Using Genetic Variation to Optimize Nutritional Preemption¹,²

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Abstract

One of the promises of nutritional genomics is a set of dietary recommendations that leverage our understanding of nutrient-gene interaction in the preemptive dietary management of complex chronic diseases. Whether nutritional genomics can deliver on this promise is a matter of debate and controversy. Although nutritional genomics is often viewed as an extension of pharmacogenomics, the pharmacogenomics paradigm is a disease-centric reductionistic model that overshadows both the complexities and opportunities to be leveraged in preemptive nutritional pharmacology. Moreover, the pharmacogenomics model tends to set clinical expectations that nutritional genomics may not be able to achieve. The biological boundaries of nutritional pharmacology are being tested in many areas of preventive medicine such as cardiovascular disease and cancer. In this regard, the lessons learned in one disease may be germane to the other. Recent results from the Vitamin Intervention for Stroke Prevention (VISP), the Norwegian Vitamin (NORVIT), and the Heart Outcomes Prevention Evaluation (HOPE) 2 trials underscore the incertitude of translating epidemiologic data into preemptive nutritional guidance. Moving ahead, the genetic determinism of the nutrigenomic model needs to take on a more holistic and phenotypic focus. To the extent this can be done, preemptive nutrition may one day become a safe and practical reality. J. Nutr. 137: 270S–274S, 2007.

With the advent of molecular nutrition, nutrition scientists have a special opportunity to become major players in the health sciences and in the development of public health policy. The human genome project, coupled with the recent completion of the HapMap [a catalogue of single-nucleotide polymorphisms (SNPs)⁵ within the genome], provides modern-day nutritionists with a knowledge base and a set of tools to explore nutrient-gene interaction to an unprecedented level of inquiry. This new and molecular endeavor has been called nutritional genomics. Initially the term nutritional genomics referred to the analysis of the effects of nutrients on gene expression; more recently the term has been expanded to include effects on proteins, metabolites, and pathways in a globally integrated model (1,2). As a subset of nutritional genomics, nutrigenetics focuses on the effect of structural variations in genes, most commonly SNPs, in an effort to understand the highly variable response of humans to diet. In an ideal scenario, it may be possible to leverage our understanding of nutritional genomics to tailor diets to the genetic background of an individual to optimize health and offset disease (3). To the extent we are successful in reaching this goal, we can maximize the application and impact of nutrition science in terms of dietary recommendations and guidelines. Along the way we will face both the opportunity and the challenge of molecular nutrition in terms of balancing the specific needs of the individual with the general needs of the population. However, before this Gordian knot is unraveled, the solution to which lies as much in ethics as it does in science, some technical challenges have to be addressed.

Pharmacogenomics to nutrigenomics

To a certain extent the principles of nutrigenomics can be modeled after the principles of pharmacogenomics, as illustrated in Figure 1 (4). However, in moving from patients with diagnosed disease to healthy consumers, there is a significant shift from disease management to disease prevention or optimization of physiological function. In moving from consumers to patients, nutrigenetics offers a preemptive nutritional strategy for delaying the onset of disease and its clinical manifestations and may even offer adjunctive approaches to pharmacotherapy.

In keeping with the pharmacogenomics → nutrigenomics analogy, the progress and pitfalls encountered in putting
pharmacogenomics into practice are germane to nutrigenomics. Despite its remarkable potential to provide clinical benefit, pharmacogenomics has been slow to evolve, and its successes have been modest (5). The formation and funding of the Pharmacogenetics Research Network via NIH; the efficacy of drugs such as Herceptin, Erbitux, and Gleevec; and the utility of molecular diagnostics for managing absorption, distribution, metabolism, and excretion and adverse reactions are obvious successes of the pharmacogenomic model. However, issues of patient privacy and consent, social and ethical considerations, lack of professional education, and an unclear regulatory landscape limit the integration of pharmacogenomics into widespread medical practice. Nutrigenomics will certainly encounter similar challenges to its adoption (6), a process that is likely to be even slower, given that it operates in the realm of a self-empowered consumer rather than a medically supervised patient.

Nutrigenomics to nutritional pharmacology

In the context of nutrigenomics, preemptive nutrition strives to optimize health or offset the risk and/or progression of disease through an integrated understanding of genetic predisposition, nutrient-gene or -SNP interaction, and appropriately timed nutritional pharmacology. Preemptive nutrition faces some special challenges in terms of nutritional pharmacology that need to be borne in mind to manage our clinical expectations. Although there may be a continuum of effector activity for a given biological target with nutrients at one end and drugs at the other, bioactivity is but 1 variable in the efficacy equation. There are many notable differences between drugs and nutrients in terms of how they elicit biological change (Fig. 2).

Differences between drugs and nutrients aside, nutritional pharmacology can be quite successful. For example, nutritional pharmacology is a strategic component of the disease management protocols for cardiometabolic disease and cancer (7,8). The nutritional management of hyperlipidemia and metabolic syndrome provides good examples of how nutritional epidemiology and medical pharmacology provide a mechanistic foundation for nutritional pharmacology. Because the number of sites of biological intervention capable of bringing about clinically meaningful changes in lipid and lipoprotein metabolism is limited, it is perhaps not surprising that drugs and nutrients tend to overlap in their sites and mechanisms of action (Fig. 3 A) (9). SNPs that are important to the response of patients to drugs may also be factors in their response to various nutrients (Fig. 3 B); this has been well documented with respect to lipid and lipoprotein metabolism (10). A similar trend was observed with respect to the prevention and treatment of breast cancer (11,12).

Although the pharmacological activity of a given nutrient may be of limited potency and efficacy, the integrated actions of a specific suite of routinely ingested nutrients can elicit clinically meaningful change. This principle was recently put into practice in the “cholesterol-lowering portfolio diet” (13). Although the extent of cholesterol lowering elicited by this diet was greater in a carefully controlled metabolic study (14) than in an open-label real-world study (15), clinically significant LDL-cholesterol

![Figure 2](https://academic.oup.com/jn/article-abstract/137/1/270S/4664415)
lowering was achieved in both cases. Of note, however, long-term compliance with the diet and individual variability in response to the diet were significant response variables. The efficacy of the cholesterol-lowering diet is affected not only by what is included in the dietary portfolio but also by what is excluded (e.g., foods high in cholesterol, saturated fatty acids, and trans fatty acids).

The nutrigenomic model of preemptive nutrition

The integration of nutrigenetic information in the practice of nutritional pharmacology ultimately leads to preemptive nutrition. The complexity of the nutrigenomic overlay is illustrated in Figure 4 A. Conceptually, there are multiple dimensions or axes inherent in the model, including a basic science axis linking the disease state with a set of genes and a nutritional solution; a clinical axis linking the key genes, tests for functionally important SNPs in these genes, and attendant biomarkers for both the SNP and the nutritional solution; and a health service axis involving nutrigenomic counseling and an empowered consumer.

As complicated as the nutrigenetic model may be, there are cases where it all appears to come together, a notable example being the biology of 1-carbon methyl metabolism of sulfur-containing amino acids (16,17), the gene for methyltetrahydrofolate reductase (MTHFR), and its common population polymorphism C677T (Fig. 4 B). The importance of this particular gene-SNP combination is underscored by its many effects on pregnancy complications and birth defects, cardiovascular disease, cognitive impairment, some types of cancer, and possibly osteoporosis.

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Figure 4 The nutrigenomic model of preemptive nutrition (A) is highly interdependent on its component parts. (B) The model in practice: folate × MTHFR (C677T) × homocysteine interaction.
position preemptive nutritional strategies in the context of pathobiological processes that are relevant to the initiation and progression of the disease and monitored by appropriate surrogate markers that may or may not be the same as the usual clinical outcome variables.

**Nutrigenomics to nutritional phenotype**

The major challenge of preemptive nutrition is to determine when we know enough to act in a preemptive manner and to have a path to reach this state of knowledge. The nutrigenomic model, although grounded in genetics, needs to develop a more holistic phenotypic focus (Fig. 5). To this end, the concept of nutritional phenotype has been put forth by the long-range planning committee of the American Society for Nutrition (36). The underlying premise of the nutritional phenotype is that there is “a defined and integrated set of genetic, proteomic, metabolomic, functional, and behavioral factors that, when measured, form the basis for assessment of human nutritional status.” The assessment of this nutritional phenotype for the disease states of interest provides us the guide to what we really need to know to reduce preemptive nutrition to practice.

**Literature Cited**