Nutrient-Gene Interaction: Metabolic Genotype-Phenotype Relationship¹–³

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ABSTRACT The U.S. Department of Health and Human Services (DHHS)/USDA Dietary Guidelines for Americans
is a science and population evidence-based guide on diet and physical activity, providing advice and recommenda-
tions to promote a healthier lifestyle and reduce the risk of chronic diseases, including cancer. These recom-
mandations are supported by the comprehensive evidence-based review on diet and cancer prevention conducted
by the American Institute for Cancer Research, National Cancer Institute, World Health Organization/International
Agency for Research on Cancer, and others. However, influencing dietary effects are the individual genetic
predispositions that are the basis for considerable interindividual variations in cancer risk within the population and
in nutrient homeostasis, which is maintained by genomic-nutrient and metabolic-phenotype interactions. Although
 genetics is an important component, it accounts for only a portion of this variation. An individual’s overall
phenotype, including health status, is achieved and maintained by the sum of metabolic activities functioning under
differing circumstances within the life cycle and the complex interactions among genotype, metabolic phenotype,
and the environment. In this postgenomic era, high-throughput groups of technologies in genomics, proteomics,
and metabolomics measure and analyze DNA sequences, RNA transcripts, proteins, and nutrient-metabolic fluxes
in a single experiment. These advances have transformed biomarker studies on nutrient-gene interactions from a
reductionist concept into a holistic practice in which many regulated genes involved in metabolism, along with its
metabolic phenotypes, can be measured through functional genomics and metabolic profiling. The overall inte-
gration of data and information from the building blocks of metabolism-based nutrient-gene interaction can lead to

KEY WORDS: • nutrient-gene interaction • genotype-phenotype continuum
• Dietary Guidelines for Americans 2005

Good nutrition is vital to good health, optimal growth and
development, and prevention of diseases. Through untold
millennia, people have come to appreciate the food-health
connection and different civilizations have incorporated this
concept into their approach to healing. With the advent of
nutritional sciences, we now understand that nutrients and
other food substances obtained when eating a wide variety of
foods promote health, maintain metabolic homeostasis, and
fulfill our energy requirements. After World War II, various
governments began to establish dietary guidelines for their
populations to address the state of nutrient deficiencies and to
conquer deficiency-related diseases through public health pol-
cy recommendations. The current U.S. dietary guidelines are
population- and evidence-based advice on diet. However, hu-
mans differ in many ways in their response to diet because of
interindividual variations in genetic, epigenetic, and meta-
bolic phenotype status. Therefore, to transform current popu-
lation-based dietary guidelines into future personalized dietary
recommendations, we will need tools and knowledge to inves-
tigate the molecular basis of genetic variation. These tools will
provide an overview of the metabolic status and biochemical
events associated with cellular and biological organ systems as
well as nutrient-specific responses, including genotype expres-
sion, which determines the metabolic phenotype that leads to
the various predispositions to diet-related diseases (1).

Although genetics is an important component, it accounts for
only a portion of this variation. An individual’s overall
phenotype, including health status, is achieved and main-
tained by the sum of metabolic activities functioning under
different circumstances within the life cycle and the complex
interactions among genotype, metabolic phenotype, diet, life-
style, and the environment. Metabolic regulation, from genes
to metabolites, dictates biochemical functions as well as the
nutritional and dietary needs of an individual. Therefore,
genetic disposition and metabolic needs are important in de-
termining the optimal diet for an individual. In this post-

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genomic era, high-throughput technologies in genomics, proteomics, and metabolomics can now measure and analyze DNA sequences, RNA transcripts, proteins, and nutrient-metabolic fluxes in a single experiment (2,3). The overall integration of information obtained through such high-throughput technologies will lead to individual metabolic genotype and phenotype analysis and can give rise to personalized nutrition and dietary recommendations to help individuals maintain a healthier nutritional status and prevent chronic diseases. This manuscript will review the current population-evidence-based Dietary Guidelines for Americans 2005 (4), the technological advances investigating the metabolic genotype-phenotype continuum, and the relationship and application of nutrigenomic concepts to individual diet and cancer prevention.

Dietary Guidelines for Americans 2005

The Dietary Guidelines for Americans was first published in 1980. The guidelines are reviewed, updated if necessary, and published every 5 years as required by public law (5). The Dietary Guidelines for Americans, which targets the general population over 2 years of age, established the direction for all U.S. government nutrition programs, including research, education, food assistance, labeling, and nutrition promotion as well as other programs focused on health promotion and risk reduction.

The process of developing the 2005 Dietary Guidelines for Americans involved 3 stages (Fig. 1). In the first stage the U.S. Department of Health and Human Services (DHHS) and USDA jointly appointed a 13-member Dietary Guidelines Advisory Committee to review new scientific information. The committee conducted an evidence-based review of the literature on diet and health, primarily reports related to evidence obtained from randomized controlled trials, cohort and case-control studies, and occasionally ecological studies—by analyzing national data sets such as those used in the Institute of Medicine's reports and comprehensive evidence-based reviews on diet and cancer prevention conducted by the American Institute for Cancer Research, National Cancer Institute, World Health Organization/International Agency for Research on Cancer, and others. In August 2004 the committee submitted its report, which was made available to the general public and government agencies for comment (6).

The 2005 Dietary Guidelines Advisory Committee report not only offers advice on how to promote health but also on how to reduce the risk of some specific diseases linked to poor diet and low physical activity, including certain cancers, cardiovascular diseases, type 2 diabetes, hypertension, osteoporosis, and obesity.

During the second stage, DHHS and USDA jointly developed key recommendations based on the advisory committee's report along with public and federal agency comment and then published the Dietary Guidelines for Americans 2005 in January 2005 (4). Finally, in the third stage, DHHS and USDA staff revised the one-size-fits-all food guideline pyramid system to the new MyPyramid Steps to a Healthier You. This new food guideline system is Web-based and can provide recommendations that take into account an individual's age, sex, and physical activity level. In addition, a few special nutrient recommendations were included for specific populations including the elderly, women, and women of childbearing age (7).

The 2005 edition of the Guidelines encourages most Americans to consume fewer calories, be more active, and make wiser food choices. The key recommendations are grouped under 9 interrelated focuses. These include: 1) consuming a variety of foods within and among the basic food groups while staying within energy needs; 2) controlling calorie intake to manage body weight; 3) being physically active every day; 4) increasing daily intake of fruits and vegetables, whole grains, and nonfat or low-fat milk and milk products; 5) selecting fats wisely for good health; 6) choosing carbohydrates wisely for good health; 7) choosing and preparing foods with little salt; 8) drinking alcoholic beverages in moderation if at all; and 9) keeping food safe to eat.

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**FIGURE 1** The process and stages of the development of the Dietary Guidelines for Americans 2005 consisted of the Dietary Guidelines Advisory Committee report; the publication of the Guidelines, and the development of a Web-based food guidance system (MyPyramid).
These recommendations are formulated using population-based evidence science for individual health promotion and disease prevention. However, as our knowledge of genetic information progresses and our understanding increases on the specific influence of certain food components on metabolic pathways and phenotype during an individual’s life cycle, we will gain the ability to tailor nutritional advice based on a person’s specific metabolic profile. Assessment of the long-term risk for disease and personalized dietary recommendations can be made based on an individual’s genotype and metabolic phenotype resulting from the complex interaction of the genotype-phenotype continuum under differing circumstances in the context of an individual’s life cycle, lifestyle, and environment. Undoubtedly, these factors will be considered in future revisions of the Guidelines (1).

**Metabolic genotype-phenotype relationship**

One of the key achievements in biological science research over the past 100 y was the elucidation of the biochemical pathways in human metabolism. The relationship of enzymes, cofactors, substrates, metabolites, and enzyme kinetics influencing metabolic pathway fluxes has been partially or fully characterized. The assembled biochemical and cellular physiological knowledge of the role of nutrients on human metabolism has transformed the practice of medicine and public health policy in mitigating nutrient deficiency. This biochemical-metabolism knowledge base has also had a major impact on our food supplies and the development of pharmaceutical and biotechnology industries (2). As Carpenter (8) pointed out in his short history of nutritional science series, the developments made in the early to mid 20th century are now seen as the “golden age of nutrition.”

In the later half of the past century, after the discovery of the structure of DNA by Watson and Crick, and the beginning of this century with the decoding of the human genome, a massive advance has been made in technological development in genomics, proteomics, and metabolomics and the bioinformatic processing of the massive data sets generated (9) (Fig. 2). Functional analysis at the level of the genome (large-scale DNA sequencing that provided insight to the heterogeneity in coding regions of genes that leads to polymorphisms), of gene expansion (transcriptomics), of protein translation (proteomics), and of metabolite network and fluxes (metabolomics) is now fully developed. These new “omic” technologies permit the investigation of the multistep molecular pathway from genome to phenotype in nutrient metabolism as a continuum, and interrelated complex metabolic network, or both (2) (Fig. 3).

These genomic tools have been used in 2 different ways in molecular nutrition research (10). The first strategy is the traditional hypothesis-driven approach: specific nutrients influence the expression of specific genes and proteins, allowing the characterization of regulatory pathways where the flow of information goes from DNA to mRNA to protein. The second strategy is the systems biology approach: genes, proteins, and metabolite nutrients or nutritional regimens are catalogued and integrated into a functional metabolism assessment tool to develop biomarkers of early metabolic dysregulation and susceptibility that are influenced by diet. The field of investigating the nutritional genotype-phenotype relationship has been given various names—nutritional genomics, nutrigenetics, and nutrigenomics (11). The systems biology method aims at understanding the genotype-phenotype relationship in cellular systems on a metabolic network. Through ‘omic’ technologies, all the DNA sequences, mRNAs, all the proteins, a large multiple feedback loop from metabolites to proteins or transcripts involved in a particular cellular process are measured. This massive database is then integrated and analyzed by
advanced computer modules and bioinformatics techniques that potentially will lead to the genotypic-phenotypic character-
erization of different cellular network systems in response to a
specific diet (12). However, functional analysis is incomplete
unless quantification of metabolic fluxes is determined by
tracer-based metabolomics (13,14). Various databases have
been created and used in developing various biological net-
works to understand the relationship of diet and cancer while
exploring the genotype-phenotype relationship (15–17).
These approaches will lead to a systems biology understanding
of the interplay among genotype, environment, and nutrition
in health (18). Eventually we hope to be able to examine
personal variations in response to specific diet and provide
knowledge of how diet influences metabolic regulation in
health and prevention of chronic diseases at the personal level
to achieve the goal of personal dietary guideline recommend-
dations throughout an individual’s life cycle (Fig. 4).

Nutritional genomics frontiers in cancer prevention

Cancer is now considered a chronic disease of the genome
that may be influenced at many stages in its natural history by
nutritional and metabolic factors that affect not only the
prevention but also the progression and treatment of this
devastating disease. The cancer phenotype is the result of the
interaction of both genetic and environmental influences and
most of the evidence for this is drawn on studies of human
populations as well as from animal experiments that model the
process of carcinogenesis (19). Perhaps the strongest evidence
environmental influence is that of diet. It is estimated that up
to 80% of colon, breast, and prostate cancer cases and one
third of all cancer cases may be influenced by diet and associ-
ated lifestyle factors. All classical nutrient categories consist
of bioactive dietary compounds, including carbohydrates,
amino acids, fatty acids and structural lipids, minerals, and
vitamins. In addition, there is an extensive list of non-nutrient
components, particularly phytochemicals, which can have an-
ticancer activity. Phytochemicals are components of plant-
based diet that possess substantial anticarcinogenic and anti-
mutagenic properties (19). An estimated 25,000 different
chemical compounds occur in fruits, vegetables, and other
plants eaten by humans. They can encompass such diverse
chemical classes as carotenoids, flavonoids, organosulfur com-
pounds, isothiocyanates, indoles, monoterpenes, phenolic ac-
cids, and chlorophyll (20). Most of these nutrients can influ-
ence gene expression of steps along the genotype-phenotype
continuum (20) (Fig. 3).

Dietary habits continue to surface as significant factors that
may influence cancer incidence and tumor behavior (20).
Alan Jackson pointed out during the 2005 AICR/WCRF Inter-
national Research Conference that nutritional program-
ming in utero has a major impact on the development of
chronic illnesses in later life (21) (Fig. 4). Therefore, it is
essential to measure new biomarkers of nutrient-gene interac-
tion in the genotype-phenotype continuum at different stages
of our life cycle. Expanding knowledge based on “omic” re-
 sponses across tissues and integrated through systems biology
potentially will provide the specificity and sensitivity of re-
 sponses to bioactive food constituencies, identify biomarkers,
and identify responders and nonresponders to a particular diet
(20). Therefore, nutritional genomics has far-reaching poten-
tial in the prevention of diet-related diseases and provides a
new frontier, challenges, and opportunities in moving nutri-
tion towards individualized health (22,23).

With the advent of the postgenomic era, biological and
medical research and clinical practice has witnessed an explo-
 sion in strategies and goals (24–26). This eventually will
revolutionize the classical practice of nutrition from the cur-
rent evidence-based medicine towards genomic-based med-
icine (1). To accomplish this goal we need appropriate bioin-
formatics to analyze data obtained by each “omic” technology
and need to be able to integrate the findings obtained from
genomic, proteomic, and metabolic measurements into a co-
herent application database to address the genotype-phenotype
relationship. Information stored in a database can only
serve the needs of science once they are coordinated with
other clinical variables such as personal and family history,
physical examinations, and laboratory and functional imaging
information of the individual. This is the great challenge
ahead of us but this is also a great opportunity in the dawn of
nutritional genomics.

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