

Special Communication

Genetic Testing for Age-Related Macular Degeneration
Not Indicated Now

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Age-related macular degeneration is a very common condition that is caused by a complex interplay of genetic and environmental factors. It is likely that, in the future, genetic testing will allow physicians to achieve better clinical outcomes by administering specific treatments to patients based on their genotypes. However, improved outcomes for genotyped patients have not yet been demonstrated in a prospective clinical trial, and as a result, the costs and risks of routine genetic testing currently outweigh the benefits for patients with age-related macular degeneration.

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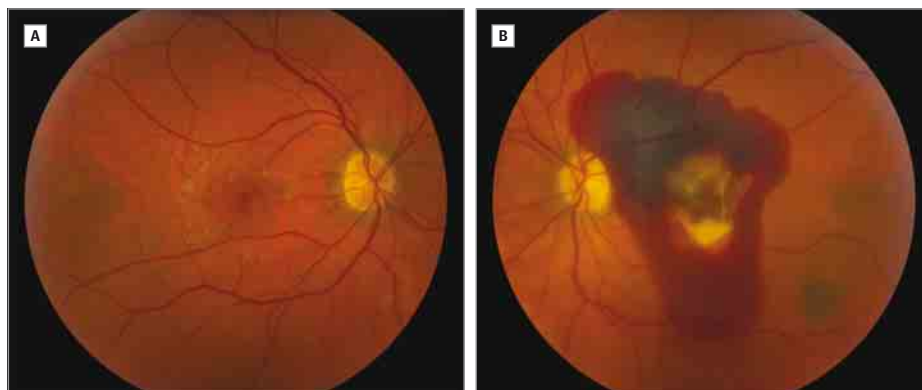
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For more than 25 years, the central premise of my professional career has been that the evaluation of genes will lead to improved diagnosis and treatment of eye disease. My colleagues and I have discovered dozens of disease-causing genes and hundreds of specific mutations and have used this information to guide everything from family planning to viral-mediated gene replacement therapy. During this time, I have also cared for many patients affected with age-related macular degeneration (AMD) and watched with horror when otherwise healthy people lost their vision to this disease. Like many people, I have a strong family history of macular degeneration; both of my maternal grandparents lost a lot of their vision to this disease. Why then, with ready access to a laboratory that analyzes thousands of DNA sequences per week, did I not screen my mother for AMD-predisposing mutations? The answer is simple: clinical examination of my mother by an experienced ophthalmologist was more predictive of her visual outcome and her need for therapy than any molecular test that I might have performed. In anything other than a research context, such a test would have been, at best, irrelevant to her care and, at worst, needlessly worrisome to her.

As I have listened to and participated in discussions about the use of genetic testing for the management of patients with AMD, the 2 things that I have found most noteworthy are the general lack of appreciation for the genetic complexity of AMD and the almost complete lack of discussion of the risks associated with such testing. The genetic training of most ophthalmologists—and indeed most physicians—is heavily weighted toward mendelian disorders like Stargardt disease or X-linked retinitis pigmentosa. In these conditions, the development of clinically detectable disease is very likely if a disease-causing genotype is present in a single gene. The counseling implications of this strong relationship between genetic variations and clinical disease are relatively easy to understand. However, most practicing ophthalmologists have not thought very much about the fact that AMD is not a mendelian disease; that is, in AMD, the genotypes of many genes appear to interact with each other and with the environment to determine whether a given patient will develop clinically significant disease.

This much weaker correlation between specific genotypes and clinical outcomes creates the situations seen in Figure 1 and Figure 2. Specifically, there are people with very-low-risk AMD genotypes who

Figure 1. Fundus Photographs of the Right (A) and Left (B) Eyes of a 69-Year-Old Patient With Age-Related Macular Degeneration and Homozygous Low-Risk Genotypes at Both the *CFH* and *ARMS2* Loci



The patient's left eye has a visual acuity of 20/300 and a large subretinal hemorrhage and subretinal pigment epithelial hemorrhage associated with a choroidal neovascular membrane.

develop sight-threatening AMD (Figure 1), and there are other people with high-risk genotypes who live to be 85 years of age without any detectable AMD (Figure 2). Standard clinical examination and imaging techniques (such as indirect ophthalmoscopy, slitlamp biomicroscopy, and optical coherence tomography) are currently much more accurate in predicting the clinical course of AMD than any existing genetic test. In addition, a periodic clinical examination can detect other things of great value to the patient, such as glaucoma, diabetic retinopathy, retinal tears, and choroidal melanomas.

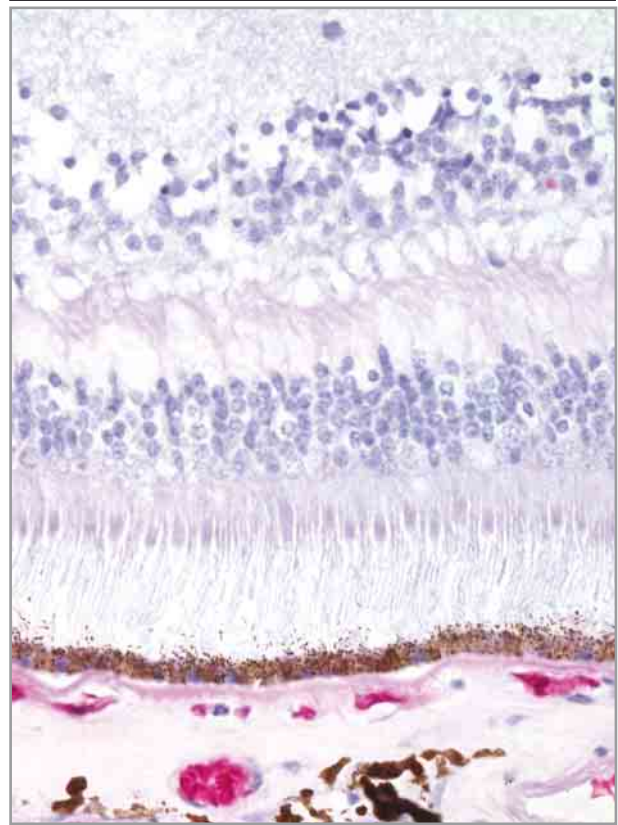
The imprecise relationship between genotype and AMD and the existence of extremely accurate clinical diagnostic methods combine to create 3 kinds of nontrivial risks for routine genetic testing of patients with AMD: decision-making risks, psychological risks, and economic risks. An example of a decision-making risk would be an individual who undergoes genetic testing because of a worrisome family history and is told that he has a very-low-risk genotype (like the patient in Figure 1). If he is reassured by the results of this genetic test to the point that he defers routine visits to an ophthalmologist, the test could actually increase his risk of vision loss by preventing the discovery of unlikely but real AMD and/or any of the many other disorders that could be found and managed during standard ophthalmological care. Another example of a decision-making risk would be an individual with a worrisome family history who is found to have a high-risk genotype and quits her well-paying job to enjoy the world before going blind only to live to be 85 years of age without developing significant macular degeneration. What is the human cost of worrying such an individual unnecessarily for 20 years (ie, the psychological risk)? At 85, would that individual be pleased with her good clinical outcome, or would she feel that she had been harmed by an overstatement of her risk at the time of her genotyping? I suspect that few clinicians who are currently using genetic tests for their patients with AMD are counseling them about the possibility that they could still develop severe vision loss despite a low-risk genotype or that they could maintain excellent vision despite a high-risk genotype.

Another type of risk associated with genetic testing for a disease as prevalent as AMD is the risk of shifting medical care dollars away from something that would have greater utility for patients. That is, people older than 65 years of age in this country are already struggling to pay for the cost of their health care, as are lawmakers. The introduction of any new form of medical care carries with it the very real risk that a patient or a health care payer will choose to pay for it instead of a service that is, in reality, more valuable to the patient, such as a regular visit to a clinical ophthalmologist.

In recognition of these risks, and in the absence of any prospective clinical trials showing better outcomes for patients with AMD who undergo genetic testing, the American Academy of Ophthalmology has made the following recommendation: "Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration...until specific treatment or surveillance strategies have been shown in one or more published clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, ophthalmologists should confine the genotyping of such patients to research studies."^{1(p2410)}

Given all this, it is interesting to consider why genetic testing for AMD is still such a hot topic at national meetings and in major journals. One reason is that money is always a hot topic, and there is an almost unfathomable amount of money spent each year diagnosing and treating patients with AMD. It is important for all practicing

Figure 2. Histological Section of the Macula of an 85-Year-Old Human Donor Who Was Homozygous for the Highest-Risk *CFH* Allele



The outer retina and retinal pigment epithelium are completely normal (hematoxylin-eosin, original magnification $\times 40$).

ophthalmologists to maintain a healthy skepticism about diagnostic or therapeutic modalities that are pitched to them by people with personal financial interests in these modalities. However, the more important reason to discuss AMD in meetings and journal articles is that it remains one of the most significant medical problems facing people in the developed world today. Depending on one's definition of the disease, it will affect about 1 in 3 people older than 75 years of age.² The number of people who are older than 75 is steadily increasing, and by 2025, there will be 44% more people in the United States in this high-risk age group than there are today. So, even if our antineovascular treatments become easier to give and longer lasting, and even if we learn to replace patches of geographic atrophy with stem cells, we will still need to develop ways to completely prevent a large fraction of AMD by 2025 just to keep from losing ground to this terrible disease.

I believe that the Achilles' heel of AMD will prove to be the genes that are involved in its pathogenesis. That is, careful studies of AMD risk genes will eventually reveal enough information about the disease mechanisms that good cell-based and animal models can be created. These models will be used to discover new drugs and other treatments that will significantly lessen the likelihood of developing AMD, much like antihypertensive and anticholesterol medications currently lessen the risk of heart disease and stroke. Once such treatments have been developed, genetic testing will allow physicians to identify the patients who

will most likely benefit from them. People at high risk will, in principle, be able to take these medications or other treatments early enough to markedly delay or even completely prevent the disease.

Between that day and this, there will be many assertions that genotyping of patients with AMD is already useful enough for widespread use. For example, Awh and coworkers^{3,4} have recently advanced the hypothesis that specific genotypes at the *ARMS2* and *CFH* loci are associated with different responses to dietary supplementation of antioxidants and zinc. This hypothesis is based on a retrospective analysis of public data gathered during the Age-Related Eye Disease Study (AREDS). Although AREDS investigators were quick to point out a number of statistical errors in this study,⁵⁻⁷ I think that it is very important for all ophthalmologists to recognize that the burden of proof of this hypothesis lies with Awh and colleagues; there is no burden of disproof for the AREDS investigators or, for that

matter, anyone else in the scientific community. I continue to recommend AREDS vitamin supplementation to my patients with AMD regardless of their genotype.

I believe that all hypotheses about the clinical utility of genetic testing for AMD should be tested in a prospective fashion, with participants randomly assigned to groups that receive either conventional care or genotype-guided care. If, in such a prospective study, the clinical outcomes of the genotype-guided groups are significantly better than the clinical outcomes of the conventionally managed groups, this, and only this, will be meaningful evidence in favor of using genetic testing to help care for patients with AMD.

In conclusion, it is important to restate and emphasize that the current recommendation of the American Academy of Ophthalmology is to avoid routine genetic testing for AMD until specific treatment or surveillance strategies have been shown in prospective studies to be of benefit to people with specific genotypes.¹

ARTICLE INFORMATION

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