

Genetic Testing for Inherited Eye Disease Called Into Question

Should patients with age-related macular degeneration undergo genetic analysis?

BY CALLAN NAVITSKY, ASSOCIATE EDITOR

Age-related macular degeneration (AMD) is a multifactorial disease influenced by both environmental and genetic factors. Recent genetic research has identified specific variations that contribute to the development of AMD. With this knowledge, several companies have created predictive tests designed to identify patients with a higher-than-average risk of developing wet AMD. The concept behind these technologies is that identifying patients at risk could enable them to receive more personalized care.

On November 11, the American Academy of Ophthalmology (AAO) published a news release reiterating its position that ophthalmologists should avoid genetic testing for complex eye disorders such as AMD and late-onset primary open-angle glaucoma. The AAO maintains that researchers' understanding of genetic components and how they interact with disease factors in AMD is far from complete, and, thus, knowing the results may not alter the course of the disease.

STATEMENT FROM THE AAO

The AAO published recommendations for genetic testing of inherited diseases in the November issue of *Ophthalmology*.¹ In its recommendations, the AAO recognized that when properly performed, interpreted, and acted on, genetic tests can improve the accuracy of diagnoses and prognoses, can improve the accuracy of genetic counseling, can reduce the risk of disease occurrence or recurrence in at-risk families, and can facilitate the development and delivery of mechanism-specific care. The AAO also pointed out the risks of

genetic analysis.

"However, like all medical interventions, genetic testing has some specific risks that vary from patient to patient," the authors wrote. "For example, the results of a genetic test can affect a patient's plans to have children, can create a sense of anxiety or guilt, and can even perturb a patient's relationships with other family members."

According to the news release, the AAO was prompted to reaffirm its position against genetic testing for AMD by the increase in marketing by genetic-testing companies. The AAO states that the currently marketed genetic tests offer little benefit or insight regarding whether a patient is significantly predisposed to a particular disease, and that a comprehensive eye exam is significantly more effective than any available genetic test for identifying treatable disease. The AAO said patients are to be discouraged from undergoing genetic testing until treatment or surveillance strategies can be shown to benefit individuals with specific disease-associated genotype. The genotyping of these patients should be reserved for research studies only, the news release said.

"In the future, genetic tests will likely allow clinicians to provide mechanism-specific treatments to patients at high risk for some molecular forms of AMD," Edwin M. Stone, MD, PhD, head of the AAO's genetic testing task force and first author of the recommendations published in *Ophthalmology*, said in the news release. "At the present time, however, the cost and risks far outweigh any benefit."

According to Dr. Stone, 3 things are needed before genetic testing will be useful in AMD diagnosis and

treatment: (1) clinically proven evidence that such tests significantly improve outcomes for patients, (2) significantly lower testing costs, and (3) sufficient infrastructure within the medical community to allow proper counseling of patients about their genetic testing results. "Until then, combining a patient's family history of eye disease with a standard eye exam will remain the best way to determine his or her risk for AMD," he said.

GENETIC TESTS FOR AMD

Several genetic tests are currently commercially available, including Macula Risk (ArcticDx; Toronto, Canada), a prognostic genetic test for patients diagnosed with early or intermediate AMD. In an interview with *Retina Today*, ArcticDx Founder Brent Zanke, MD, PhD, FRCPC, explained the advantages of genetic analysis and expressed concern with the opinion that genetic testing for AMD provides no proven advantage in preventing or treating the disease.

"We as a company and our scientific advisors recognize that there is a huge opportunity for saving vision

by detecting a group of individuals who are going to progress from dry AMD to advanced AMD because these people can be followed more carefully, imaged more intensively, and treated before their visual acuity deteriorates," Dr. Zanke said.

Using an algorithm based on the complete combination of AMD genes and smoking history, the ArcticDx genetic test identifies patients who are most likely to progress to advanced AMD with vision loss. Test patients are stratified into risk categories. In this grouping, 20% of patients are predicted to have a higher-than-average lifetime risk of advanced AMD, with 1% of these falling into a high-risk group with a predicted 65% chance of developing geographic atrophy or choroidal neovascularization (CNV).

Several studies have shown that early detection of subfoveal CNV, resulting in early management, may lead to effective prevention of AMD-associated blindness.²⁻⁴ Once identified, high-risk individuals can be enrolled in surveillance programs before vision loss occurs and can be equipped with a clinical approach to early detection, management, and sight preservation,⁵

THE AAO'S SPECIFIC RECOMMENDATIONS FOR GENETIC TESTING¹

1. Offer genetic testing to patients with clinical findings suggestive of a Mendelian disorder whose causative gene(s) have been identified. If unfamiliar with such testing, refer the patient to a physician or counselor who is. In all cases, ensure that the patient receives counseling from a physician with expertise in inherited disease or a certified genetic counselor.
2. Use Clinical Laboratories Improvement Amendments-approved laboratories for all clinical testing. When possible, use laboratories that include in their reports estimates of the pathogenicity of observed genetic variants that are based on a review of the medical literature and databases of disease-causing and non-disease-causing variants.
3. Provide a copy of each genetic test report to the patient so that she or he will be able independently to seek mechanism-specific information, such as the availability of gene-specific clinical trials, should the patient wish to do so.
4. Avoid direct-to-consumer genetic testing and discourage patients from obtaining such tests themselves. Encourage the involvement of a trained physician, genetic counselor, or both for all genetic tests so that appropriate interpretation and counseling can be provided.
5. Avoid unnecessary parallel testing—order the most specific test(s) available given the patient's clinical findings. Restrict massively parallel strategies like whole-exome sequencing and whole-genome sequencing to research studies conducted at tertiary care facilities.
6. Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies.
7. Avoid testing asymptomatic minors for untreatable disorders except in extraordinary circumstances. For the few cases in which such testing is believed to be warranted, the following steps should be taken before the test is performed: (1) the parents and child should undergo formal genetic counseling, (2) the certified counselor or physician performing the counseling should state his or her opinion in writing that the test is in the family's best interest, and (3) all parents with custodial responsibility for the child should agree in writing with the decision to perform the test.

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–Brent Zanke, MD, PhD, FRCPC

Dr. Zanke explained.

“The AAO has said that genetic testing is not a substitution for an accurate physical examination, and we agree,” Dr. Zanke said. “We think that a direct-to-consumer approach to providing genetic testing is wrong because you need to combine both genes and examination, and patients need to be connected to a physical mode of medical care that is going to follow them along and manage their risk. We strongly believe that the medical literature supports the conclusion that a modern test should contain both phenotype and genotype, and we were slightly distressed by the AAO’s guidelines.”

Additionally, despite the costs of a genetic analysis, which is reimbursable by most health care providers including Medicare, the health care system may save money through earlier identification and treatment of high-risk patients, according to Dr. Zanke. Based on early economic analyses (unpublished data), if only 1 out of 400 of the patients who present with wet AMD could be caused to present earlier rather than later, there would likely be a net savings for the health care system, he said.

CONCLUSION

The AAO recommendations state that genetic testing can have a positive impact on patients and families affected by inherited eye disease. However, the organization does not yet find genetic testing for AMD to be of value in caring for these individuals. It is possible that additional clinical trials may elucidate the role of genetic testing for AMD and clarify ways to maximize the benefits and minimize risks associated with the intervention. ■

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