for developing heart disease. The nutritional genomics practitioner scans their electronic genome cards for their genetic profiles with respect to lifestyle-related genes. From this information, the practitioner provides each person with a perspective on the intersection of his or her diet and lifestyle with his or her genes and develops appropriate, targeted recommendations.

During the session, the practitioner learns additional key information. The husband's father died at age 55 years from an acute myocardial infarction. The wife has had difficulty controlling her significantly elevated low-density lipoprotein (LDL) cholesterol level with diet and exercise; several different statin drugs have been tried but with little effect. Nutrition and physical assessments reflect the couple's attention to a healthful lifestyle. Their diet histories reveal total fat intake ≤30% of total energy, polyunsaturated fatty acid (PUFA) intake is about 5% of total energy, monounsaturated fat intake is 17% of total energy, and saturated fat makes up approximately 7% of total energy.

Conventional nutrition wisdom suggests the couple's fat intake is appropriate. However, the wife's genome includes a polymorphism in the *APOA1* gene. This particular polymorphism typically results in a low high-density lipoprotein (HDL) level when PUFA intake is low (1). Therefore, the wife will need to increase her current intake of PUFAs to achieve HDL levels that are protective against heart disease. Her genome also contains a polymorphism in the hepatic lipase gene. This polymorphism is beneficial because it raises HDL levels when fat intake is less than 30% of total energy (2). Additionally, her 3-hydroxy-3-methyl-glutaryl-CoA reductase gene pro-

file includes a variant that may explain the lack of response of her blood lipids to the variety of statin drugs she has tried (3). Lifestyle changes may be her only option for controlling her atherogenic lipid profile.

The practitioner educates the wife about ways to keep PUFA intake relatively elevated while maintaining a diet low in animal fat and about the role of additional dietary/lifestyle choices in lowering LDL cholesterol and increasing HDL cholesterol levels. Other than these lipid-focused recommendations, the wife's diet and lifestyle approaches are health-promoting for her genotype.

The husband, on the other hand, has normal LDL and HDL cholesterol levels but a body mass index (BMI) that indicates he is overweight. His genome card reveals variations in the *IL1A*, *IL1B*, and *IL1RN* genes, which indicate a propensity for heart disease (4). Not surprisingly, his high-sensitivity C-reactive protein inflammatory biomarker levels are elevated (5). He may benefit from increasing his intake of anti-inflammatory PUFAs, specifically n-3 fatty acids. The practitioner suggests ways that the husband and wife can increase their intakes of n-3 fatty acids (6). She also recommends the husband try some of the newer functional foods in the market that can modulate his propensity for inflammation, such as green tea safflower wafers enriched with d-α-tocopherol (7,8). She also works with the husband to enhance his readiness to make lifestyle changes that will help control his inflammation, decrease his BMI, and promote longevity (9,10). Specific goals are reducing energy intake and participating with his wife in her regular aerobic/strength conditioning regimen.

The practitioner uses a holographic food guide education tool to demonstrate the proportional differences in fat intake recommended for this couple. Finally, she enters each person's genetic and nutrition data into a disease progression model that visually demonstrates their health-risk trajectories with and without the recommended dietary modifications. The couples' nutrition and lifestyle prescriptions are downloaded to their electronic notebooks, along with nutrition and physical activity software that makes it easy for them to record and analyze their progress. Finally, the husband and wife schedule Web-based follow-up visits with the practitioner and agree to transmit their data regularly so the practitioner can coach them as they integrate these lifestyle changes into their lives.

THE INTEGRATION OF GENETICS/GENOMICS INTO HEALTH CARE

Although considerable research and validation are needed before the above vignette becomes reality, it provides a provocative glimpse into the anticipated influence of genetic research on nutrition practice. With the completion of the initial phase of the Human Genome Project, the stage has been set for the integration of genetic science and technology into health care. Medical and pharmacologic applications to disease prevention and treatment are rapidly evolving. The pharmacologic applications have given rise to the field of pharmacogenomics. A similar integration of genetics into nutrition science and food science is in its infancy. This emerging field of nutritional genomics holds the promise of improving therapeutic outcomes for existing disease and, perhaps more importantly, for preventing disease.

For the foreseeable future, nutritional genomics research will focus on identifying gene–diet interactions, determining the underlying mechanisms, and validating the tools developed. Multiple well-designed studies are needed to build the foundation upon which gene-directed nutrition therapy will be based. As the field of nutritional genomics evolves and moves from the laboratory to the clinic, so will dietetics evolve to a new level of practice. The sum of the expected advances will enable individuals to make personalized dietary and other lifestyle choices. Dietetics professionals will be the health care professionals of choice to work with persons to maximize their genetic potential and minimize their risk of disease. Using carefully-chosen foods, specially-designed functional foods, and dietary supplements that each target pivotal points in the gene-based mechanisms underlying the person's health status, the dietetics professional will be able to customize dietary advice. Anticipated outcomes are improved treatment and prevention of chronic diseases and, ultimately, the ability to maximize one's genetic potential.

NUTRITIONAL GENOMICS, NUTRIGENETICS, AND NUTRIGENOMICS

Although the field is in its early stages of development and the terminology will likely continue to evolve (see the Glossary at the end of the article), the working definition of "nutritional genomics" encompasses both nutrigenetics and nutrigenomics (11). Genetics is the biological field that explores the mechanisms for inheriting specific traits and the differences in those traits that can be explained by variations in genes or in how genes combine. Genomics, in contrast, explores which genes and proteins in the body are activated under different conditions and the influence of environmental factors on gene expression. Studies in genomics generally employ various technologies to examine large numbers of nucleotide sequences, genes, and proteins. Nutrigenomics is concerned with the effects of bioactive dietary components on the genome, proteome (the sum total of all proteins), and metabolome (the sum of all metabolites), whereas nutrigenetics is concerned with how genetic variation affects the interaction between these bioactive dietary components and the health and disease potential of individual persons. In a nutshell, nutritional genomics is concerned with determining the nutritional components that are most compatible with health, which requires an understanding of how dietary substances interact with the genome and how that interaction influences observable clinical features. In practice, the convergence of the two sets of knowledge that comprise genomics and genetics will be needed to fully realize the promise of nutritional genomics.

The Center of Excellence for Nutritional Genomics at the University of California, Davis sets forth the following five tenets of nutritional genomics to serve as a conceptual basis for understanding the focus and promise of this emerging field (12):

- Under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases.

- Common dietary chemicals can act on the human genome, either directly or indirectly, to alter gene expression or structure.
- The degree to which diet influences the balance between healthy and disease states may depend on a person's genetic makeup.
- Some diet-modulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases.
- Dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype (ie, personalized nutrition) can be used to prevent, mitigate, or cure chronic disease.

The suspicion that diet was a risk factor in the development of chronic disease was first provided by epidemiologic studies. The differences among countries in disease prevalence and the incidence of disease among first- and second-generation immigrants resembling that of their new (rather than their original) homeland were strong clues that dietary choices were critical to the development of many chronic diseases. As causative dietary agents were identified, epidemiologic studies gave rise to prospective studies and the connection of diet to chronic disease grew stronger. It became clear that there was heterogeneity in the response to dietary regimens. Nutritional genomics research will determine the genetic basis for that heterogeneity, clarify the molecular basis by which specific genotypes respond to dietary components and other environmental signals, generate analytical tools for determining the genotype of a person, and provide targeted therapeutic interventions for disease amelioration and prevention.

Among the diet-related diseases that will benefit from nutritional genomics research and applications are the chronic disorders, such as cardiovascular disease (CVD), cancers, diabetes, neurological disorders, obesity, osteoporosis, and a variety of inflammatory disorders. These diseases represent disturbances in homeostasis. A person's genetic makeup sets the stage for homeostatic dysfunction, but it is the action upon that genotype that determines whether homeostasis is perturbed and to what extent. Among the most potent homeostasis-influencing agents are environmental signals such as bioactive dietary components, which include both nutrient and non-nutrient factors. These signals are detected by cellular sensor systems that, in turn, influence gene and protein expression and, thereby, metabolite expression and, ultimately, physiological function.

Nutritional genomics research will yield detailed molecular data on the nature and interaction of bioactive dietary components with the genome and the influence on homeostasis, from details of the signaling transduction processes by which these components communicate with the genome to the genes involved and the roles of their related proteins and metabolites. Extensive information is also anticipated concerning the biomarkers that serve as early warning signs of dietary-induced perturbations and that represent pivotal changes in the progression from health to disease. Clearly, diet–gene interactions are complex. Unlike the comparative simplicity of the single-gene disorders, chronic diseases are likely the composite result of multiple genes and multiple variants of each gene interacting with multiple environmental factors, each combination making a relatively small contribution to overall homeostasis, function, and health. The challenge is great, but the promise for improved global health is even greater.

NUTRIGENOMICS AND CARDIOVASCULAR BIOMARKERS

One of the more puzzling aspects of the studies that have explored the association between dietary factors and disease is the seemingly inconsistent data generated. Dietary factors that are strongly correlated with disease have different effects in different persons. For example, high dietary fat intake adversely influences the lipid profile in some individuals but not in others. Individuals with normal cholesterol levels may have elevated inflammation levels, thereby significantly increasing their risk for first heart attacks. The lack of a homogeneous, highly predictable response from study participants is the result of the genetic variation among these participants. Each is responding according to how dietary factors interact with his or her particular genotype in a logical, even predictable, response for that genotype. However, the total response of the study population is heterogeneous and reflects current limited understanding of the underlying genetic basis for the biochemical or physiological parameter being measured. As the underlying mechanisms emerge through nutritional genomics research, response to particular bioactive dietary components will become far more understandable and predictable.

Our introductory vignette illustrates the thought processes, tools, and interventions that are likely to be used in a nutritional genomics-based practice. CVD is the primary diet-related chronic disease of modern times, and inflammation is emerging as underlying many chronic disorders, including CVD. CVD claims more lives each year than the next five leading causes of death combined—cancer, chronic lower respiratory disease, accidents, diabetes mellitus, and influenza and pneumonia (13). In addition, the aging of the population will undoubtedly result in an increased incidence of chronic CVD, including coronary artery disease (CAD), peripheral vascular disease, heart failure, and stroke (14). CVD is now recognized as an inflammatory disorder, and understanding the role of inflammation in the development of atherosclerosis is a research priority (15-17).

CVD and inflammation provide useful examples for exploring the connection of genetics to nutrition and food. The new concept of atherosclerotic CVD is depicted in Figure 1, which shows atherosclerosis as resulting from the influence of both cholesterol and inflammation. Therapeutic approaches to the prevention of atherosclerosis continue to be directed at lowering total and LDL cholesterol but now also aim to reduce inflammation. Recent studies have shown that the statin class of drugs not only alters lipid profiles but also reduces inflammation, which has led some investigators to propose that the effectiveness of statins in decreasing cardiovascular events may be attributable to effects on both lipids and inflammation (3,17).

Like diabetes, obesity, and cancer, CVD has both genetic and environmental (diet) factors. Until now, nutrition professionals have focused on modifying the environmental risk factors related to CVD, particularly CAD,

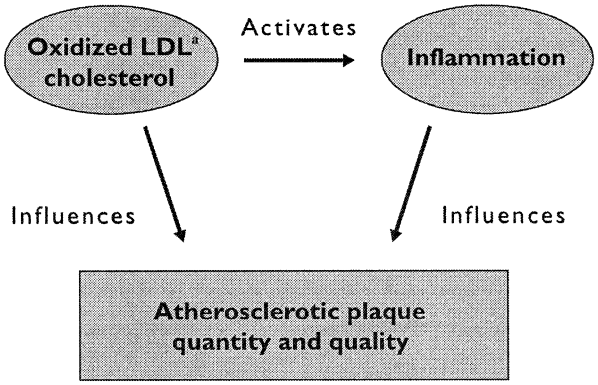

Figure 1. Cholesterol and inflammation both influence the nature of atherosclerosis. [a]LDL=low-density lipoprotein.

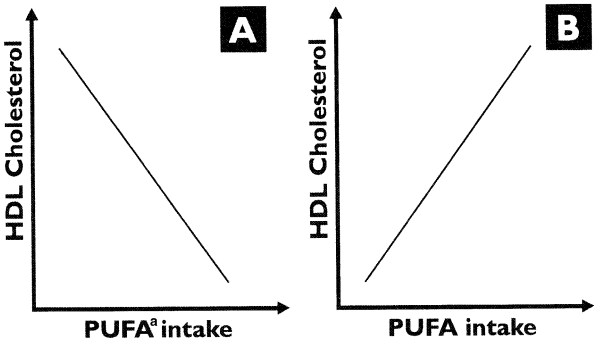

Figure 2. Effect of polyunsaturated fatty acid intake on high-density lipoprotein (HDL) cholesterol blood levels. Panel A depicts conventional wisdom as reflected in women with the –75 GG genotype at the *APOA1* gene (G allele frequency=0.835). Panel B illustrates a new understanding of gene–diet interaction, as reflected in women with the –75 G/A and A/A genotypes at the *APOA1* gene (A allele frequency=0.165). [a]PUFA=polyunsaturated fatty acid.

because there was virtually no information about the genetic predictors of heart disease risk in the general population. Therefore, most prevention and treatment interventions have focused on the role that dietary intervention plays in the reduction of known cardiovascular risk factors, such as low levels of HDL cholesterol and elevated LDL cholesterol levels. However, 2 decades of research, coupled with the sequencing of the human genome and the availability of public gene databases and state-of-the-art technologies, are leading to a new set of treatment and prevention paradigms. These strategies will eventually allow practitioners to develop dietary recommendations that are based on individualized genetic responses to dietary variables.

Conventional wisdom tells us that high HDL cholesterol and low LDL cholesterol levels are associated with a decreased risk of CAD. In general, HDL cholesterol increases with either physical activity or alcohol consumption and decreases with smoking or diets rich in PUFAs. Conventional wisdom also tells us diets rich in PUFAs can decrease LDL cholesterol levels. It is not prudent to suggest that the general population increase alcohol intake beyond current recommendations in order to raise HDL cholesterol levels, so the lifestyle approach of choice is to increase physical activity and PUFA intake. If all individuals had the same genetic makeup, conventional wisdom would suffice and dietary interventions could be designed in a generic manner.

From a genetic perspective, however, such an approach is neither efficacious nor scientifically sound. For example, the *APOA1* gene codes for the major protein in HDL cholesterol and plays a central role in lipid metabolism. A particular variant of this gene in which A (adenosine) is substituted for G (guanosine) at position –75 affects how the person responds to PUFAs (18). When researchers evaluated the effect of PUFA intake on HDL cholesterol levels in different populations, a significant sex difference was noted. Women with the GG allele had higher HDL cholesterol concentrations in response to low levels of PUFA (<4% of energy), whereas GA women had higher HDL cholesterol concentrations only when PUFA intake was >8% of total energy (Figure 2). These same genetic–dietary interactions were not significant in men (18). This type of knowledge is helpful in allowing clinicians to target their recommendations to those who will benefit from a diet rich in PUFAs and those who will not or may even be harmed by such a recommendation.

Other studies have shown that variations in genetic makeup can affect the way animal fat interacts with HDL cholesterol. The *LIPC* gene codes for the enzyme hepatic lipase, which plays a role in the binding and uptake of lipoproteins. Generally, HDL cholesterol concentrations decrease when hepatic lipase is overexpressed and increase when hepatic lipase is underexpressed. One variant allele of the *LIPC* gene, –514(C/T), is associated with increased HDL cholesterol concentrations. Individuals homozygous for this variant (ie, have the TT genotype with respect to this particular locus within the gene) tend to have higher HDL cholesterol levels than those with the normal genotype (ie, CC). However, when researchers analyzed data from the Framingham Study with respect to the effects of dietary fat on HDL cholesterol levels in persons with various forms of this gene, they found that HDL cholesterol concentrations were higher in TT subjects only when consuming <30% energy from fat. When total fat intake was ≥30% of energy, mean HDL cholesterol concentrations were lowest among those with the TT genotype, with no differences noted between CC and CT persons (2). This effect was seen only with animal fat, not with fats of vegetable origin. It is interesting to speculate that the deleterious effects of high-fat diets in TT subjects might be prevented by a diet that is higher in vegetable fats and plant foods, such as a Mediterranean-style diet. Information about one's genotype can be translated into food choices, in this case the types and amounts of dietary fat that will support the health of that person.

Framingham researchers have also analyzed the effects of alcohol and genetics on LDL cholesterol levels. Nondrinkers across several different *APOE* gene groups had LDL cholesterol levels that were not different across the groups. However, in male drinkers, two of the *APOE* variants were associated with highly significant differences between high and low levels of LDL cholesterol. The gene–alcohol interaction remained significant after controlling for age, BMI, smoking, and fat and energy

intake. This same effect was not evident in women (19). Again, having this type of genetic information will contribute to the development of more effective recommendations relative to alcohol consumption and prevention of CVD.

Another area of gene–dietary interaction and CVD relates to n-3 fatty acids. Early populations consumed diets rich in n-3s as compared to n-6s. Over time, however, the ratio of n-6s to n-3s in the diet of human beings has reversed, with Western diets now relatively deficient in n-3 fatty acids. As the ratio of n-6 to n-3 has increased, the rate of CVD has risen. Some research has shown that a high n-6 to n-3 ratio promotes the pathogenesis of CVD, cancer, and inflammatory and autoimmune diseases, including arthritis and asthma (20).

MODULATION OF GENE EXPRESSION BY BIOACTIVE DIETARY COMPONENTS

There are several ways in which bioactive dietary components can alter the action of specific genes and their variants. A primary mechanism for modulating gene expression involves transcription factors (TFs). Cells respond to their local environments by sensing extracellular molecules, such as oxidized-LDL cholesterol, through specific receptors on the cell surface. The binding of an extracellular molecule to its cell-surface receptor triggers the process of signal transduction, a cascade of biochemical reactions that ultimately produces a molecule that enters the nucleus, binds to specific sequences of the genome, and selectively switches on or off genes that guide the cell's response to its environment. The molecules that enter the nucleus and bind to specific DNA sequences are called TFs, and the specific DNA sequences they bind are appropriately called TF binding sites (or DNA elements). In some situations the extracellular molecule itself enters the nucleus and binds a receptor; the resultant complex serves as the TF. In other situations, the TF can bind one or more additional molecules to form the TF complex, which then binds to the DNA. The binding of the TF causes a conformational change in the DNA and promotes or inhibits transcription, as needed for the appropriate response to the environment.

Bioactive dietary components are examples of this latter situation where these components do not themselves serve as TFs but influence the ability of TFs to bind to their DNA elements. For example, vitamin A modifies expression of several genes through the retinoic acid receptor TF. PUFAs influence the ability of peroxisome proliferator activator receptor/retinoic acid receptor complexes to bind to their DNA elements. Flavonoids regulate various genes through three TFs: nuclear factor-kappaB, estrogen receptor, and activating protein-1. In each case, the bioactive dietary components influence gene expression and thereby alter genetic outcomes.

An example of the role of bioactive dietary components in transcriptional control of gene expression concerns the synthesis of inflammatory mediators. Inflammation appears to play a critical role in numerous chronic diseases in addition to CVD and has multiple implications for nutritional genomics. Inflammation is the first organized reaction to an injurious challenge to the body, such as a bacterial infection or oxidized-LDL cholesterol. It is a well-coordinated process that involves the migration of blood leukocytes to specific tissues and the activation of leukocytes to guide an explosive series of biochemical and cellular events. The genes for interleukin-1 (IL-1) are among the first to be activated when the body is exposed to a challenge. IL-1 is a pivotal molecule in that it activates the production of many other molecules critical to the inflammatory cascade, thereby strongly influencing the coordinated response characteristic of inflammation.

Human beings all have IL-1 genes but some have variations in those genes. Those variants that involve a change in a single nucleotide within the genetic material and occur frequently enough that >1% of the population has the change are called polymorphisms, specifically single nucleotide polymorphisms (SNPs), also called "snips." SNPs are similar to variations in a recipe. Each gene is a recipe for a specific protein or group of proteins that either regulate biological functions or serve as structural building blocks for tissues (eg, collagen). Some SNPs change the recipe for the gene so that either a different quantity of the protein is produced or the structure of the protein molecule is altered.

Some individuals consistently produce higher levels of inflammatory mediators than others, and certain IL-1 SNPs have been associated with interperson differences in the levels of IL-1 and other inflammatory mediators (21). Some of the IL-1 variants (alleles) that have been associated with increased levels of inflammatory mediators are also associated with increased severity of several chronic diseases, including Alzheimer's disease (22,23) and periodontal disease (24-26).

This proinflammatory IL-1 genotype pattern has recently been associated with cardiovascular acute coronary events. For example, despite having total cholesterol levels <5.2 mmol/L, certain individuals (white men under age 60 years) who were homozygous for a specific IL-1 SNP were four times ($P<.01$) more likely to have a first heart attack during an 11-year monitoring period than comparable individuals with the same level of cholesterol but who did not have this IL-1 genotype. Individuals with this IL-1 genotype also had significantly higher levels of inflammatory mediators than persons with other IL-1 genotypes (unpublished data, 2004, Interleukin Genetics, Inc, Waltham, MA). The mechanism assumed to explain the role of IL-1 genetic variations in CVD is depicted in Figure 3, which shows that, at a certain cholesterol level, person B has a higher inflammatory response than person A.

Recognition of the role of inflammation in heart disease and the evidence that some individuals with normal cholesterol but proinflammatory gene variations have an increased risk of cardiovascular events raises the potential of targeting one's diet to reduce inflammation. Some dietary components, such as n-3 fatty acids, α-tocopherol, and green tea (*Camellia sinensis*) constituents, are known to reduce IL-1 and other key inflammatory mediators (6-8). Further research is needed to evaluate the combined effect of such anti-inflammatory bioactive dietary components on individuals who have a genetic predisposition to lifelong inflammation. The ability to identify such individuals and to intervene effectively is one of the key promises of nutritional genomics.

Inflammation is emerging as a significant component of many chronic disorders in addition to CVD, such as obe-

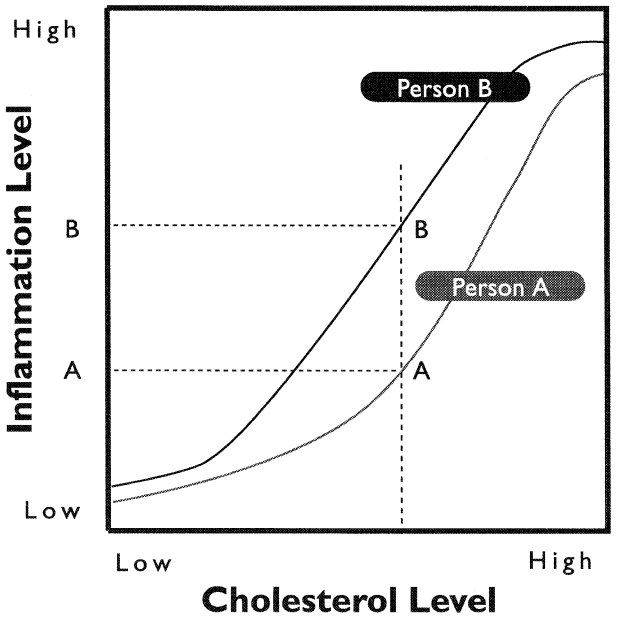

Figure 3. Comparison of inflammatory responses between two individuals with the same blood cholesterol levels.

sity, the metabolic syndrome, type 2 diabetes, osteoporosis, periodontal disease, rheumatoid arthritis, neurological degenerative disorders, and the inflammatory bowel disorders. The nutritional genomic approaches outlined here for CVD and inflammation are also being applied to these other complex, chronic disorders. Each complex interrelationship among environmental conditions, bioactive dietary components, diet-related genes, and the control of their expression can be dissected using genetic technologies. Well-designed and conducted laboratory and clinical studies will provide insight into the underlying mechanisms involved, the genes and the roles of their products, the details of molecular signaling and regulation of gene expression by specific dietary components, and the influence of variation in these genes on each of the key processes associated with these conditions. Ultimately, these efforts will provide practitioners with logical targets for interventional strategies. The complexity of these chronic disorders presents a formidable challenge to researchers in terms of unraveling the interrelationships among the various genes and environmental factors that lead to dysfunction. Nutritional genomics researchers will, however, be able to draw from decades of research in human biology, biochemistry, metabolism, and genetics and to benefit from the availability of sophisticated genetic technologies and bioinformatics. The potential is for nutritional genomics research to continue to progress steadily and to provide practitioners with the fundamentals needed for developing targeted, efficacious, therapeutic, and preventive approaches to diet-related disease.

OPPORTUNITIES FOR DIETETICS PROFESSIONALS

Clearly, nutritional genomics will fill a critical gap in developing evidence-based nutritional interventions. As research proceeds, today's generalized nutrition recommendations will give way to interventions that are targeted to the specific molecular mechanisms that underlie a health condition. This major change in how nutrition therapy is approached has the potential for expanding the role and contribution of dietetics professionals considerably and, thereby, the scope of practice. Among the primary opportunities for expansion will be those in research, education, and clinical practice. Research will encompass laboratory research that identifies bioactive dietary components that influence gene expression and examines the mechanisms by which they have their effects. Food scientists will be concerned with analyzing foods to identify the bioactive dietary components, as well as using this information to develop functional foods that target specific steps in disease prevention or intervention. Clinical trials will focus on using functional foods and dietary supplements to prevent disease or slow its progression. Consumer research relating to acceptance of the functional foods developed will be necessary. Nutritional genomics-related research will require dietetics professionals at a variety of education and skill levels, from laboratory technologists to clinical trial coordinators to principal investigators.

Research into both the nutrition and food aspects of nutritional genomics will need to be translated into practical applications to help consumers maximize their health potential. Among the focus areas open to dietetics professionals is work with individuals who have what we now think of as traditional genetic disorders: chromosomal disorders and monogenic disorders that lead to the classical inborn errors of metabolism. To help individuals and their families understand a disorder and its management, a dietetics professional must understand the underlying genetic lesion and its biochemical and physiological consequences. This information will need to be translated into an action plan for managing the disease, which will require the integration of diet, exercise, and other lifestyle choices.

In addition to the opportunity to work with individuals with these relatively rare disorders is the opportunity to apply nutritional genomics to the amelioration, modulation, and prevention of chronic disease. These disorders are far more complex in etiology and involve interaction among multiple genes and multiple environmental factors. Dietetics professionals will need a thorough knowledge of the disorder at the genetic, biochemical, metabolic, and dietary manipulation levels in order to teach clients about their disorders, their risks, and their lifestyle options.

In addition to lifestyle counseling and coaching, dietetics professionals will need to develop foundational skills in genetic counseling to assist consumers in understanding diseases and the use of genetic testing for confirmation or predictive purposes. Realistically, given the limited number of certified genetic counselors available, other health care professionals will need to help educate consumers about the genetic basis of their disorders, the biochemical consequences, and the genetic testing options and procedures; and, upon receiving their test results, help them to understand the results and the implications of various lifestyle choices. Traditionally, genetic testing has been ordered by a physician who is a clinical geneticist, and physicians and genetic counselors have filled

Books

- DeBusk RM. *Genetics: The Nutrition Connection.* Chicago, IL: American Dietetic Association; 2003.
- Moustaïd N, Berdanier CD. *Nutrient-Gene Interactions in Health and Disease.* Boca Raton, FL: CRC Press; 2001.
- Zempleni J, Hannelore D, eds. *Molecular Nutrition.* Wallingford, England: CABI Publishing; 2003.

Reviews of Nutritional Genomics

- Elliott R, Ong TJ. Nutritional genomics. *BMJ.* 2002;321:1438-1442.
- Fairweather-Tait SJ. Human nutrition and food research in the post-genomics era. *Philos Trans R Soc London B Biol Sci.* 2003;358: 1709-1727.
- German JB, Roberts MA, Watkins SM. Personal metabolomics as a next generation nutritional assessment. *J Nutr.* 2003;133:4260-4266.
- German JB, Roberts MA, Watkins SM. Genomics and metabolomics as markers for the interaction of diet and health: Lessons from lipids. *J Nutr.* 2003;133(suppl 6):S2078-S2083.
- Guengerich FP. Functional genomics and proteomics applied to the study of nutritional metabolism. *Nutr Rev.* 2001;59:268.

Nutritional Genomics Articles

- Nutritional genomics and proteomics in cancer prevention. *J Nutr.* 2003;133(suppl 7):S2399-S2504.
- Nutrigenomics—Special issue. *Nutrition.* 2004;20:1-172.
- Kaput J, Rodriguez RL. Nutritional genomics: The next frontier in the postgenomic era. *Physiol Genomics.* 2004;16:166-177.
- Kornman KS, Martha PM, Duff GW. Genetic variations and inflammation: A practical nutrigenomics opportunity. *Nutrition.* 2004;20:44-49.
- Masson LF, McNeill G, Avenell A. Genetic variation and the lipid response to dietary intervention: A systematic review. *Am J Clin Nutr.* 2003;77:1098-1111.
- Milner JA. Incorporating basic nutrition science into health interventions for cancer prevention. *J Nutr.* 2003;133(suppl 11):S3820-S3826.
- Müller M, Kersten S. Nutrigenomics: Goals and strategies. *Nature Rev.* 2003;4:315-322.
- *New England Journal of Medicine* series on genomic medicine. Available at: http://www.nejm.org.
- Olson RE. Nutrition and genetics: An expanding frontier. *Am J Clin Nutr.* 2003;78:201-208.
- Ordovas JM, Mooser V. Nutrigenomics and nutrigenetics. *Curr Opin Lipidol.* 2004;15:101-108.
- Patterson RE, Eaton DL, Potter JD. The genetic revolution: Change and challenge for the dietetics profession. *J Am Diet Assoc.* 1999;99: 1412-1420.
- Simopoulos AP. Genetic variation and dietary response: Nutrigenetics/nutrigenomics. *Asia Pac J Clin Nutr.* 2002;11(suppl 6):S117-S128.
- Stover PJ. New paradigms for nutrient control of genome translation. *Nutr Rev.* 2003;61:427-431.
- Stover PJ. Nutritional genomics. *Physiol Genomics.* 2004;16:161-165.
- van Ommen B. Nutrigenomics: Exploiting systems biology in the nutrition and health arenas. *Nutrition.* 2004;20:4-8.

Web Sites

- National Human Genome Research Institute. Available at: http://www.genome.gov
- US Department of Energy Genome Programs. Available at: http://www.doegenomes.org
- Center of Excellence for Nutritional Genomics at the University of California, Davis. Available at: http://nutrigenomics.ucdavis.edu
- Centre for Human Nutrigenomics at Wageningen University, Wageningen, The Netherlands. Available at: http://www.nutrigenomics.nl

Figure 4. Resources for study in nutritional genomics.

patients' needs for interpretation and follow-up. With the breadth of nutrition and lifestyle modification knowledge that such testing will now encompass, dietetics professionals are positioned to play a primary role in meeting these needs. Direct-to-consumer tests have begun to appear in the marketplace, and consumers need knowledgeable health care professionals who can help them consider their options and translate the findings into health-promoting action plans. Practitioners will need to use critical-thinking skills to assist even the most sophisticated consumers in evaluating the testing options, interpreting the results, and developing appropriate comprehensive lifestyle plans. Dietetics practitioners may also consider partnering with these companies to ensure that credible testing programs enter the marketplace.

Nutrigenomics will also need to be taken into account in developing public health policy. The American Heart Association Dietary Guidelines (27) have already acknowledged the influence genetics will have on future policy decisions. Nutritional genomics research should result in better understanding of the optimal levels of nutrients required for health, the influence of particular polymorphisms on nutrient requirements, and the frequency of such polymorphisms within subpopulations. Subsequently, nutrition policy will target sizeable subpopulations affected by nutritionally modifiable genetic variations. Policy makers will need to contemplate the potential influence of communicating multiple nutrient intake reference categories to the public. The incorporation of nutritional genomics information into public policy is essential if we are to develop meaningful dietary guidelines.

PREPARATION OF DIETETICS PROFESSIONALS IN THE ERA OF NUTRITIONAL GENOMICS

Dietetics professionals of the future will need to have a solid foundation in a variety of scientific disciplines. The basic sciences should include biology (anatomy/physiology, cell biology, microbiology, exercise physiology), chemistry (general, organic, biochemistry, analytical), and physics. Added to this foundation will be genetics (basic transmission and molecular genetics, human genetics, population genetics);

nutrition science (metabolism, diet design and development, dietary supplements, nutritional genomics); food science; critical thinking; and research study design, execution, and analysis, including statistical analysis. Additionally, a social science base must be laid: counseling skills relating to diet, exercise, other lifestyle choices, and genetic counseling will be essential, with competency in psychology, bioethics, and public policymaking desirable. Many dietetics professionals specializing in the practice of nutritional genomics will also need to develop business skills, such as those needed for operating and strategically developing a profitable business (eg, accounting, finance, and legal aspects), marketing and selling, and managing personnel. The American Dietetic Association can share in this monumental task by considering ways to support the growth of the field and the evolution of skills needed for functioning in myriad practice venues.

Although it is unlikely such a breadth of expertise can be acquired during the undergraduate years alone, university educators should incorporate genetic concepts and an evidence-based approach to the scientific disciplines into their teachings wherever possible. Additionally, fostering a lifelong approach to learning is essential, particularly in a field that is constantly evolving. Students should be encouraged from the beginning of their academic tenure to assume responsibility for their career preparation and for developing independent study skills that will serve them well throughout their careers.

To assume the leadership roles envisioned for dietetics professionals within nutritional genomics, graduate-level study is required. Further, such study must be multidisciplinary. Research projects that foster collaboration with investigators in genetics-related fields outside dietetics should be encouraged. For those planning to develop lifestyle counseling practices that focus on nutritional genomics, an advanced practice credential that combines graduate study, a supervised practicum, and a certification exam is highly desirable. A list of suggested resources for further study is listed in Figure 4. A recent article by Skipper (28) compares the needs of emerging dietetics professionals to those of advanced registered nurse practitioners. Such an approach should be considered as the next step in preparing dietetics professionals to assume a more vital role within health care. The American Dietetic Association can play a key role in facilitating such an evolution of today's dietetics professionals.

CONCLUSION

The far-reaching potential for nutritional genomics is the prevention of diet-related disease. It is highly likely that during the next decade the nutritional supplement and functional food industries will experience robust growth in response to advances in nutritional genomics research and its applications. Parallel to this growth will be impressive progress in understanding the specific influence of certain food components on metabolic pathways and their role in health and disease. It will become increasingly less expensive to generate genetic information about individual persons, and such data are likely to redefine the current concept of preventive medicine. Dietetics professionals have the potential to harness this information and influence health promotion and disease prevention on a global scale. For these reasons, the dietetics profession has an exciting opportunity that, if seized and properly executed, could enhance the scientific foundation of clinical practice, increase the therapeutic value of interactions with clients, and substantially improve the economic status of practitioners. The future of dietetics is unquestionably intertwined with nutritional genomics.

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Glossary

Glossary of nutritional genomics terms[a] (29-31). © 2003 American Dietetic Association. Used with permission.

Allele	One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different alleles produce variation in inherited characteristics, such as hair color or blood type. In a person, one form of the allele (the dominant one) may be expressed more than another form (the recessive one).
Cytokine	A protein or peptide that is outside the cell and serves as a communication signal to cells. Examples are interleukins, interferons, and tumor necrosis factors that facilitate the inflammatory response.
DNA sequencing	The process by which the exact order of the base pairs in a segment of DNA is determined.
Gene	A segment of DNA that contains the information necessary to make a protein.
Gene expression	The process of converting the information encoded in the DNA into RNA (mRNA, tRNA, and rRNA); most genes are transcribed into mRNA and, ultimately, into a protein product.
Genetic counseling	A short-term educational counseling process for persons and families who have an inherited disease or who are at risk for such a disease. Genetic counseling provides persons with information about their condition and helps them make informed decisions.
Genetics	The study of inheritance patterns of specific traits.
Genome	The sum total of all the genetic information in an organism; its instruction book—the blueprint that directs the development and functioning of human beings and other organisms.
Genomics	The study of genes and their function.
Genotype	The genetic makeup of a person, as opposed to the phenotype, which is the physiological manifestation of the genotype and its expression.
Heterozygote/heterozygous	Possessing two different forms of a particular gene, one inherited from each parent; a heterozygous person is also called a carrier.

Glossary

Glossary of nutritional genomics terms[a] (29-31) (continued)

3-Hydroxy-3-Methyl-Glutaryl-CoA (HMG-CoA) reductase	Key enzyme in the synthesis of cholesterol and a target of the statin class of cholesterol-lowering drugs.
Homozygote/homozygous	Possessing two identical forms of a particular gene, one inherited from each parent.
Human Genome Project	An international research project to map each human gene and to completely sequence human DNA; the goals of the project have expanded over time to sequencing the genomes of other organisms and to identifying the products of human genes and their functions.
Locus/loci	The actual physical position of a gene or marker on a chromosome, a kind of address for the gene.
Metabolome/metabolomics	The metabolome is the sum total of all the metabolites in an organism; metabolomics is concerned with the identification of each metabolic pathway, its metabolic products, and their role in the organism's function.
Monogenic	A characteristic only influenced by information from a single gene.
Multifactorial	A pattern of inherited characteristics, such as physical traits or diseases, that results from the interaction of genes and the environment.
Multigenic	A characteristic resulting from information contained in more than one gene.
Nutrigenetics	The study of the mechanisms by which bioactive dietary components communicate with the genetic material and how genetic variation affects the interaction between these bioactive dietary components and the health and disease potential of a person.
Nutrigenomics	Concerned with the effects of bioactive dietary components on the genome, proteome (the sum total of all proteins), and metabolome (the sum of all metabolites) at a global, population level.
Nutritional genomics	The study of how dietary and other lifestyle choices influence the function of living beings at the molecular, cellular, organismal, and population levels; includes nutrigenetics and nutrigenomics.
Phenotype	The observable traits of characteristics of an organism, such as hair color or weight, or the presence or absence of a disease. Phenotypic traits are not necessarily genetic.
Polygenic	Characteristic resulting from the combined action of alleles of more than one gene (eg, heart disease, diabetes, and some cancers). Such characteristics are inherited but they depend on the simultaneous presence of several alleles, which typically results in hereditary patterns that are more complex than those of single gene traits.
Polymorphism	A common variation among persons in the sequence of DNA; technically a locus is polymorphic when two or more of the alleles at this locus are present in $>1\%$ of the population.
Proteome/proteomics	A proteome is the sum total of all proteins coded for in an organism's genetic material; proteomics is the study of the full set of proteins encoded by a genome, their identity, and function.
Signal transduction	Process by which chemical or physical messages are communicated between the surface of a cell and its interior in a step-wise manner that results in a response by the cell.
Single gene disorder	An inherited condition caused by a mutant allele at a single locus in the DNA; such a trait is monogenic (eg, Duchenne muscular dystrophy and sickle cell disease).
Single nucleotide polymorphism (SNP)	A genetic variation caused by a change in a single DNA nucleotide; most of the variation among persons is due to SNPs; the number of different SNPs in the human population are thought to be in the millions. SNP is pronounced "snip."
Trait	A characteristic associated with a gene that can be quantified or described, such as eye color, flower color, height, intelligence, or the presence of an enzyme.
Transcriptome/transcriptomics	A transcriptome is the sum total of all the transcribed messenger RNA in an organism; transcriptomics is the study of the full complement of activated genes, mRNAs, or transcripts in a particular tissue at a particular time.

[a]Reprinted from (29).

References

1. Ordovas J. Gene-diet interaction and plasma lipid responses to dietary intervention. *Biochem Soc Trans*. 2002;30:68-73.
2. Ordovas J, Corella D, Serkalem D. Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase gene promoter on high-density lipoprotein metabolism. *Circulation*. 2002;106:2315-2321.
3. Chasman DI, Posada D, Subrahmanyan L, Cook NR, Stanton VP, Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA*. 2004;291:2821-2827.
4. Offenbacher S, Beck JD, Pankow J, Chambless L, Bray M, Couper D, Martha PM, Huttner K, Rogus J, Duff GW. Association of coronary heart disease with interleukin 1 gene variants in the Atherosclerosis Risk in Communities Study. In: *Proceedings of The American College of Cardiology Annual Scientific Session*. Bethesda, MD: American College of Cardiology; 2004. Abstract No. 1028-166.
5. Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation*. 2003;107:363-369.
6. Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JW, Cannon JG, Rogers TS, Klempner MS, Weber PC, Schaefer EJ, Wolff SM, Dinarello CA. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med*. 1989;320:265-271.
7. Murray CA, Clements MP, Lynch MA. Interleukin-1 induces lipid peroxidation and membrane changes in rat hippocampus: An age-related study. *Gerontology*. 1999;45:136-142.

8. Varilek GW, Yang F, Lee EY, deVilliers WJ, Zhong J, Oz HS, Westberry KF, McClain CJ. Green tea polyphenol extract attenuates inflammation in interleukin-2-deficient mice, a model of autoimmunity. *J Nutr*. 2001;131:2034-2039.
9. Chung HY, Kim HJ, Kim JW, Yu BP. The inflammation hypothesis of aging: Molecular modulation by calorie restriction. *Ann N Y Acad Sci*. 2001;928:327-335.
10. Sarkin JA, Johnson SS, Prochaska JO, Prochaska JM. Applying the transtheoretical model to regular moderate exercise in an overweight population: Validation of a stages of change measure. *Prev Med*. 2001;33:462-469.
11. Ordovas JM, Mooser V. Nutrigenomics and nutrigenetics. *Curr Opin Lipidol*. 2004;15:101-108.
12. Center of Excellence for Nutritional Genomics at the University of California at Davis. Nutrigenomics. Available at: http://nutrigenomics.ucdavis.edu. Accessed June 29, 2004.
13. American Heart Association. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, TX: American Heart Association; 2003.
14. Bonow R, Smaha L, Smith S, Mensah G, Lenfant C. World Heart Day 2002: The international burden of cardiovascular disease: Responding to the emerging global epidemic. *Circulation*. 2002;106:1602-1605.
15. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115-126.
16. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868-874.
17. Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: From concept to clinical practice to clinical benefit. *Am Heart J*. 2004; 148:S19-S26.
18. Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, Coltell O, Wilson PW, Schaefer EJ, Tucker K. Polyunsaturated fatty acids modulate the effects of the APOA1 G-A polymorphism on HDL-cholesterol concentrations in a sex-specific manner: The Framingham Study. *Am J Clin Nutr*. 2002;75: 38-46.
19. Corella D, Tucker K, Lahoz C, Coltell O, Cupples LA, Wilson PW, Schaefer EJ, Ordovas JM. Alcohol drinking determines the effect of the APOE locus on LDL-cholesterol concentrations in men: The Framingham Offspring Study. *Am J Clin Nutr*. 2001;73:736-745.
20. Simopolous AP. The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed Pharmacother*. 2002;56:365-379.
21. Duff G. Chapter 7: The cytokine network. In: Balkwill F, ed. *Frontiers in Molecular Biology*. London, England: Oxford University Press; 2000:152-173.
22. Griffin WS, Nicoll JA, Grimaldi LM, Sheng JG, Mrak RE. The pervasiveness of interleukin-1 in Alzheimer pathogenesis: A role for specific polymorphisms in disease risk. *Exp Gerontol*. 2000;35:481-487.
23. Grimaldi LM, Casadei VM, Ferri C, Veglia F, Licastro F, Annoni G, Biunno I, DeBellis G, Sorbi S, Mariani C, Canal N, Griffin WS, Franceschi M. Association of early-onset Alzheimer's disease with an interleukin-1 alpha gene polymorphism. *Ann Neurol*. 2000;47:361-365.
24. Kornman KS, Crane A, Wang H-Y, di Giovine FS, Newman MG, Pirk FW, Wilson TG Jr, Higginbottom FL, Duff GW. The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontal*. 1997;24:72-77.
25. McGuire MK, Nunn ME. Prognosis versus actual outcome. IV. The effectiveness of clinical parameters and IL-1 genotype in accurately predicting prognoses and tooth survival. *J Periodontol*. 1999;70:49-56.
26. Meisel P, Siegemund A, Grimm R, Hermann FH, John U, Schwahn C, Kocher T. The interleukin-1 polymorphism, smoking, and the risk of periodontal disease in the population-based SHIP study. *J Dent Res*. 2003;82:189-193.
27. Krauss RM, Eckel RH, Howard B, Appel LJ, Daniels SR, Deckelbaum RJ, Erdman JW Jr, Kris-Etherton P, Goldberg IJ, Kotchen TA, Lichtenstein AH, Mitch WE, Mullis R, Robinson K, Wylie-Rosett J, St Jeor S, Suttie J, Tribble DL, Bazzarre TL. AHA Dietary Guidelines: Revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation*. 2000; 102:2284-2299.
28. Skipper A. The history and development of advanced practice nursing: Lessons for dietetics. *J Am Diet Assoc*. 2004;104:1007-1012.
29. DeBusk RM. *Genetics: The Nutrition Connection*. Chicago, IL: American Dietetic Association; 2003.
30. National Human Genome Research Institute of the National Institutes of Health. Talking glossary of genetic terms. Available at: http://www.genome.gov/10002096. Accessed January 13, 2005.
31. Oak Ridge National Laboratory, US Dept of Energy. The genome glossary. Available at: http://www.ornl.gov/sci/techresources/Human_Genome/glossary/glossary_a.shtml. Accessed January 13, 2005.