Inherited retinal diseases (IRDs) are a clinically and genetically heterogeneous group of retinal disorders that consists of more than 100 individual disease entities, with more than 300 causative gene mutations. Globally, the prevalence of IRDs is estimated at about one in 2,000 and is the leading cause of visual impairment in the Western working-age world.1-3

There are four IRDs that have clinical trials or FDA-approved gene therapies: achromatopsia (ACHM), choroideremia (CHM), Leber congenital amaurosis (LCA), and retinitis pigmentosa (RP). This article reviews our current understanding of these four IRDs, genetic testing, available gene therapies, and related clinical trials, as well as the importance of providing ongoing rehabilitation services and support for patients with an IRD who are facing lifelong vision impairment.

**CLINICAL DIAGNOSIS**

When making a clinical diagnosis, I typically perform a family history, and perhaps a pedigree tree, to determine whether there is consanguinity in the patient’s family. I ask about onset of symptoms and duration of progression and measure visual acuity. I also examine the posterior segment to see what typical clinical signs are present, if any, and perform OCT imaging to look at the cross-section of the retina. Additionally, I can perform autofluorescence, and I have access to an electroretinogram (ERG) machine at my academic center to determine rod-cone response in the various phenotypes. My clinic also has a Goldman visual field perimeter that plots out to 180° and can test for different intensities of vision loss.

**Achromatopsia**

ACHM is inherited in an autosomal recessive manner, with six different genes expressing various phenotypes. Prevalence is about one in 30,000 patients.11 Typically, individuals with ACHM have moderate to severe visual impairment (eg, 20/80 to 20/200) and lack of color vision. A central scotoma can be viewed clinically with visual field testing, and an ERG would yield no photopic response in these patients.

Applied Genetic Therapies Corporation (AGTC) is conducting two separate phase 1/2 clinical trials to evaluate the safety and efficacy of adeno-associated viruses (AAV) gene therapy product.
candidates in patients with ACHM caused by CNGB3 or CNGA3 mutations.\textsuperscript{6,7} MeiraGTx also has two phase 1/2 clinical stage programs in co-development with Janssen Pharmaceuticals for ACHM caused by CNGB3 and CNGA3.

Choroideremia

CHM is an X-linked recessive genetic condition that typically affects males; however, female carriers can experience mild symptoms without vision loss.\textsuperscript{8} Prevalence ranges from about one in 50,000 to one in 100,000.\textsuperscript{9,10} Initially, patients often report night blindness and poor dark adaptation. A ring scotoma may be observed with visual field testing, and ERG will show rod-cone degeneration. Central macular vision is usually preserved until the fifth or sixth decade of life.\textsuperscript{13}

Leber Congenital Amaurosis

LCA is commonly inherited as an autosomal recessive genetic condition. Prevalence is two to three in 100,000 in the population,\textsuperscript{12} and it comprises 5% of all IRDs.\textsuperscript{14} There are 17 phenotypes of this disease, the most common of which is caused by mutations in the \textit{RPE65} gene. Patients with this type of LCA tend to have the worst vision of all the IRDs.\textsuperscript{14}

Typically, patients with LCA have VA of 20/200 or worse, and can be legally blind for most of their lives. They also tend to have sluggish pupils, photophobia, and nystagmus. LCA can be associated with keratoconus and developmental delay. Upon examination, there is little to no ERG detected in patients with LCA.

Voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) was approved in 2017 for patients with IRDs due to mutations in both copies of the \textit{RPE65} gene. There are clinical trials underway for the treatment of LCA caused by \textit{CEP290} mutations.

Retinitis Pigmentosa

RP is the most common IRD and comprises 40% of all IRDs.\textsuperscript{15} It has a variety of inheritance patterns and can be autosomal recessive, autosomal dominant, or X-linked, the last of which is the most severe form and is only expressed in males.\textsuperscript{4} Patients with RP often experience tunnel vision and poor night vision, especially while driving.\textsuperscript{5} The prevalence is one in 4,000, and 15% of patients have the X-linked variety. RP can be associated with Usher syndrome or Bardet-Biedl syndrome.\textsuperscript{4}

\textbf{WHY GENETIC TESTING & COUNSELING?}

Genetic testing allows us to confirm a patient’s diagnosis and determine whether any systemic problems may be associated with their condition. In turn, the diagnosis can help us better understand the prognosis of their eye disease.

\textbf{AT A GLANCE}

- Optometrists can play a vital role in the diagnosis of inherited retinal disease (IRD) and provide parallel and ongoing vision rehabilitation services and resources.
- Genetic testing can confirm a patient’s diagnosis, establish a pattern of inheritance, and allow patients and practitioners to find available therapies or clinical trials.
- Retinitis pigmentosa is the most common IRD and comprises 40% of all IRDs.
can help us better understand the prognosis of their eye disease.

Genetic testing is also helpful in establishing a pattern of inheritance, or the manner in which a genetic trait is passed on from one generation to the next. This is important when assessing any risk to relatives, which is key if the patient plans on having biological children. By identifying a culprit gene through testing, I can determine whether any clinical trials or FDA-approved therapies could benefit the patient.

Genetic counseling can be critical for many patients. In my department’s retinal dystrophy clinic, we have two full-time genetic counselors who discuss results with patients and their families.

**Commercially Available Genetic Tests and Counseling**

There are two genetic tests commercially available: ID Your IRD (Spark Therapeutics) and the Blueprint Genetics Retinal Dystrophy Panel (Blueprint Genetics, in partnership with The Foundation Fighting Blindness). Both tests take blood, saliva, or buccal samples and can be ordered by any optometrist or ophthalmologist. They evaluate approximately 293 to 300 genes associated with IRDs, and the companies have now shortened their time frames to provide results in as few as 3 weeks. Both companies offer free genetic testing.

**WHAT’S NEXT?**

Once gene testing is done and you’ve identified a patient’s IRD, you can find out whether gene therapy or clinical trials are available. (There is only one FDA-approved gene therapy, voretigene, for LCA RPE65, administered at 10 centers around the world.) All clinical trials can be found at www.clinicaltrials.gov. You’ll also want to provide or refer your patients to low vision rehabilitation and resources.

**Methods of Delivering Gene Therapy**

There are two types of gene therapy: that which replaces, or edits, a gene, and that which suppresses it. If you’re targeting an autosomal dominant gene, you would want to suppress the activity of the mutated gene; with a recessive gene, such as X-linked LCA, you would want to replace or edit it.

There are different ways of delivering therapy, but subretinal injection gets closest to the genes that are affected, versus an intravitreal approach. Intravitreal injections have to pass through the vitreous to get to the retina to be effective, whereas the subretinal space is more accessible. Subretinal and intravitreal delivery both typically use an AAV vector, which allows the vector to replicate inside the patient but does not change the patient’s DNA.

In my team’s retrospective chart review, 23 eyes of 12 patients were treated with voretigene between January 2019 and December 2020. Eight of 12 (67%) patients were male and 10 of 12 (83%) were White. The average age was 10.4 years (standard deviation = 5.5), and the mean follow-up was 278 days (standard deviation = 126). The treatment was well-tolerated and led to improvements in retinal sensitivity and visual field.

For one case, we completed a Goldman visual field out to 180˚, looking for any increase in the visual field to test the effect of the gene therapy. This 11-year-old child had taken quite a few Goldman visual fields in the years with us and has been fairly consistent. She exhibited an approximately 30% increase in the visual field 3 years post gene therapy treatment in a clinical trial, which we considered a significant effect.

**Low Vision Resources**

At the Kellogg Eye Center, our team includes low vision optometrists, an occupational therapist, an orientation mobility specialist, and a social worker. With IRDs affecting many children, these patients are concurrently managed in our low vision clinic and prescribed age-appropriate assistive devices for specific vision demands.
PROVIDE RESOURCES AND HOPE

Patients with IRDs will live with lifelong vision impairment. Gene therapy at this stage is not going to give them normal vision, but it can still be useful in conjunction with low vision rehabilitation and resources, similar to any other medical treatment. That’s why we have to catch these patients early in life, so that they don’t fall behind and are able to maintain independence, remain competitive in school, and have hope of living a productive life. That’s one of the most important roles, for me—to give my patients hope for the future and give their parents the resources they need. Optometrists play a vital role in enabling these patients with parallel and ongoing vision rehabilitation services and resources.


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