

COMPREHENSIVE

Genetic Testing for Inherited Eye Disease: Why, How, and Who

BY ANNIE STUART, CONTRIBUTING WRITER

INTERVIEWING EDWIN M. STONE, MD, PHD, AND JANEY WIGGS, MD, PHD

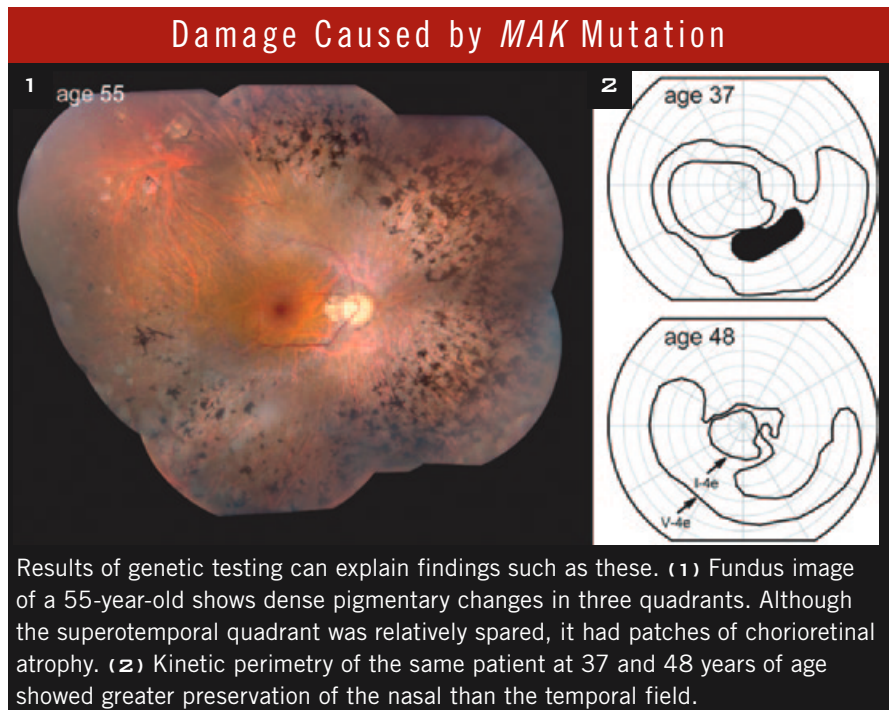
In the past 15 years, genetics experts have identified approximately 500 genes that contribute to inherited eye diseases.¹ Testing technology has become more powerful and sophisticated, and the clinician must be savvy about the whys and hows of responsible use of these genetic tests. From the benefits of testing to the testing process and appropriate patient selection, two experts share their thoughts on this subject.

Why Test?

Genetic testing currently offers several benefits.

Peace of mind for patients. Genetic testing may increase the accuracy and specificity of a diagnosis, which can give patients peace of mind. Also, genetic testing is a great asset for prospective parents with a family or personal history of certain genetic eye diseases, said Janey Wiggs, MD, PhD, specialist in glaucoma and genetic eye disease and associate professor of ophthalmology at Harvard Medical School in Boston.

Therapy. Where therapies already exist or are in development, such as for Leber congenital amaurosis, testing also paves the way for participation in clinical trials of new treatments, said Edwin M. Stone, MD, PhD, professor of ophthalmology at the University of Iowa and director of the Carver Non-profit Genetic Testing Laboratory. And other patients with once untreatable diseases will likely become the beneficiaries of gene replacement and stem



Results of genetic testing can explain findings such as these. (1) Fundus image of a 55-year-old shows dense pigmentary changes in three quadrants. Although the superotemporal quadrant was relatively spared, it had patches of chorioretinal atrophy. (2) Kinetic perimetry of the same patient at 37 and 48 years of age showed greater preservation of the nasal than the temporal field.

cell therapies in the future, he added.

Discovery. Testing also can lead to unexpected advances. Last year, Dr. Stone and colleagues at the University of Iowa reported a disease-causing mutation in an individual with recessive retinitis pigmentosa (RP).^{2,3} They then screened nearly 1,800 other patients with RP and identified the same mutation (Figs. 1, 2) in more than 20 additional families, many of whom had Jewish surnames. "It turned out to be a Jewish founder mutation, dating back to at least the 1400s and accounting for up to one-third of all retinitis pigmentosa cases in Jewish people," he said. Although the original research subject

had advanced RP and no family history of eye disease, this single individual held a vital clue to the most common cause of RP in a specific population.

How to Test

Dr. Stone noted that genetic tests are prone to the same kinds of errors as all medical tests, including sample mix-ups, and may yield clinically irrelevant information. "The key is to have a well-developed clinical diagnosis before ordering a test and to interpret the result in the context of the patient's findings," he said. "A genetic test is not a substitute for a good doctor. It is just a tool that a good doctor can use to get

to a better answer.” Dr. Stone also emphasized that genetic testing should be a partnership between clinicians and genetic counselors.

Role of genetics specialist. Trained to look in the eye and know what they’re seeing, ophthalmologists are the starting point in the process, not an afterthought, said Dr. Stone. But many physicians aren’t comfortable explaining risks based on particular mutations or inheritance patterns observed with a gene or disease, said Dr. Wiggs. In such instances, it’s important to enlist the help of a genetic counselor or genetics specialist. This person’s expertise is in statistical thinking and understanding the probability that a particular patient has a particular disease, noted Dr. Stone, and, more important, in explaining it to the layperson. In addition, the genetics expert is well trained in carefully eliciting a family history, advising on which tests to order, and answering questions, he said.

Many ophthalmologists have sufficient knowledge of genetic eye disease to order tests and to work effectively with a genetic counselor, said Dr. Stone. However, some busy clinicians choose to refer these patients to a genetics specialist in their geographic area. What is becoming less and less acceptable, he said, is to tell patients who have an inherited eye disease, “There’s nothing we can do for you.” Not only is this disheartening but it’s also increasingly inaccurate.

Locate a lab. No matter who orders the test—the ophthalmologist or the genetics specialist—perhaps the best way to find a laboratory that offers a test for a specific patient’s disease is through the new Genetic Testing Registry of the National Institutes of Health (www.ncbi.nlm.nih.gov/gtr), said Dr. Stone. This website includes a database of CLIA-approved genetic testing laboratories⁴ as well as links to other valuable resources such as *Gene Reviews*, PubMed, and records from the Online Mendelian Inheritance in Man (OMIM) compendium. It also includes links to the American College of Medical Genetics, the American Board

Academy Recommendations

The Academy recently drafted Recommendations for Genetic Testing of Inherited Eye Diseases. Here is an abridged version of its specific recommendations:

1. Offer genetic testing to patients with clinical findings suggestive of a Mendelian disorder whose causative gene(s) have been identified.
2. Use CLIA-approved laboratories for all clinical testing. When possible, utilize laboratories that include in their reports estimates of the pathogenicity of observed genetic variants.
3. Provide a copy of each genetic test report to the patient.
4. Avoid direct-to-consumer genetic testing and discourage patients from obtaining such tests themselves. Encourage the involvement of a trained physician and/or genetic counselor for all genetic tests.
5. Avoid unnecessary parallel testing—order the most specific test(s) available given the patient’s clinical findings.
6. Avoid routine genetic testing for genetically complex disorders until specific treatment or surveillance strategies have been shown to be of benefit.
7. Avoid testing asymptomatic minors with untreatable disorders except in extraordinary circumstances.

To view the full recommendations, visit www.aao.org/one. Select “Practice Guidelines,” then “Clinical Statements.”

of Genetic Counseling, and the National Society of Genetic Counselors. The websites of the latter organizations provide listings of genetics professionals by zip code.

Have patience. A good deal of time is needed to arrive at answers—sometimes months, said Dr. Wiggs. “It can require substantial person power to work through the sequencing of the gene. And, if the lab finds a mutation, we always go back and confirm it a second time to ensure it’s not just an experimental artifact.” Dr. Wiggs also noted that interpreting the written report itself requires time; it goes directly to the physician to digest the results. Dr. Stone recommends that patients also receive a copy of their report, which will allow them to pursue gene-specific research or clinical trials, if they choose to do so.

Understand clinical grading. With genetic testing, one shouldn’t expect an all-or-nothing result, said Dr. Stone. “Many putative disease-causing variants have been seen in only one or two families to date, and thus our confidence in them is much less than it is for variations that have been observed dozens of times.”

To help convey the degree of certainty associated with genetic diseases, Dr. Stone assisted in developing a clinical grading system, known as the estimate of pathogenic probability (EPP). An EPP score of 0 indicates that a variation is *extremely unlikely* to be responsible for the patient’s disease, whereas a score of 3 indicates that a variation is *extremely likely* to be responsible for the disease.⁵

The best situation occurs when both the clinical and molecular data are very strong. “If a physician is very certain that his or her patient has a specific autosomal recessive disease,” said Dr. Stone, “and a genetic test finds two variations with an EPP of 3 in a gene known to cause that disease, those variations are very likely to be the cause of that patient’s condition.”

Whom to Test

“Shotgun” testing is rarely indicated in the practice of medicine, and this is especially true for genetic testing, said Dr. Stone. The very large amount of non-disease-causing variation in the genome makes it difficult to interpret the results if the net is cast too widely. For example, even if you limit your

focus to genes already known to cause human retinal disease, he said, you will still find 10 to 15 very plausible disease-causing variations in most individuals. Instead, he encourages clinicians to target their hypotheses. “What you want is a physician to look at the patient and say, ‘I think this is Usher syndrome,’” said Dr. Stone. “We then have a much more constrained hypothesis than if someone were to say ‘Eye disease, not otherwise specified.’”

Which patients, then, to test?

Patients with Mendelian diseases.

The rarer the disease, the more likely it is caused by variations in a single gene, said Dr. Stone. Therefore, it is appropriate to offer genetic testing to patients whose clinical features indicate a Mendelian disorder for which the causative gene is known.

Dr. Wiggs provided a few examples of cases for which she offers testing to her glaucoma patients:

- Babies with congenital glaucoma (CYP11B1 and LTBP2)
- Children and teens with glaucoma (PITX2, FOXC1, PAX6, LMX1B, and mutations in the myocilin gene if a family history of glaucoma exists)
- Adults younger than age 50 with glaucoma and a strong family history (mutations in the myocilin gene)
- Patients with optic nerve disease and a family history of normal tension glaucoma but no personal history of elevated intraocular pressure (optineurin gene)

In most cases, results of these tests do not alter treatment but are helpful for genetic counseling, said Dr. Wiggs. “We can screen all the other family members and identify who’s also at risk or a carrier.” However, in some cases, testing can separate those with slight and possibly benign ocular hypertension from, for example, those requiring medication at the earliest possible stage.

“Unlike with early-onset glaucomas,” said Dr. Wiggs, “where mutations can be identified in only about 10 to 20 percent of patients, in retinal degenerations, there are more known genes, making it possible to identify a mutation in about 50 percent of pa-

tients, some of whom may be eligible for clinical trials.”

Patients with other types of diseases also might benefit from genetic testing, said Dr. Wiggs, including those with eye movement disorders, optic neuropathies, and corneal dystrophies.

Individuals with predisposing risk factors. Unlike the highly penetrant mutations of Mendelian diseases, risk alleles associated with complex diseases such as adult-onset glaucoma or age-related macular degeneration (AMD) are very common, said Dr. Wiggs. “People may have the risk alleles but not the disease—and they may never develop it.” There is simply a statistical association between particular risk factors and the predisposition to certain diseases, especially when those factors are combined with environmental risks. For this reason, routine genetic testing for genetically complex disorders is not recommended until specific treatment or surveillance strategies have proved to be beneficial in one or more published clinical studies. “What happens if you tell a 40-year-old they have an allele known to be associated with AMD?” asked Dr. Stone. “It just creates a fear of future vision loss without providing a means of reducing that risk that is any more effective than routine eye examinations. On the other hand, if someone came out of a lab and said, ‘I’ve got an inexpensive, safe, and effective oral medication that completely blocks the AMD-predisposing effect of the Y402H variant in complement factor H,’ you could justify testing everybody for that variant beginning that very day.”

Bottom line? Finding a genetic variant known to be associated with a complex disease in a specific individual doesn’t mean that the disease will occur. Likewise, the absence of such a variant does not guarantee lifelong protection from the disease.

Avoid asymptomatic minors. Although adults with a dominant disease often ask to have their clinically unaffected children tested for the presence of a disease-causing mutation, Dr. Stone suggests avoiding this unless the disease is treatable. However, he

recommends examining these children clinically, from time to time, until they reach adulthood. If they still have no sign of the disease as an adult and want information to help make decisions about starting their own families, they can then make that choice. “But if we make the decision for them now, it’s taken out of their hands.” In the few cases in which presymptomatic testing may be of benefit, both parents must agree to it, he said. “That’s because wanting to not know trumps wanting to know.”

- 1 www.nei.nih.gov/resources/eyegene.asp
- 2 Stone EM et al. *Invest Ophthalmol Vis Sci.* 2011;52(13):9665-9673.
- 3 Tucker B et al. *Proc Natl Acad Sci USA.* 2011;108(34):E569-E576.
- 4 CLIA stands for Clinical Laboratory Improvement Amendments.
- 5 Stone EM. *Trans Am Ophthalmol Soc.* 2003;101:437-484.

Drs. Stone and Wiggs report no related financial interests.

More at the Meeting

At this year’s Joint Meeting (Nov. 10 to 13), the instruction course titled “Approach to Genetic Eye Diseases for the Comprehensive Ophthalmologist” will focus on the comprehensive ophthalmologist’s role in the treatment of genetic eye diseases. It will review the pertinent medical background; review the availability of diagnostic testing, including how to obtain tests; and discuss nondirective counseling.



Participants will come away with an understanding of 1) how to approach and evaluate a patient and family with a genetic disorder, 2) the principles of inheritance patterns, 3) where to find reliable information and laboratory diagnostics, and 4) guidelines on genetic counseling.

This course takes place Tuesday, Nov. 13, 11:30 a.m. to 12:30 p.m.; event code 556.