

The Promise of Genetic Testing

BY ARON SHAPIRO; AND ASHLEY LAFOND

Through recent advances in ophthalmic genetics, genetic testing is beginning to drive medical vision care and slowly weave itself into clinical practice. Our knowledge of the human genetic landscape is evolving through efforts such as the Human Genome Project and the International Haplotype Map (HapMap) Project,^{1,2} and enthusiastic predictions about personalized medicine have followed from the sequencing of the human genome. Developments in molecular genetic testing heighten the expectation that, in the future, knowledge of genetic factors will play a role in disease prevention, early diagnosis, and management of common eye diseases that are the main causes of visual loss in the general population.

GENETIC PROGRESS

Nearly 25 centuries ago, Hippocrates recognized that the trait of blue eyes is inherited, and, in 350 BC, Aristotle commented on the transmission of vision impairment across generations.³ Yet even with such early recognitions of genetics, there has been a slow translation of genomic discoveries from the laboratory to the clinic, perhaps due in part to the vagaries of intellectual property law or the different strategies countries have chosen to pay for the medical care of their citizens.⁴ Still, our understanding of the genes involved in inherited eye diseases has far advanced since those first observations many centuries ago, and ophthalmic genetics has progressed to identify several hundred genes that may cause or contribute to ocular disease and blindness.

Genetic eye diseases range in prevalence from relatively common disorders such as age-related macular degeneration (AMD) to specific subtypes of rare conditions that occur in small numbers of patients. AMD is estimated to affect 1.75 million people in the United States, although more than 7 million adults are believed to exhibit clinical signs of AMD and are therefore at substantial risk of developing the disease.⁵ Prior to 2005, understanding of the heritability of AMD was limited and based largely on familial aggregation studies. A genetic breakthrough occurred when a common

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coding variant in the complement factor H (CFH) gene was identified and shown to account for nearly 40% of the genetic risk for AMD cases.⁶⁻⁸

Since the completion of the HapMap Project, which compiled a collection of millions of single nucleotide polymorphisms (SNPs: normal variations in gene structure that may protect against or predispose to various conditions), several genes have been associated with increased AMD risk.⁹⁻¹⁴ Multigene testing may identify individuals who are at high risk due to the inheritance of multiple risk variants. For example, one study estimated that individuals who are homozygous for 2 different gene variants associated with AMD have a 50-fold elevated risk for the disease.¹⁵ Further, genetic testing may also provide insight into whether known AMD risk factors, such as smoking and obesity, interact with genetic risk associated with CFH alleles and other genes.¹⁵⁻¹⁷ This effort was highlighted in February 2006, when the National Institutes of Health announced the Genes, Environment and Health Initiative project, a program initiated to support research that will lead to the understanding of genetic contributions and gene-environment interactions in common disease.¹⁸

USING GENETIC RISK FOR PERSONALIZED MEDICINE

The underpinning of any clinical genetic test is the assumption that there is a “predictable relationship between the presence or absence of certain sequence variations and a patient’s clinical appearance or disease outcome.”¹⁴ Genetic testing enables personalized treatment and is a tangible sign to patients and their families that they may be part of a more optimistic

future with regard to both treatment plans and visual outcome.

There are at least 4 features of a genetic test that are of interest to a clinician and his or her patient: the cost, the turnaround time, the report, and the likelihood that the test will assist in the management of the patient's disease.⁴ While none of these parameters create an absolute barrier to the use of this type of test, clinical utility relies on the practicality of the test to the general population in order to be considered standard of care.

The clinical need for and benefit of relevant genetic testing is exemplified by the predictive and preventive measures that can be employed with such information. For example, early detection of subfoveal choroidal neovascularization, resulting in early management, may lead to effective prevention of AMD-associated blindness.¹⁹⁻²¹ Recent advances in the recognition of genetic predictors of AMD allow the identification of individuals at high risk. High-risk individuals can then be enrolled in surveillance programs before vision loss and can be equipped with a clinical approach to early detection, management, and sight preservation.²² Genetic testing is also useful as a guide for suggesting lifestyle changes. Research suggests that identifying patients at increased risk for AMD may provide them with an incentive for lifestyle changes such as smoking cessation or dieting, as both smoking and obesity are risk factors.¹⁵

Two companies actively pursuing products in the genetic testing marketplace are ArcticDx (Toronto, Canada) and Sequenom (San Diego, CA). ArcticDx has developed Macula Risk, a laboratory-developed test using all known and validated genetic markers to detect AMD predisposition. This test is used commonly to assess the risk of progression from early or intermediate AMD to advanced AMD.²³ Sequenom is focused on innovative technology, instrumentation, and tests that target the clinical research and clinical molecular diagnostics markets. The company's proprietary MassARRAY system is a high-performance mass spectrometry-based DNA analysis platform that efficiently measures the amount of genetic target material and variations.²⁴

FUTURE OF PERSONALIZED MEDICINE

Genetic tests are becoming faster, more affordable, more likely to yield a useful result, and more likely to be covered by insurance. Although genetic tests may provide new tools for identifying genetic predispositions, they do not change the primary goal of clinicians: to adapt medical tests and technologies for the benefit

of each individual patient. As genetic tests become more widely available in the clinical setting, personalized medicine will undoubtedly include assisting patients in making wise use of genetic risk assessment. Advances in genomic technologies are being transitioned to the clinical setting with the hopes that the knowledge of genetic factors will provide information on disease prevention, diagnosis, and treatment that was previously unattainable. ■

Aron Shapiro is Vice President of Retina at Ora, Inc., in Andover, MA.

Ashley Lafond is a medical writer at Ora, Inc.



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