

eyeInsights™

# Genetic Therapies for Inherited Retinal Disorders

- IRDs and genetic testing
- Current gene therapies for IRDs
- Access to clinical trials
- Treatment and outcomes



Mass General Brigham  
**Mass Eye and Ear**



Dear Colleagues,

Research in gene augmentation and genome editing for the treatment of inherited retinal disorders (IRDs) is thriving. It is estimated that IRDs affect about 200,000-300,000 people in the United States and 4-6 million people worldwide. Most patients with these conditions become blind by the age of 60, if left untreated.

Therapies being developed and tested at Mass Eye and Ear could help to slow disease progression and potentially even improve vision in these patients. Additionally, with recent advances in genetic testing, we are often able to identify the genes that trigger the diverse genetic conditions responsible for destroying the light-sensing photoreceptors of the retina. These data allow researchers to target specific genes when developing the latest gene therapies and gene-editing treatments.

While gene therapy is not yet widely available for IRDs, researchers are making exciting discoveries, and the future looks more promising than ever before. In this issue of *eye Insights*, we provide a look into current offerings in gene therapy, and a glimpse into the exciting prospects brought forth by clinical trials being led by our own researchers, here at Mass Eye and Ear.

A handwritten signature in black ink that reads "Joan W. Miller". The signature is fluid and cursive.

**Joan W. Miller, MD**

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# IRDs and genetic testing

Inherited retinal disorders are rare, hereditary disorders caused by mutations in genes that encode proteins needed for normal retinal health and function. The first gene associated with retinitis pigmentosa was identified at Mass Eye and Ear in 1990, and since then, over 250 IRD-causing genes have been discovered. Genetic testing is now routinely used to identify the genetic cause of disease in nearly two-thirds of IRD patients. This information has value for understanding a patient's condition, as well as risk to family members. It also provides a therapeutic target: If we know the specific molecular cause of disease, can we design a gene-specific intervention that prevents further retinal degeneration or even improves vision?





# Ask the expert

## Rachel M. Huckfeldt, MD, PhD

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## Gene therapy, gene editing, and IRDs

### Gene-augmentation therapy

Gene therapy typically refers to gene-augmentation therapy. In this approach, a healthy version of the mutated gene is packaged inside an engineered and nonpathogenic form of adeno-associated virus (AAV), with the virus serving as a vector to carry the gene. AAV does not cause disease in humans. The primary delivery method at this time is by the subretinal injection of a small volume of the gene-containing AAV during a vitrectomy. The virus is then in an optimal location to deliver its cargo—the healthy gene—to retinal cells, thus enabling synthesis of normal protein.

Gene-augmentation therapy is an appropriate strategy when genetic mutations result in absent or diminished protein function. In contrast, if a genetic mutation results in a protein that is toxic or damaging to the retina, then adding normal copies of the gene may not help.

We hope that both of these DNA-targeting therapies will have durable effects over time.

In addition, some genes are too large to package into viruses. Genome editing, or gene-editing, offers a solution in these scenarios.

### Gene editing

The discovery of the CRISPR/Cas9 system, which was adapted from a bacterial defense system in the early 2010s, paved the way for current genome-editing strategies. This system allows the targeting of specific sequences of DNA to correct errors in the genetic sequence, remove segments of a gene that result in dysfunctional protein, or selectively disable a mutated copy of a gene. Like gene-augmentation therapy, the components of the CRISPR/Cas9 system can be packaged into AAVs and delivered by a subretinal injection during vitrectomy. In contrast to gene-augmentation therapy, CRISPR/Cas9 genome editing is specific not only to a particular gene, but also to certain mutations in that gene.

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A third category of therapy is antisense oligonucleotides. These drugs target RNA, which is the intermediary between DNA and protein. These drugs are injected into the vitreous and have the potential to address some of the same types of scenarios as genome editing, but repeated ongoing treatment will be required if this method is successful.

# Current gene therapies for IRDs

The first gene-augmentation therapy for an IRD was approved by the U.S. Food and Drug Administration (FDA) in December 2017 after nearly two decades of development in preclinical models and clinical trials. The drug, known as Luxturna®, is for individuals with autosomal recessive retinal dystrophies resulting from mutations in the gene RPE65.

Genetic testing and clinical testing are needed before treatment to confirm that individuals are eligible. Luxturna® is available at a limited number of centers in the United States, including Mass Eye and Ear as well as a steadily increasing number of locations internationally.

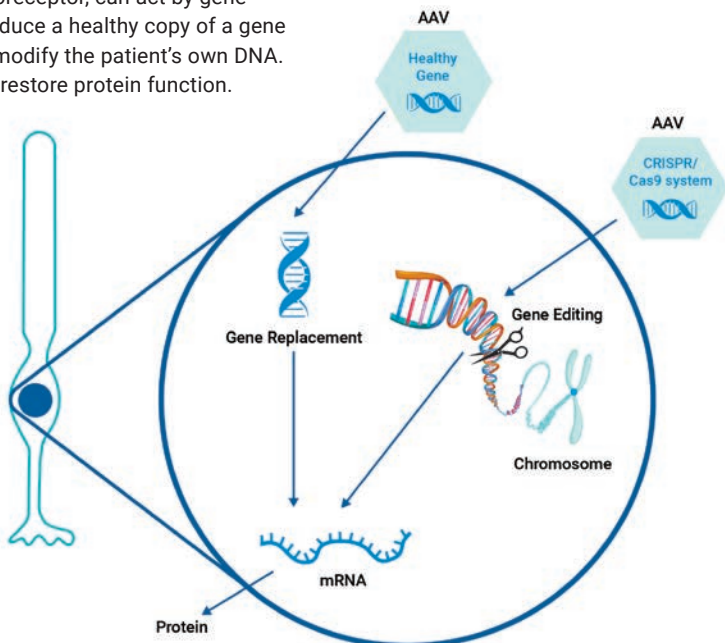
## Access to clinical trials

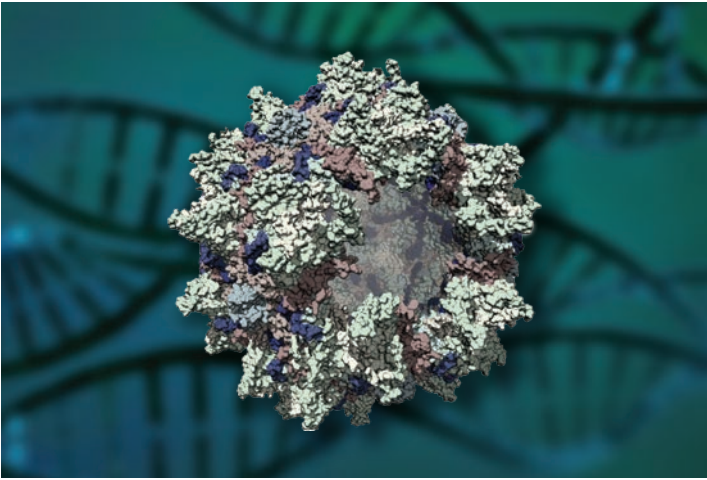
An expanding number of genetic therapies for IRDs are currently being tested in clinical trials including many that are ongoing at Mass Eye and Ear and at Boston Children's

Hospital. Many of these trials are still in early first-in-human phase 1 and 2 stages in which establishing safety is the primary goal, although efficacy is always being considered as well. A few studies have proceeded to phase 3 trials that enroll a larger number of patients. Most of the trials currently underway are using gene-augmentation approaches, but a trial at Mass Eye and Ear and other sites is assessing CRISPR/Cas9 genome editing. A smaller number of trials are also assessing antisense oligonucleotides.

A first step for individuals with IRDs who are interested in their eligibility for clinical trials of gene-specific therapies is establishing a genetic diagnosis. For individuals with mutations in genes that are currently being assessed in clinical trials, clinical evaluation is also needed to assess whether other aspects of eligibility are met.

**FIGURE 1** Gene therapies, shown here acting in the nucleus of a photoreceptor, can act by gene-augmentation to introduce a healthy copy of a gene or by gene editing to modify the patient's own DNA. Both approaches can restore protein function.





**LEFT** Image of an Adeno-Associated Virus (AAV) Credit: Brian Zinn, PhD, Vandenberghe Laboratory for Gene Therapy

## Treatment and outcomes for IRDs

Until the approval of Luxturna®, there were no definitive treatments for any IRDs. Today, with the success of Luxturna®, preliminary results from therapies currently under investigation, and an expanding therapeutic toolkit, we have good reason for optimism. We envision a future in which gene-specific therapies allow a growing number of individuals with IRDs to maintain and potentially improve their vision.

Even with this optimism, however, continuing current efforts into other

treatment strategies is important.

We also want to continue to develop therapies that can help individuals for whom identifying a genetic disease is more challenging, or, those at a stage of disease where genetic therapy is not the best solution. We hope that ongoing research into gene-agnostic neuroprotective agents, stem cells, and light restoration therapies, including optogenetics and retinal prostheses will also result in new therapies and better outcomes for patients with IRDs and other retinal disorders.

## Gene therapy for other ophthalmic conditions

Advances in the future may include viral vectors, non-viral vectors, and delivery methods that allow treatment of a greater retinal expanse and an expanded approach to technical challenges related to gene size and disease mechanisms. Genetic therapies for non-retinal ophthalmic diseases are also being tested with gene-augmentation therapy for Leber hereditary optic neuropathy as one example.

Efforts are also underway to develop genetic therapies for ophthalmic conditions with multifactorial causation such as age-related macular degeneration (AMD). Rather than targeting a specific disease-causing gene, as can be done for IRDs, gene therapies in this scenario are used to increase the levels of proteins that may reduce or alter disease progression. Clinical trials of genetic therapies for wet and dry AMD are currently underway.

# Applications to other diseases

The same types of genetic strategies currently being tested for IRDs are also being tested and beginning to receive regulatory approvals in other areas of medicine. For example, the FDA has approved both gene-augmentation therapy and antisense oligonucleotide therapy for a specific type of the hereditary degenerative disease spinal muscular atrophy.

Genetic strategies are also being used for ex vivo (outside the body) treatment in conditions like sickle cell anemia and blood cancers. In these diseases, the target cell type is removed from the body and treated in a laboratory so that it expresses the therapeutic gene before being returned to the patient. In the years ahead, genetic therapies are likely to become a facet of care throughout the field of medicine.

## Referral guidelines

Genetic testing accompanied by genetic counseling, as well as clinical evaluation by an ophthalmologist knowledgeable about retinal dystrophies, is advised for individuals suspected or known to have a retinal dystrophy. Genetic testing has become increasingly accessible in recent years in large part due to sponsored programs that provide free testing. Individuals with genetic results that make them eligible to receive Luxturna® should be referred to one of the specialized treatment centers like Mass Eye and Ear that are able to administer this gene therapy for further evaluation and potential treatment.

### Further reading

Botto et al. Early and late stage gene therapy interventions for inherited retinal degenerations. *Prog Retina Eye Res.* 2021 May 29; 100975.

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