Nutrigenomics: The Rubicon of molecular nutrition

PETER J. GILLIES, PhD, FAHA

ABSTRACT

The success of the Human Genome Project and the powerful tools of molecular biology have ushered in a new era of medicine and nutrition. The pharmaceutical industry expects to leverage data from the Human Genome Project to develop new drugs based on the genetic constitution of the patient; likewise, the food industry has an opportunity to position food and nutritional bioactives to promote health and prevent disease based on the genetic constitution of the consumer. This new era of molecular nutrition—that is, nutrient-gene interaction—can unfold in dichotomous directions. One could focus on the effects of nutrients or food bioactives on the regulation of gene expression (ie, nutrigenomics) or on the impact of variations in gene structure on one's response to nutrients or food bioactives (ie, nutrigenetics). The challenge of the public health nutritionist will be to balance the needs of the community with those of the individual. In this regard, the excitement and promise of molecular nutrition should be tempered by the need to validate the scientific data emerging from the disciplines of nutrigenomics and nutrigenetics and the need to educate practitioners and communicate the value to consumers—and to do it all within a socially responsible bioethical framework. *J Am Diet Assoc. 2003; 103:S50-S55.*

Nutrition science is crossing the Rubicon of molecular nutrition—that is, the study of nutrient-gene interaction. In forging these waters, it moves a step closer to following the prescient advice of Hippocrates who offered that, "Positive health requires a knowledge of man's primary constitution and the powers of various foods, both those natural to them and those resulting from human skill."

As molecular nutrition unfolds and is reduced to practice by the food and agricultural industries, one can foresee an evolution of new trends and technologies as suggested in Figure 1. Of the many forces of change in nutrition science, there are three with unusually high-impact coefficients: (a) the success of the Human Genome Project, (b) open and unprecedented access to information about health and nutrition via the Internet, and (c) the emergence of empowered consumers. These forces intersect in the realm of personal nutrition and nutrigenomics. Notably, recent surveys forecast that 33% of US consumers may be collecting and acting upon nutrigenomic information by 2010 (1).

NUTRIGENOMICS AND NUTRIGENETICS: DEFINITIONS AND DISTINCTIONS

The term nutritional genomics, or nutrigenomics, appears to have its origins in the context of plant biology wherein it referred to work at the interface of plant biochemistry (specifi-

P. J. Gillies is an adjunct professor in the Department of Nutritional Sciences at the University of Toronto in Toronto, Canada, and director, Human Health Sciences, DuPont Nutrition & Health, Haskell Laboratory for Health and Environmental Sciences, Newark, DE.

Address correspondence to: Peter J. Gillies, PhD, FAHA, Dupont Nutrition & Health, Haskell Laboratory for Health and Environmental Sciences, 1090 Elkton Rd, Newark, DE 19714-0050. E-mail: peter.j.gillies@usa.dupont.com.

0002-8223/03/10312-2009$30.00/0

doi: 10.1016/j.jada.2003.09.037

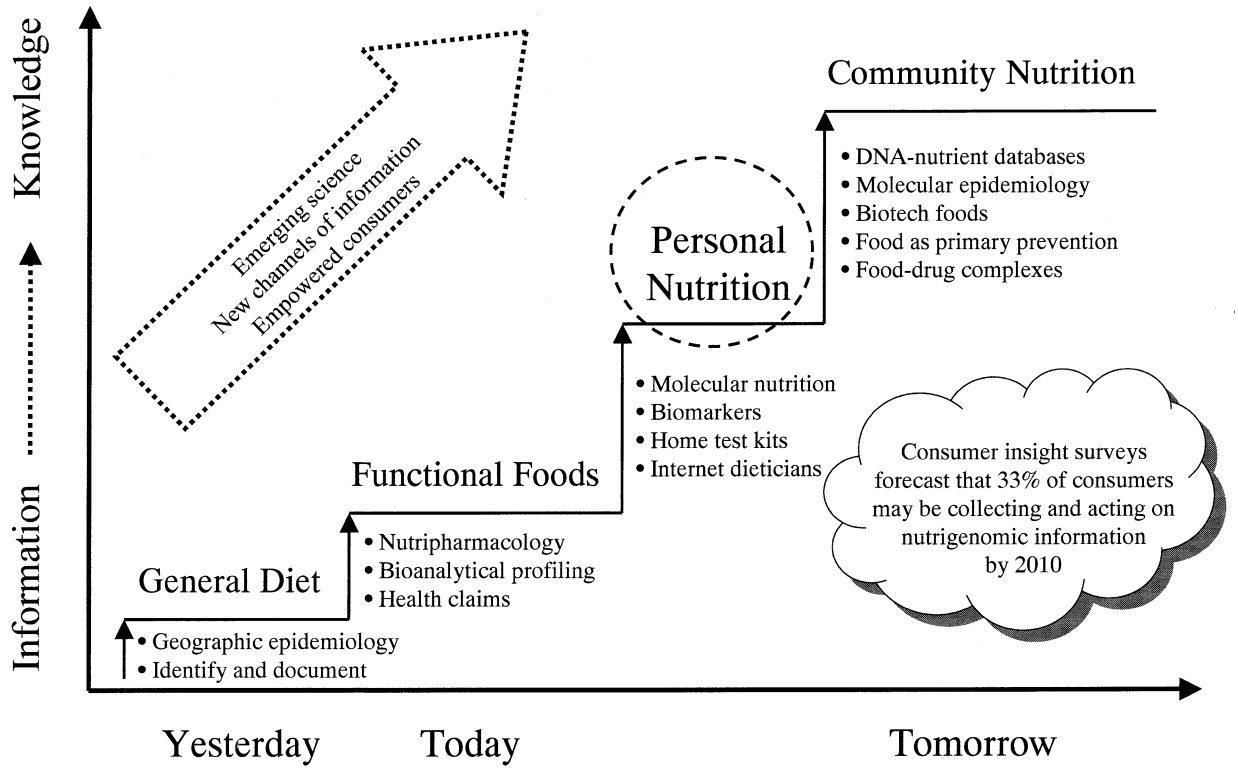

FIG 1. Trends and technologies in nutrition science.

cally, secondary metabolism), genomics, and human nutrition (2). More recently, and as used in this article, the term is used in the context of human biology in reference to the integration of functional genomics, nutrition, and health. A closely related term, nutrigenetics, is often used interchangeably with nutrigenomics even though the two terms have different etymological origins. By analogy to the field of pharmacogenomics (3), the following definitions and distinctions may be obtained for these terms. Nutrigenomics refers to the prospective analysis of differences among nutrients with regard to the regulation of gene expression. In this context, nutrigenomics is a discovery science driven by the paradigms of molecular biology, enabled by microarray technology, and integrated on an informatics platform (4,5). In contrast, nutrigenetics refers to the retrospective analysis of genetic variations among individuals with regard to their clinical response to specific nutrients. In this context, nutrigenetics is an applied science driven by the paradigms of nutritional pharmacology in the context of genetic polymorphisms and clinical experience. Although the directionality of these distinctions is a useful interim construct, the distinctions are likely to erode and the concepts coalesce as the databases of the human genome and nutriome merge into a unifying paradigm of molecular nutrition (Figure 2). The principles of nutrigenetics follow naturally from those of pharmacogenetics as illustrated in Figure 3.

Just as pharmacogenetics seeks to tailor drugs to the genetic constitution of the patient based on variations in the genes of xenobiotic metabolism coupled with genetic variations in the drug target, nutrigenetics offers the promise of personalizing nutrition to the genetic constitution of the consumer based on a knowledge of variations in the genes of nutrient metabolism and genetic variations in nutrient targets. Although both fields of endeavor are in their infancy, there are a number of new drugs and nutritional bioactives that validate the principles presented in Figure 3 and offer glimpses of opportunities to come. For example, Gleevec (Novartis, Basel, Switzerland) and Herceptin (Genentech, San Francisco, CA) are drugs prescribed for the treatment chronic myeloid leukemia and breast cancer, respectively, based on the underlying pathogenetics of the disease (6). Similarly, phenylalanine-restricted tyrosine-supplemented diets and galactose-free diets are prescribed for the nutritional treatment of type 1 phenylketonuria and galactosemia (galactose 1-phosphate uridyltransferase deficiency), respectively, based on routine genetic tests (7,8). Not all genes that are important to clinical outcome variables are directly involved in the pathogenesis of the disease or nutritional benefit. For example, polymorphisms in apolipoprotein E modify the clinical effectiveness of Cognex (9) and the potential dietary benefits of vitamin E in Alzheimer disease (10). The apolipoprotein E example is instructive as it highlights the importance of polymorphisms in genes and underscores the value of developing an ongoing dialogue between the fields of pharmacogenetics and nutrigenetics.

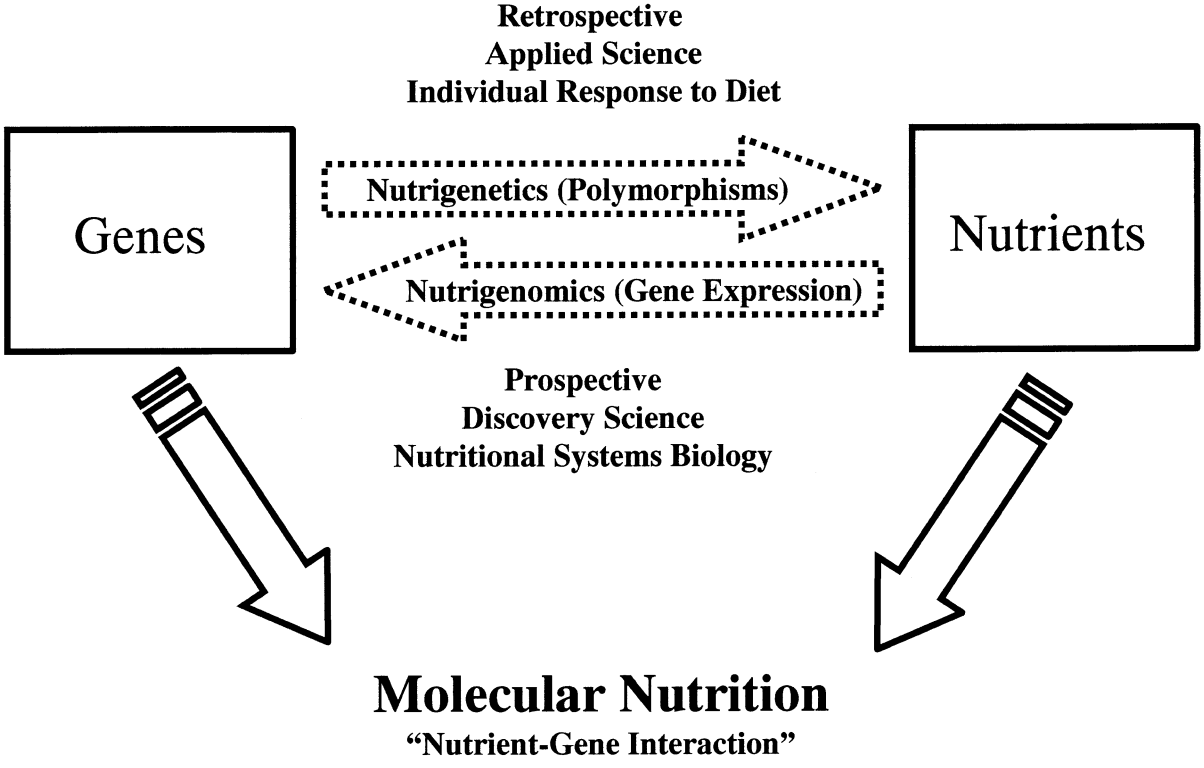

FIG 2. Molecular nutrition.

THE IMPORTANCE OF SINGLE NUCLEOTIDE POLYMORPHISMS

In a simple classification of nutritionally modifiable genes as being either constitutive or inducible, it is the second-order classification of these same genes as being either wild type or polymorphic that underlies the highly variable response of humans to a given diet (Figure 4). The most common form of polymorphism is the single nucleotide polymorphism (SNP). Given that there is approximately 1 SNP per 1.91 kilobases of DNA sequence or 1 SNP per 1.08 kilobases of gene sequence (11), the critical issue is which ones matter? Herein some criteria may provide some guidance. In order for a SNP to be of practical significance in the nutrigenetic paradigm, the SNP is likely to present with a number of characteristics such as exhibiting a high frequency in the general population of interest, modifying or regulating proteins at the top of biological cascades or at rate-limiting steps in intermediary metabolism, and having attendant biomarkers that provide surrogate measures of clinical effect. At the present time, there are only a few SNPs that meet these criteria, but from those that do, we can learn a great deal. The biology of methylenetetrahydrofolate reductase (MTHFR) and interleukin 1 (IL-1) are instructive examples of the importance of coding and noncoding SNPs, respectively, as genetic levers for managing health (Figure 4).

A common biochemical effect of coding SNPs in enzymes is to increase the K_m for substrate or cofactors (12). This is illustrated in the case of a common polymorphism in the coding region of MTHFR wherein a 677C→T transition substitutes valine for alanine at position 222, resulting in an increased K_m for FAD with a subsequent reduction in enzyme activity (13). With respect to the aforementioned criteria, the TT polymorphism is relatively common, that is, 10% to 20% worldwide; MTHFR plays a central role in the regulation of folate and methionine metabolism; and serum homocysteine levels serve as a biomarker of clinical effect. Consistent with Michaelis-Menton kinetics, the decrease in K_m can be obviated by folate-rich diets or folic acid supplementation with commensurate decreases in homocysteinemia (14). Not all SNPs are coding entities, but they can be important just the same. For example, noncoding SNPs located in regulatory segments of DNA can have important quantitative effects on gene products. This is illustrated by the −31 "gain-of-function" polymorphism in the promoter region of IL-1β that pushes individuals into a proinflammatory state (15,16). The biology of IL-1 is subject to multiple levels of genetic complexity as it is part of a gene cluster that codes for two proinflammatory cytokines (IL-1α and IL-1β) plus an anti-inflammatory receptor-blocking protein (IL-1ra) (17). Consistent with the aforementioned criteria, IL-1 levels can be regulated at the level of transcription by long-chain n-3 polyunsaturated fatty acids and antioxidants (18,19), and C-reactive protein levels offer a biomarker of effect (20).

To understand our personal uniqueness with regard to nutrigenomic SNPs is to open the door to managing and optimizing our health through tailored nutrition. Clearly this is a lofty and distant goal; equally true is the fact that we have already started the journey toward it. The sign posts along the way include the ever-increasing number of scientific conferences convened on the topic of nutrigenomics, such as the Interna-

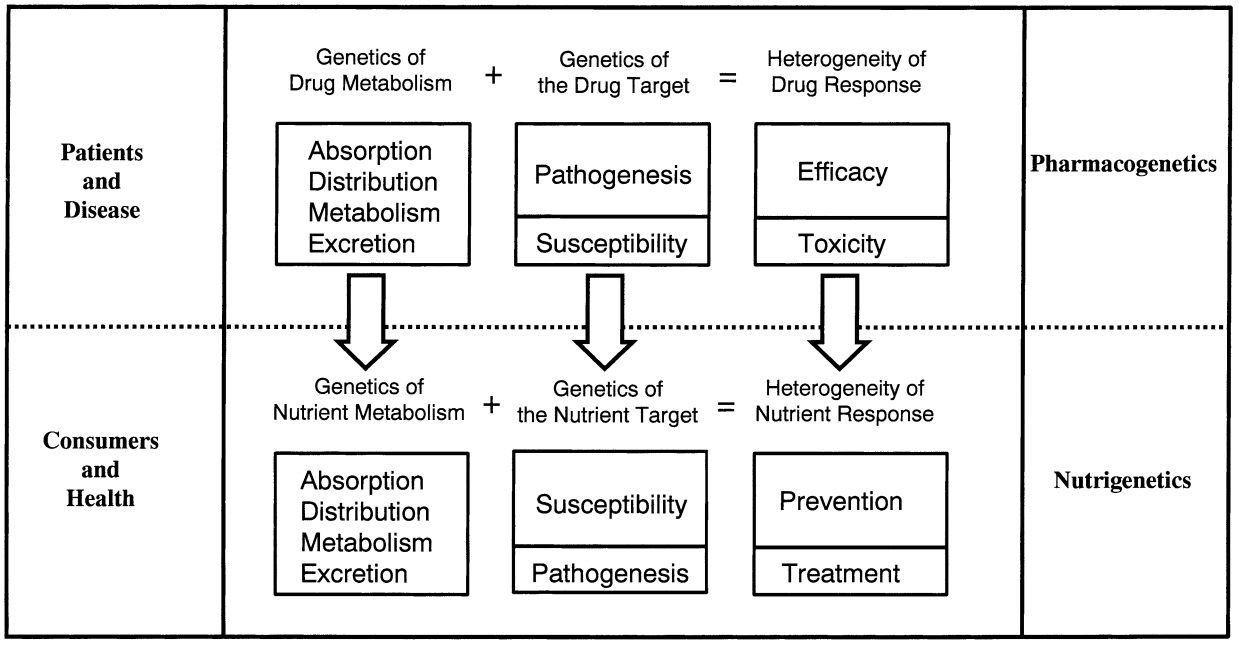

FIG 3. Pharmacogenetics to nutrigenetics.

Genes	Constitutive	Wild type	*MTHFR*
		SNPs[a]	*MTHFR* 677C→ T
	Inducible	Wild type	*IL-1*
		SNPs	*IL-1* –31T→ C

FIG 4. A simple nutrigenomic classification nutritionally modifiable genes. [a]SNP=single nucleotide polymorphism.

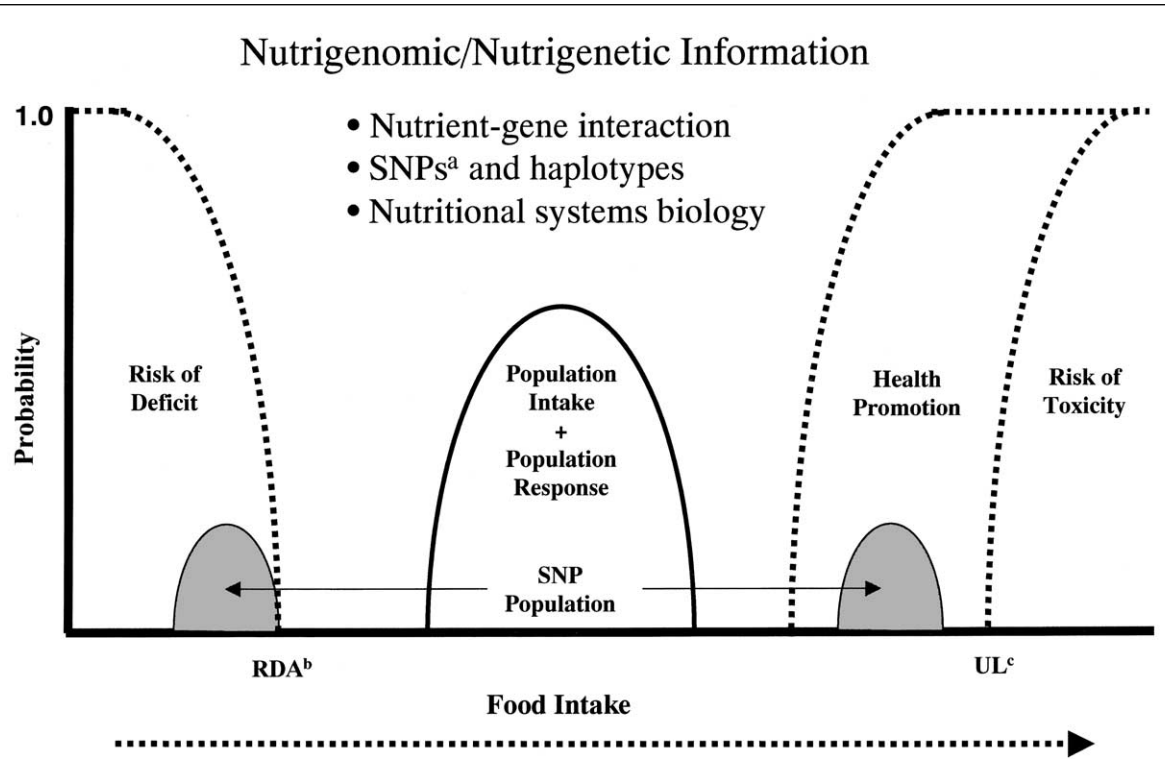

FIG 5. Integration of new genetic information into the development of food-based dietary guidelines. [a]SNP=single nucleotide polymorphism, [b]RDA=Recommended Dietary Allowance, [c]UL=Upper limits.

tional Nutrigenomic Conferences in the Netherlands (21) and the ILSI North America symposium on "Food, Genomics and Human Genetics" (22), the establishment of nutrigenomic research laboratories within academia (23) and government (24), and the funding of international research initiatives such Functional Foods Against Colorectal Cancer (25). Finally, and perhaps most importantly, nutrigenomics is reaching out of the scientific domain and into the consumer domain as evidenced by the formation of new businesses based on nutrigenomic counseling (26) and DNA data-banking (27).

EXPECTATIONS FOR THE FUTURE

Peter Medawar is credited with the comment that wise people may develop expectations about the future, but only the foolish make predictions (28); this is sage advice for molecular nutritionists. One of the expectations of nutrigenomics and nutrigenetics is that a wide range of nutrient modifiable genes and related SNPs will be identified, validated, and incorporated into dietary strategies for the optimization of health and the prevention of disease. This will introduce a massive set of new data and compound the biological complexity of developing food-based dietary guidelines (Figure 5).

Although the promotion of health and prevention of disease are long-standing goals of nutrition science, the powerful tools of molecular biology and computational power of informatics are dramatically accelerating progress toward these goals. This will raise challenging questions and issues as to who should be the "gatekeepers of genetic information" in the era of molecular nutrition. As always, it will be incumbent upon scientists and physicians to deliver and communicate sound science and medical advice. Herein the rigor of evidence-based medicine may have an important role to play in the timing and promulgation of nutrigenetic recommendations. Dietitians may have a special opportunity to redefine their role in the health care community. In this endeavor, dietitians could take on the role of "nutrigenetic counselors" with its attendant new training and responsibilities. Policymakers and regulators can expect to wrestle with the complex issue of subpopulations as the simplicity of "one-size-fits-all" erodes in the full light of nutrigenomic knowledge. Similarly, the food industry may expect to encounter challenging new business demands as mass-marketing moves toward mass-customization. Finally, should society move to adopt nutrigenetic practices, it may see a bioethical debate ensue over the impact of a growing "genomic divide" in personal and global health equity. In this regard, the development of nutrigenetic guidelines may be an activity whose time has come (29,30).

References

1. Massoud M, Ragozin H, Schmid G, Spalding L. Forecast: Nutrigenomics and consumers in 2010. The Future of nutrition: Consumers engage with science. Menlo Park, CA: Institute for the Future; 2001:87-100. Publication SR-731.
2. DellaPenna D. Nutritional genomics: Manipulating plant micronutrients to improve human health. *Science*. 1999;285:375-379.
3. Lindpaintner K. The role of pharmacogenomcs in drug discovery and therapy. Pharmacogenomics: The Search of Individualized Therapies. Weinheim, Germany: Wiley-VCH Verlag GmbH; 2002:127-142.
4. Elliott R, Ong TJ. Nutritional genomics. *BMJ*. 2002;324:1438-1442.

5. Ommen BV, Stierum R. Nutrigenomics: Exploiting systems biology in the nutrition and health arena. *Curr Opin Biotechnol*. 2002;13:517-521.
6. *Physicians Desk Reference* Electronic Library, Thomson, MICROMEDEX, January 2002.
7. Longo N. Inherited disorders of amino acid metabolism and storage. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine.* New York: McGraw-Hill; 2001: 2301-2306.
8. Chen YT. Glycogen storage diseases and other inherited disorders of carbohydrate metabolism. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine.* New York: McGraw-Hill; 2001:2288-2289.
9. Poirier J, Delisle MC, Quirion R, Aubert I, Farlow M, Lahiri D, Hui S, Bertrand P, Nalbantoglu J, Gilfix BM, Gauthier S. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. *Proc Natl Acad Sci USA.* 1995;92:12260-12264.
10. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Wilson RS, Scherr PA. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA*. 2002;287: 3230-3237.
11. Chakravarti A. Single nucleotide polymorphisms: To a future of genetic medicine. *Nature*. 2001;409:822-823.
12. Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K_m): Relevance to genetic disease and polymorphisms. *Am J Clin Nutr*. 2002;75:616-658.
13. Yamada K, Chen Z, Rozen R, Matthews RG. Effects of common polymorphisms on the properties of recombinant human methylenetetrahydrofolate reductase. *Proc Natl Acad Sci USA.* 2001;98:14853-14858.
14. Ashfield-Watt PAL, Pullin CH, Whiting JM, Clark ZE, Moat SJ, Newcombe RG, Burr ML, Lewis MJ, Powers HJ, McDowell IFW. Methylenetetrahydrofolate reductase 677C→T genotype modulates homocysteine responses to a folate-rich diet or a low-dose folic acid supplement: A randomized controlled trial. *Am J Clin Nutr*. 2002;76:180-186.
15. El-Omar EM, Carrington M, Chow WH, McColl KEL, Bream JH, Young HA, Herrera J, Lissowska J, Yuan CC, Rothman N, Lanyon G, Martin M, Fraumeni JF Jr, Rabkin CS. *Nature*. 2000;404:398-402.
16. El-Omar EM, Carrington M, Chow WH, McColl KEL, Bream JH, Young HA, Herrera J, Lissoswka J, Yuan CC, Rothman M, Lanyon G, Martin M, Fraumeni JF Jr, Rabkin CS. *Nature*. 2001;412:99-100.
17. Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood*. 1996;87: 2095-2147.
18. Mantzioris E, Cleland LG, Gibson RA, Neumann MA, Demasi M, James MJ. Biochemical effects of a diet containing foods enriched with n-3 fatty acids. *Am J Clin Nutr*. 2000;72:42-48.
19. Devaraj S, Jialal L. α-Tocopherol decreases interleukin-1 β release from activated human monocytes by inhibition of 5-lipoxygenase. *Arterioscler Thromb Vasc Biol*. 1999;19:1125-1133.
20. Madsen T, Skou HA, Hansen VE, Fog L, Christensen JH, Togt E, Schmidt EB. C-Reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease. *Am J Cardiol*. 2001;88:1139-1142.
21. International Nutrigenomic Conferences. Bastiaanse-Communications, The Netherlands. Available at: genomics@bastiaanse-communications.com.
22. ILSI North American annual meeting. Symposium: "Food, Genomics and Human Genetics" January 21, 2003, Miami, Florida.
23. National Center of Excellence in Nutritional Genomics established at the University of California, Davis, and the Children's Hospital Oakland Research Institute. The center is supported by a five-year grant of $6.5 million from the National Center on Minority Health and Health Disparities, a division of the National Institutes of Health. Available at: http://nutrigenomics.ucdavis.edu.
24. USDA/Tufts University, Dr. Jose Ordovas, Director of the Nutrigenomics Laboratory (personal communication).
25. Stierum R, Burgemeister R, Helvoort AV, Peijnenburg A, Schutze K, Seidelin M, Vang O, Ommen BV. Functional foods against colorectal cancer: An example project integrating functional genomics, nutrition and health. *Nutr Metab Cardiovasc Dis.* 2001;4(suppl):1-5.
26. Sciona, Ltd. 25 Broadmarsh Innovation Centre, Harts Farm Way, Havant, HANTS P09 1HS, United Kingdom. Available at: http://www.sciona.com.
27. Guttmacher AE. Human genetics on the web. *Annu Rev Genomics Hum Genet*. 2001;2:213-233.
28. Campbell P. Tales of the expected. *Nature*. 1999;402(suppl):C7-C9.
29. Editorial: Defining a new bioethic. *Nat Genet*. 2001;28:297-298.
30. Singer P. University of Toronto Program in Applied Ethics and Biotechnology; Canadian Program in Genomics and Global Health. 2001. Available at: www.utoronto.ca/jcb.