As the medical community has accepted that age-related macular degeneration (AMD) is a disease influenced by genetics, so too has it uncovered patterns in patients’ genetic profiles that suggest some individuals are at increased risk for initiation or progression of the disease. However, genetics is not everything, and retina specialists need to remember that AMD is a complex disorder that is also influenced by nongenetic factors.

WHY GENETICS?

There are two basic reasons why clinicians and scientists are endeavoring to build genetic or mixed-risk models for AMD. Physicians who are able to identify individuals who will be diagnosed with the disease prior to disease development can take steps to mitigate the disease’s onset and/or progression. The second major reason for developing genetic or mixed-risk models is to identify individuals who may exhibit a differential response to therapies, which would allow physicians and patients to selectively and cost-effectively manage the disease.

In the case of early detection, the value of testing is highly dependent on having an intervention that prevents or slows disease. Even if one has the means of identifying patients with differential responses to therapy, physicians must have alternative therapies available to apply based on the risk model. At this time, neither our genetic risk models nor our current treatment options can satisfy their respective requirements. The current interventions for slowing AMD progression are primarily restricted to dietary and lifestyle choices that would be beneficial for the majority of the population regardless of AMD risk. The therapies for treating AMD (currently focused on exudative AMD) may have varying degrees of efficacy based on an individual’s genetic risk factors, but at this time, there is no rationale for limiting or selecting a particular therapy based on a genetic profile.

Although genetic testing has the potential to shed some light on our understanding of AMD, it also has its limitations. Complex genetic disorders tend to manifest a spectrum of clinical features, and it is unlikely that one can simply attribute specific ones, such as type of drusen or polypoidal choroidopathy, to a set of genetic variants. One can perhaps show differing contributions of multiple genes to some AMD features, and this may help researchers better understand their pathogenesis. In some cases, shared asso-
associations of genetic variants (such as those that are associated with AMD and those with polypoidal choroidopathy) may indicate shared pathways of pathogenesis.

**DEVELOPING A RISK MODEL FOR MACULAR DEGENERATION**

Retina specialists must rely on evidence-based methods for using genetic information to inform their patient counseling and treatment decisions. Molecular genetic testing is not a substitute for taking an appropriate family history, and such information should be used in an integrated manner.

Given the current sensitivity and specificity of AMD risk models based solely on genetic factors, using such testing for the general population will result in an excess of false positive tests. One can reduce the percentage of false-positives by limiting the population to be tested to those who already have an elevated risk of disease due to family history, early clinical findings, and known risk factors (such as smoking). The most effective current risk models incorporate genetics as well as these other components, with more than half of the risk determined by the presence of clinical findings that are associated with early AMD.

There is considerable interest in finding potential biomarkers in the blood that may indicate altered inflammatory, lipid, metabolic, or immune states that contribute to AMD. There is also great interest in identifying clinical markers of early retinal dysfunction or structural changes. Combining molecular genetic profiles with clinical markers may create risk models that are sufficiently sensitive and specific to serve as part of clinical care.

**LIMITATIONS OF GENETIC TESTING**

The presence of AMD-associated variants in noncoding regions presents a challenge for our understanding of molecular genetics. Some of these variants may affect levels of transcription of a distant gene, alter the pattern of alternative splicing, or even affect the transcription of embedded genetic elements that are not translated into proteins but serve a regulatory role in the cell. Even after complete genomic sequencing, any determination of disease likelihood for a patient is limited because the possible variants in every critical region of DNA cannot be identified. Patients should be advised during genetic counseling sessions that a negative test result—such as one that does not identify a genetic variant—does not mean that they have no risk for a particular disease; it simply means that no risk was identified. This is especially true for individuals who have a positive family history for AMD and are concerned about their own risk of developing the disease. The current genetic tests do not include rare variants that may influence heritability within an AMD family, and the risk profile based on common variants may be misleading.

It is important to note that the phenotypic expression of genetic variations first learned in Mendelian genetics become more complex and varied as scientists understand more about the human genome. Mutations can result in a number of phenotypes. For example, patients who have the ABCA4 mutation have phenotypic expressions ranging from Stargardt disease, to AMD, to cone dystrophy. Thus, the presence of a certain phenotype is not necessarily associated with specific genes or variants. These are some of the uncertainties that one has to accept when dealing in genetic profiling.

There have been no reliable data establishing a clear-cut relationship between genetic profiles and the severity or rate of AMD progression. Most of the associations of genetic variants with AMD have concerned different stages of AMD (early, intermediate, or late/advanced) compared with controls, but not with the rates of progression of the condition or of specific phenotypic features such as drusen. Only the RetnaGene test (Nicox Inc. and Sequenom Laboratories), which includes genetic and nongenetic factors, has been validated with longitudinal data from the AREDS cohort and offers some prediction of disease progression.1

**SHOULD WE DO GENETIC TESTING FOR AMD?**

Our understanding of the complex relationship between genetic profiles and phenotypic expression continues to evolve as a dynamic model, and genetic tests currently available are not yet sophisticated enough to reliably guide treatment decisions. Today's tests are not effective in diagnosis or management, and therefore should not be used. Physicians trying to reinforce medical recommendations by pointing to an elevated genetic risk for a particular condition could be employing a form of coercion, especially considering the considerable uncertainty that the patient will actually develop the disease in question. Because all patients would benefit from current recommendations (ie, healthy diet, smoking cessation, etc.), and considering that those recommendations possess little or no risk, physicians should not need to resort to genetic profiling.

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Financial disclosure: Dr. Gorin receives funding from the Harold and Pauline Price Foundation, Research to Prevent Blindness, and the Stein Eye Institute. He is a coinventor of a patent held by the University of Pittsburgh for the 10q26 AMD susceptibility locus that has been licensed to Sequenom.