The field of retinal genetics and gene therapy has exploded over the past several years. With the first retinal gene therapy approved in December and a multitude of gene therapy trials currently under way (see the Table on page 41 of Dr. Benjamin Bakall’s article), genetic testing has become a critical component in the diagnosis and management of inherited retinal diseases (IRDs). I would even argue that genetic testing may be considered a new standard of care for patients with IRDs, whereas 10 years ago this would have typically been considered a research-related activity.

Retina specialists are increasingly expected to be aware of updates in the field of retinal genetics and retinal gene therapy, and we should be able to facilitate discussions with our patients involving the importance of diagnosis and confirmation of genotype. This article provides an overview of the growing role of genetic testing in the management of patients with IRDs.

**LIFE BEFORE GENETIC TESTING**

In the past, patients with IRDs were seen in retina clinics, where special testing, including electrophysiology, kinetic visual field testing, and multiple imaging modalities were used to diagnose and follow disease progression. Diagnoses were made clinically, and diseases were often named after the person who first described the given disease (eg, Best disease, Stargardt disease). Inheritance patterns were established from gathering histories and drawing careful and complex family pedigrees. Counseling regarding progression was dependent upon the IRD specialist’s accuracy of diagnosis.

Today, although imaging and testing are still an important part of the workup, genetic confirmation of disease can now be pursued and can add accuracy to diagnosis, allow genotype/phenotype correlation and improved natural history counseling, and likely influence management and therapeutic options.

**WHEN TO USE GENETIC TESTING**

An American Academy of Ophthalmology task force released a position statement in 2016 regarding the role of genetic testing in retinal disease. The statement reads, in part: “At this time, genetic testing should be used in Mendelian disease (monogenetic disease), such as retinitis pigmentosa...”

**AT A GLANCE**

- Genetic testing is critical for individuals with a diagnosis of Leber congenital amaurosis or retinitis pigmentosa and for patients who may be candidates for an ongoing gene therapy clinical trial.
- Referral for ocular genetic counseling should be offered to patients who have undergone genetic testing.
- For a limited time, patients who are members of the Foundation Fighting Blindness registry and who have an appropriate IRD diagnosis may be eligible for a free genetic testing and ocular genetic counseling study.
or Stargardt disease.” A question that remains after this recommendation, and one that is often posed to me by colleagues, is this: Should we now test for all Mendelian IRDs, or is there a priority list?

Now that an FDA-approved treatment is available for RPE65-associated retinal degeneration (voretigene neparvovec-rzyl [Luxturna], Spark Therapeutics) it is mandatory that we obtain genetic testing for individuals with a diagnosis of Leber congenital amaurosis (LCA) or early onset retinitis pigmentosa (RP). Likewise, it is crucial to perform genetic testing on patients with a clinical diagnosis of an IRD who are currently undergoing evaluation for gene therapy in a phase 1/2 clinical trial in order to determine their candidacy for those trials. I also believe genetic testing is paramount for purposes of family counseling if a diagnosis of autosomal dominant disease or X-linked disease is suspected.

For all other types of IRD (eg, autosomal recessive RP) genetic testing is certainly useful for confirming diagnosis and inheritance pattern, and it may influence counseling regarding prognostic implications, but I would explain to patients that there may be no direct or immediate trial or treatment option that arises based on the results. The caveat here is that we don’t know what we don’t know. If genetic testing reveals a surprising result and challenges our clinical diagnosis (eg, ABCA4 mutations can certainly be uncovered, even if the clinical diagnosis is recessive RP; LCA has often been misdiagnosed and uncovered even in late adulthood; and X-linked RP can be missed if the inheritance pattern is unclear), then perhaps the genetic testing result would be critical to know now and would change treatment or clinical trial options.

It is also useful to explain to patients that, even if no gene therapy trial or treatment is available for an IRD that is identified, the only way we can plausibly get closer to a therapy is to add to our collective body of knowledge on genetic eye disease by genetically classifying all inherited clinical entities. All things considered, I try to obtain genetic testing for all of my patients with IRDs.

**THE NEXT STEPS**

Once we have decided that a patient should have genetic testing, what comes next? There are several factors to consider when choosing which genetic testing laboratory to use. First, certification under the Clinical Laboratory Improvements Amendments is mandatory for clinical genetic testing in the United States. In addition, the genetic analysis provided by the lab should follow American College of Medical Genetics and Genomics standards. With next-generation sequencing, skilled interpretation of the pathogenicity of identified variants (mutations) is mandatory.

Some labs offer comprehensive IRD panels. These are often the most useful because they allow a shotgun approach to genotyping a patient, sequencing for multiple common IRD genes. Logistical considerations, such as whether the lab directly preauthorizes and bills insurance, whether the lab provides home collection blood or saliva kits and prepaid return envelopes, and the turnaround time for results should also be considered.

Several commercial ocular genetics laboratories offer comprehensive, large, next-generation sequencing retinal dystrophy panels with rapid turnaround of results. These companies also provide interpretation of results, with analysis of pathogenicity and clinical significance of mutations. Some of the commercially available labs that I have experience with include Blueprint Genetics, Molecular Vision Laboratory, and Prevention Genetics. There are also nonprofit laboratories, such as The John and Marcia Carver Nonprofit Genetic Testing Laboratory at The University of Iowa, and Massachusetts Eye and Ear.

With the recent approval of voretigene, its maker Spark Therapeutics offers single-gene testing for RPE65 if a diagnosis of RPE65-associated retinal degeneration is expected (RPE65 mutations are associated with clinical diagnosis of both LCA and RP).

**OCULAR GENETIC COUNSELING**

It is important that we offer patients who have undergone genetic testing a referral for ocular genetic counseling, which can be provided by a geneticist or genetic counselor. It is helpful to know that there is a telemedicine option for ocular genetic counseling, I encourage patients to consider using Informed DNA, an excellent ocular genetic telemedicine company that bills the patient’s insurance for a genetic counseling appointment. This service can eliminate the logistical issues associated with receiving genetic testing from your clinic by offering the entire package, including pretesting genetic counseling, which includes obtaining a detailed history and inheritance pattern; posttest counseling, explaining results and prevalence/prognosis if known; preauthorization of insurance for testing; and selection of appropriate genetic testing laboratories.

Perhaps the most useful update I can share regarding ocular genetic testing is that, for a limited time, thanks to generous donations from The George Gund Foundation, Sofia Sees Hope, and other supporters, patients who are
members of the Foundation Fighting Blindness registry, who reside in the United States and who have a clinical diagnosis of an orphan IRD studied by the Foundation, can participate in a free genetic testing and ocular genetic counseling study with the assistance of their eye health care provider. This research study is available through the Foundation Fighting Blindness’s free online My Retina Tracker registry (www.myretinatracker.org/). The My Retina Tracker protocol is approved by the Western Institutional Review Board. Members of the My Retina Tracker registry provide informed consent to share their deidentified data in the registry, and these deidentified data are accessible to researchers and industry to accelerate research and clinical trials on IRDs.

Because the individual privacy of members is a high priority, the accessible member profiles display only a unique, anonymous registry number to database users. To contact members with a profile of interest, researchers must demonstrate that they have an institutional review board–approved protocol and contact letter and provide the registry numbers of the participants they wish to contact. Registry staff share the contact information with these members, who then decide if they wish to engage. The certified genetic testing laboratories used for testing are Blueprint Genetics and the Ocular Genomics Institute of the Department of Ophthalmology, Massachusetts Eye and Ear and Harvard Medical School, both of which offer a comprehensive retinal dystrophy gene panel that contains more than 260 genes. Ocular genetic counseling is required in the study and is provided either by the ordering clinician’s genetic counselor or by the telephone-based counseling service of Informed DNA. There are no out-of-pocket expenses or insurance billing for the testing or counseling. Physician fees are not covered by the study.

**KNOWING WHEN TO MANAGE OR REFER**

With a rapidly expanding horizon of retinal gene therapy before us, we are living in a new landscape of genetic testing for IRDs, and retina specialists must be up to date on the latest information in order to effectively counsel, manage, or, when needed, refer patients with IRDs. We must be familiar with genetic testing options and either be able and willing to provide this service to patients in our clinics or refer these patients to an IRD center than can facilitate their diagnostic workup and genetic testing.


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