

Nutrigenetic Testing

Considerations for Clinicians

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As the relevance of genes to health and disease becomes increasingly apparent, clinicians can look forward to the development of a variety of gene-based tools and therapeutic approaches to patient care, particularly for managing and preventing chronic disease. Historically the linkage between genes and disease has been centered on disorders in which single genes have strong influences on measurable outcomes so that, when there is an alteration to a gene's structure or expression, negative consequences to the functioning of the affected individual are manifested.

Examples of such disorders include cystic fibrosis, sickle-cell anemia, and metabolic disorders such as phenylketonuria. Chronic diseases, however, appear to result from genetic variations that do not, in themselves, have a strong enough influence to impair function. Instead, these variations create a susceptibility to a disease but are silent in their effects until one or more additional factors are present to make the disease become manifest. Those factors may be triggers from the external environment, such as toxins or food components, or multiple gene alterations that may have a synergistic effect. The end result is a sustained metabolic imbalance that typically impairs function. Examples include atherosclerosis, hypertension, type 2 diabetes, and obesity.

The scientific discipline concerned with genetic variations and their influence on function is *nutritional genomics*. *Genomics* is the science of understanding how information is stored within the sequence of nucleotides comprising the genetic material, DNA, and how the expression (transcription) of this information affects an organism's function. *Nutritional genomics* focuses on the influence of the genome, its structure, or expression on the nutritional aspects of health and includes the fields of *nutrigenetics*, *nutrigenomics*, and *nutritional epigenetics*.

Nutrigenetics is concerned with the influence of an individual's genetic variations on the ability to digest, absorb, and use the nutrients in food that is consumed. *Nutrigenomics* focuses on the influence of the environment on gene expression, decoding of information contained within the DNA, and that information's translation into key molecules needed for function. These terms describe actions at the level of the genome—

either changes to the nucleotide sequence of the DNA encoding information or to the ability of the DNA to respond appropriately to signals to express/not express the information within a coding sequence. Either option can influence function, either by producing an altered gene product that influences function or by making less or more of the usual gene product.

In contrast, the science of *nutritional epigenetics* is concerned with an additional set of instructions that does not alter the structure of the DNA sequence but does alter the ability of the information in the DNA to be expressed. Epigenetic mechanisms for activating or silencing gene expression can be thought of as mechanical processes that allow or disallow transcription, the process of expressing the information in the DNA.

One common mechanism involves compressing or expanding the DNA by altering the structure of its associated histone proteins, a process known as histone protein modification. When the DNA/histone protein complex is compressed and tightly coiled, the DNA is not transcribed. A second common mechanism involves adding or removing chemical groups, such as methyl groups, to or from the DNA molecule itself. Essentially, these “tags” on the DNA serve as “stop signs” that prevent the transcribing enzyme (RNA polymerase) from accessing the DNA and expressing the information. Methylation is essential for the one-carbon transfers that are needed for a myriad of metabolic reactions. Given that the primary supplier of methyl groups, folate, is obtained solely through the diet, understanding nutritional epigenetics and its clinical applications is becoming increasingly important in clinical nutrition. Effective nutritional interventions are, in turn, critical for chronic-disease management and prevention.

Genetic Technology for Nutritional Genomics Applications

Nutritional genomics makes use of technologies that detect alterations in the DNA. The more commonly used technologies focus on identifying changes in the DNA structure, production of a gene product, or the presence or absence of epigenetic

“tags” (e.g., methyl groups) covalently attached to DNA. Single-nucleotide polymorphisms (SNPs) involve a change in a single nucleotide building block within the DNA structure and are currently the basis for most of nutrigenetic testing. Alternatively, the sequence of nucleotides in an individual’s DNA can

The technology used in nutrigenetic testing is well-established.

be determined and analyzed for multiple nucleotide changes. In addition, technological advances now enable detection of the presence or absence of methyl groups attached to DNA.

Much controversy has surrounded nutrigenetic testing, particularly the testing itself. The technology used in nutrigenetic testing is well-established and has been used by molecular biologists for decades. The present controversies concern whether or not such tests have clinical validity and clinical utility. For any laboratory test to meet these criteria, there must it purports to measure, within appropriate error limits, and if the test provides meaningful results. For clinical utility, the genetic variations being detected by a nutrigenetic test must occur frequently in the population being tested, there must be a strong association between a change in the genome or epigenome and a measurable effect on function, and there must be a

therapeutic approach that can improve function. Furthermore, these relationships must be well-researched and subjected to scientific peer review.

Currently the U.S. Food and Drug Administration (FDA) does not require premarket approval for nutrigenetic tests, although the FDA continues to study the need for such action. The FDA regulates these tests as “medical devices” and exercises discretion in its enforcement, depending on the intended use of a particular test and the risks to the person tested of an inaccurate test result. In general, nutrigenetic tests have been considered to be class I “medical devices,” the lowest level of risk to users when an inaccurate result is reported. However, on November 22, 2013, the FDA issued a “warning letter” to 23andMe (a popular DNA testing group) with regard to its health-related genetic test (visit: www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm). This company was unique in the marketplace for offering a test that reported on a large number of health-related risks that the FDA felt were not sufficiently substantiated (i.e., the clinical utility of the test is questionable). Essentially, there are gaps in attempts to consider the relationship between specific gene variants and the influence of such variants on increasing the risk of developing particular diseases or conditions.

Herein lie the challenges regarding whether or not nutrigenetic testing is “ready for prime time.” The scientific foundation for nutrigenetic testing lies within the nutrition sciences, which historically have not integrated the influence of gene–

Table 1. Examples of Nutrigenetic Testing Laboratories in North America

Laboratory	Website	Testing options
Enterolab	www.enterolab.com	Gluten sensitivity gene test
foru International	www.foru.com	Personalized nutrition & weight management
Genova Diagnostics	www.gdx.net	Chronic disease-focused panels: cardio-; detoxification-; estrogen-; immune-; neuro-; & osteo-related tests
GenoVive	www.genovive.com	Weight-management panel
Interleukin Genetics	www.InherentHealth.com	Inherent Health brand: bone health; heart health; nutritional needs; & weight management
Kimble Genetics (now Esoterix)	www.esoterix.com	Atherosclerosis, celiac disease, hemochromatosis, methylation, narcolepsy, thrombosis & drug metabolism
Market America	www.marketamerica.com	Gene single-nucleotide polymorphisms, personalized nutrition & exercise
Molecular Diagnostics Laboratory	www.mdl-labs.com	Atherosclerosis, hypertension, inflammation, lung cancer, methylation & thrombosis
Myriad Genetics	www.myriad.com	Cancer genetics
Nutrigenomix	www.nutrigenomix.com	Nutritional needs/wellness
Nutriline/Amway Corporation	www.nutriline.com	Inherent Health brand: bone health; heart health; nutritional needs; & weight management
Pathway Genomics	www.pathwaygenomics.com	Cardiac genomics, chronic diseases, medication response, mental health, weight management & wellness
Prometheus Laboratories	www.prometheuslabs.com	Celiac genetics, inflammatory bowel disease & primary lactase nonpersistence
23andMe	www.23andme.com	Single scan of multiple genes

Note: www.nextgdx.com provides a search-and-compare site for genetic tests offered by U.S. Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories.

Recommended Reading

Articles

Review of weight management–related single-nucleotide polymorphisms

Abete I, Navas-Carratero S, Marti A, Martinez JA. Nutrigenetics and nutrigenomics of caloric restriction. *Prog Molec Biol Transl Sci* 2012;108:323–346.

Description of the role of nutritional epigenetics in personalizing health recommendations

Burdge GC, Hoile SP, Lillycrop KA. Epigenetics: Are there implications for personalised nutrition? *Curr Opin Clin Nutr Metab Care* 2012;15:442–447.

Discussion about ethical considerations and consumer acceptance of nutrigenetic testing

de Roos B. Personalised nutrition: Ready for practice? *Proc Nutr Soc* 2013;72:48–52.

Review, with a focus on omega-3 fatty acids (important considerations for susceptibility to a proinflammatory state)

Merched AJ, Chan L. Nutrigenetics and nutrigenomics of atherosclerosis. *Curr Atheroscler Rep* 2013;15:328.

Review of single-nucleotide polymorphisms and metabolic disease, particularly obesity, metabolic syndrome, and type 2 diabetes

Phillips CM. Nutrigenetics and metabolic disease: Current status and implications for personalised nutrition. *Nutrients* 2013;5:32–57.

Discussion about direct-to-consumer testing

Sauuko PM, Reed M, Britten N, Hogarth S. Negotiating the boundary between medicine and consumer culture: Online marketing of nutrigenetic tests. *Soc Sci Med* 2010;70:744–753.

Website

The Genetic Information Nondiscrimination Act of 2008. Online document at: www.eeoc.gov/laws/statutes/gina.cfm Accessed October 27, 2013.

environment interactions into nutrition research. As a result, the foundation needed to identify gene–function links, gene variant–dysfunction links, and, ultimately, nutrition therapies to restore function in the presence of a gene variant is only now being developed. Fortunately, this gap in our knowledge base is now being addressed. Excellent studies are being conducted by researchers around the world, and the volume of peer-reviewed literature in this field is increasing exponentially. In time, we can expect to have a solid foundation from which to understand the interactions among genes, environments, and functional ability, and from which to develop effective interventions for disease management and prevention.

Information for Clinicians

How to Choose a Laboratory

What can clinicians do while the research foundation is being built? Know the testing laboratory in terms of the laboratory's credentialing (laboratory and personnel, and attention to quality assurance and quality control) and the scientific bases for the tests offered. Be clear about the information needed from the testing. Do you want to know if a patient is at increased risk for inflammation and, thereby, to a host of chronic disorders, or are you looking for guidance on the appropriate diet for the patient needing to lose weight? The box entitled Information to Obtain from a Nutrigenetic Testing Laboratory provides key questions to ask a testing laboratory prior to ordering nutrigenetic tests. In my experience working with laboratories that provide nutrigenetic testing services, I have been impressed with the scientific rigor applied to selection of the genetic variations included in the tests and to the standards in place within the laboratory operations.

Types of Tests Currently Available

Tests of clinical interest focus on general wellness, specific nutritional needs, or specific health concerns, such as vascular health, weight management, bone health, biotransformation/

Information to Obtain from a Nutrigenetic Testing Laboratory

Test concerns

- Which gene variants are tested?
- Are these variants common for the ethnicity associated with my patient?
- For each variant tested, is there action that can be taken to reduce risk, improve health?
- How strong is the scientific documentation for the test?
- Has the test been validated?
- What is the cost of the test?
- How long before the results will be available?
- How will the test results be reported?

- Will the report contain actionable recommendations?

Laboratory concerns

- Is the laboratory appropriately credentialed (e.g., state licensure, Clinical Laboratory Improvement Amendments [CLIA] certification, accreditation)
- Is the test accompanied by informed consent?
- Is there a credentialed professional available for assistance in interpreting the results?

Privacy/discrimination

- How will privacy be protected?
- What happens to the DNA sample after testing?

detoxification, and susceptibility to overexpression of inflammation. Table 1 provides an overview of the types of nutrigenetic tests currently available in North America and a representative listing of laboratories. In addition, standard clinical laboratories, such as LabCorp and Quest Diagnostics, offer some nutrigenetic tests. The majority of the tests detect specific changes in DNA structure through identification of SNPs, one SNP at a time. The 23andMe testing looks at the entire DNA sequence and reports changes in multiple genes. Sequencing the entire genome has been laborious and costly until recently, but automation and increased market demand suggest that, ultimately, laboratories will examine the entire genome of an individual routinely. Costs range from \$99 to more than \$3,000. For the most part, these tests are not yet covered by insurance, although that determination varies among insurance plans, and laboratories typically will assist in determining whether a patient's insurance will cover a particular test.

Conclusion

Although developing the needed research foundation to support the clinical utility of nutrigenetic testing is a long-term endeavor that may be successful in time, these tests hold the promise of identifying an individual's propensity to be well or to be ill. Once the relationships among gene variants, their influences on specific mechanisms that underlie diseases, and interventions that can be used effectively to manage or prevent these changes in function, clinicians will have new tools for identifying patients' susceptibility to various chronic disorders. Clinicians will also be able to find ways to manage these disorders better, and, ultimately, prevent their development.

Nutrigenetic testing represents an important leap forward in getting to the root cause of a patient's health challenges and to developing strategies for minimizing risk of disease. The potential for understanding gene–environment interactions can provide new insight into preventing genetic susceptibilities from manifesting as chronic diseases. Currently, the research and clinical focus is primarily on genetic variations that impair function and lead to disease. However, as the focus shifts to early detection of genetic susceptibilities for which lifelong appropriate diet and lifestyle choices can prevent disease from developing, the potential exists for improved quality of life for individuals and decreased economic burdens of chronic disease for societies. The emergence of new clinical tools for refocusing health care to health promotion and disease prevention bodes well for the future of health care.

Disclosure Statement

Although, in the past Dr. DeBusk has consulted with several companies that are developing nutrigenetic tests and testing laboratories, no current financial conflicts exist. ■

Ruth DeBusk, PhD, RD, has a clinical practice, in Tallahassee, Florida. Her practice in functional nutrition has a focus on nutritional genomics.

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