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Genomics in the Era of Molecular Ophthalmology: Reflections on the National Ophthalmic Disease Genotyping Network (eyeGENE™)

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That the *Archives of Ophthalmology* is devoting this issue to genomics in ophthalmology just over one year from its two issues on genetics in ophthalmology is a testament to that fact that the era of genomic medicine is rapidly being incorporated into ophthalmology.(1) The evolution of genetic medicine has been accelerated following the full sequencing of the human genome,(2) the HapMap Project,(3) and the identification important genetic components to complex diseases such as macular degeneration and glaucoma.(4–7) Science has moved forward at a rapid pace. Now is the time to put this knowledge into clinical practice. Approximately 71% of respondents to a recent survey wanted more information from their physicians about genetic conditions in their family.(8) Our patients are looking for us as ophthalmologists to take the lead.

The Challenges of Genetic Ophthalmology

One can expect that in this new millennium, genetic ophthalmology is becoming as much of a recognized sub-specialty as pediatric ophthalmology or vitreoretinal surgery.(1) Like any other sub-specialty, it requires, first and foremost, an ophthalmologist who is able to carefully describe a patient's phenotype and interpret the specialized testing. It also requires knowledge of both science and medicine, as many new strategies for therapeutics are making their way from the laboratory to the clinic.

At least at first, this trip from bedside to bench and back again can appear quite daunting. Some 38 million Americans have vision-limiting eye diseases--many of which have genetic component.(9) A great deal of research to date has focused on cases where a genetic vision disorder is inherited in a Mendelian fashion. For some of these disorders, such as retinitis pigmentosa and Leber congenital amaurosis, several different genes are potentially responsible.(10) Finding a causative mutation in such families often means sequencing through many individual candidate genes. Although efficient testing strategies are being developed,

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(10–12) molecular testing can still be complicated, time-consuming and expensive. Further, the cost of molecular testing and the genetic counseling that ought to precede and follow-up such testing frequently is not fully covered by medical insurance.(13,14)

Accessibility and ease-of-use provide further challenges. Web-based resources such as provided by GeneTests (www.genetests.org) have greatly improved access to information on laboratories performing genetic testing. Such testing requires careful attention to the details of sample handling, which may be daunting for the busy ophthalmology practice not accustomed to such procedures. Because many independent laboratories offer testing of different genes, the clinician may not be familiar with efficient and effective molecular testing strategies.

There is also the challenge of the future. By this, we mean that a practicing clinician not only wants to be able to tell his or her patients that their condition is due to a mutation in a specific gene, but that they will be included in the research that is moving forward nationwide for their disease. Affected individuals want as many talented scientists as possible to work with their samples and to study their diseases. They also want to know about clinical studies or trials for which they might qualify. Likely, if a mutation is not found in genes known to cause their disease today, they want to know that their physician will try to follow-up in time as new discoveries are made.

The Response: The National Ophthalmic Disease Genotyping Network

To answer this challenge, the National Eye Institute, in consultation with leading clinicians, scientists, genetic counselors and ethics/policy experts, has created the National Ophthalmic Disease Genotyping Network or eyeGENE™. This endeavor is intended to create a shared resource in ophthalmic genetics that is led by the vision research community. eyeGENE™ received its first sample in September 2006. The effort has grown to involve ten academic institutions across the nation; 49 genes for 21 diseases are currently being offered for testing. This effort involves experts from diverse backgrounds ranging from corneal and lens diseases, to strabismus, glaucoma, and retinal degenerations. We expect that this effort will grow to include additional labs offering testing for more genes and diseases in the near future.

The goals of eyeGENE™ are to provide a research repository of DNA and blood coupled to anonymous phenotypic information for researchers and thereby to provide timely, accurate diagnostic genotyping to patients with inherited eye diseases. Eventually, eyeGENE™ will thereby establish genotype-phenotype correlations for genetic eye diseases and enhance recruitment for clinical trials in inherited eye diseases. The eyeGENE™ program is a national resource, through which ophthalmologists and their patients will have greater access to diagnostic gene testing and genetic information. For the present, eyeGENE™ is focused on Mendelian disorders that affect vision and not more common and complex disorders such as age-related macular degeneration.

The principle goal of eyeGENE™ is to advance research. As such, in order to obtain genetic testing, a patient must be willing to allow his or her DNA sample to be de-identified and used for vision research. The referring ophthalmologist must also answer a few short questions online about the patient's clinical presentation. The net result of this for the research community will be a nationwide, robust phenotypic database coupled to a DNA and blood repository from which samples can be requested. For the clinician, eyeGENE™ provides convenient, centralized specimen handling and collection, as well as testing by CLIA-certified diagnostic laboratories. Patients are asked at the time of consenting whether they wish to be re-contacted in the future if eyeGENE™ learns of a clinical study for which they might qualify. This option keeps the patient "plugged into" ongoing research long after the results of a DNA test are reported. Furthermore, as appropriate new genes are added to the program, eyeGENE™ will retest samples for which initial study fails to identify a gene mutation. Complete details on this

program and how to submit samples to eyeGENE™ can be found at http://www.nei.nih.gov/resources/eyegene.asp.

The eyeGENE™ program hopes to smooth the path between the bench and the bedside. We hope to reduce some of the barriers between research and clinical care—barriers that have been to the detriment of both endeavors. Moreover, we hope to create a resource and a sense of shared purpose for the vision community at large that benefits researchers, clinicians and patients and accelerates our move toward improved diagnosis and treatment of inherited eye diseases.

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