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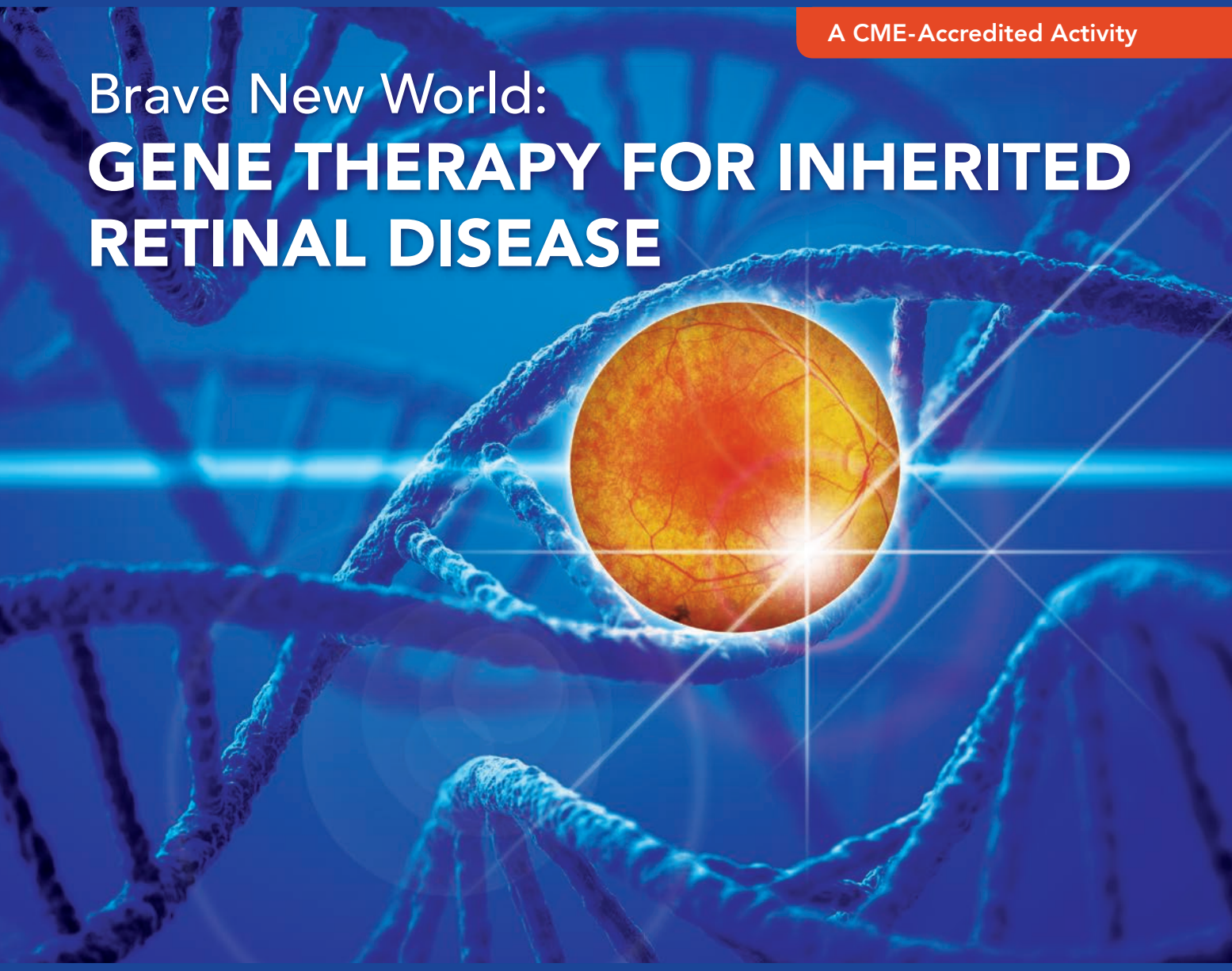
A CME-Accredited Activity

Brave New World:
GENE THERAPY FOR INHERITED RETINAL DISEASE



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Learning Objectives

After participating in this activity, participants will be better able to demonstrate the ability to:

- Recognize the urgency of early and accurate genetic diagnosis in IRD
- Discuss the challenges of living with an IRD, including impact on functional vision and quality of life
- Describe the variety of approaches to gene therapy, including current and emerging treatment options for IRD
- Summarize the safety and efficacy of investigational IRD gene therapies
- Design a patient-centered approach to the diagnosis and management of IRD

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Introduction

Inherited retinal diseases (IRDs) are a class of rare, single-gene disorders that represent the major cause of familial blindness in the Western world and, until recently, have been untreatable.[1] The recent approval of the first gene therapy for IRD, voretigene neparvovec for retinal dystrophies caused by biallelic *RPE65* mutations, and the growing number of active clinical gene therapy trials for other IRDs signal the dawn of a new era in caring for patients with IRDs. For the first time, ophthalmologists can offer hope.

Few natural history studies have been completed for IRDs, resulting in a lack of information regarding disease course and outcomes.[2-6] This limited information combined with a lack of direct experience with IRD patients results in limited understanding of the extent to which disease progression affects a patient's daily activities, or how even small improvements in functional vision can translate to significant gains in quality of life. One in-depth study showed that patients with retinitis pigmentosa (RP) have significant difficulties adjusting to blindness across multiple psychosocial domains, including distressed relationships with healthcare professionals and family members, poor ability to adjust at work or school, and impaired participation in social activities.[7] Such patients also have high levels of depression, anxiety, and isolation.[8] Additionally, 60-70% of blind Americans are unemployed, while almost 30% live below the poverty line.[9,10] Only 15% earn a bachelor's degree or higher.[9] Therefore, career limitations and unemployment are major psychological stressors for IRD patients.[7] It is critical for physicians to understand the functional impact that gene therapy can have on a patient's life. Although perfect vision may not be restored with treatment, any visual acuity, visual field, and/or light sensitivity that is retained or improved is significant and may ameliorate some of the psychosocial impacts of progressive vision loss.

In this supplement, we present updated guidelines for diagnosis, referral patterns, and treatment—all of which have changed dramatically in the past year. While it is impossible to provide a comprehensive text on this huge and rapidly evolving subject in such limited space, our goal is to present a common-sense approach to IRD management that can be used in every eye care setting to optimize outcomes for patients. For all of us—clinicians and patients alike—it is, indeed, a brave new world. – ***Bart P. Leroy, MD, PhD***

Inherited Retinal Disease Overview

Collectively, IRDs are blinding conditions affecting approximately 200,000 people in the US, often presenting in childhood and persisting for life.[11,12] In addition to severe vision loss, an IRD may be part of a systemic syndrome, possibly as the first presenting feature, requiring timely diagnosis and appropriate multidisciplinary management for the patient's optimal health and development.[12]

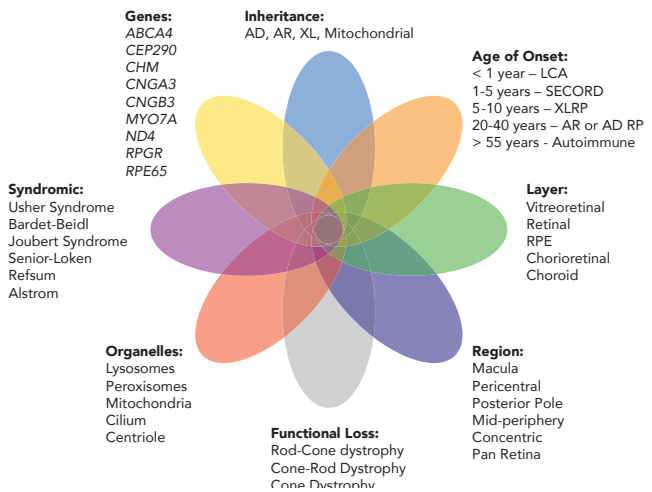
Classification of Inherited Retinal Disease

The IRD spectrum may be described in a variety of overlapping ways, including the type of functional loss, region or layer of the retina affected, inheritance, progressive nature, etc., as shown in **Figure 1**. As we will see, these classifications are useful in reaching a clinical diagnosis, but ultimately, all clinical descriptions must lead to genetic testing for definitive diagnosis.

To date, more than 260 genes causing IRDs have been identified and another 37 have been mapped to a chromosomal location with gene identification in progress.[13] The pace of discovery has been rapid, with approximately 50 genes identified every four years over the last two decades. [13] However, mutations in the same gene can cause a range of clinical presentations, or phenotypes, whereas similar phenotypes can result from abnormalities in one of many different genes.[13,14] Therefore, a clear one-to-one genotype-phenotype correlation is rare in this group of diseases, which is currently considered the most genetically heterogeneous in humans.[11,13,14] For this reason, a clinical diagnosis in the absence of genetic testing is incomplete.

FIGURE 1

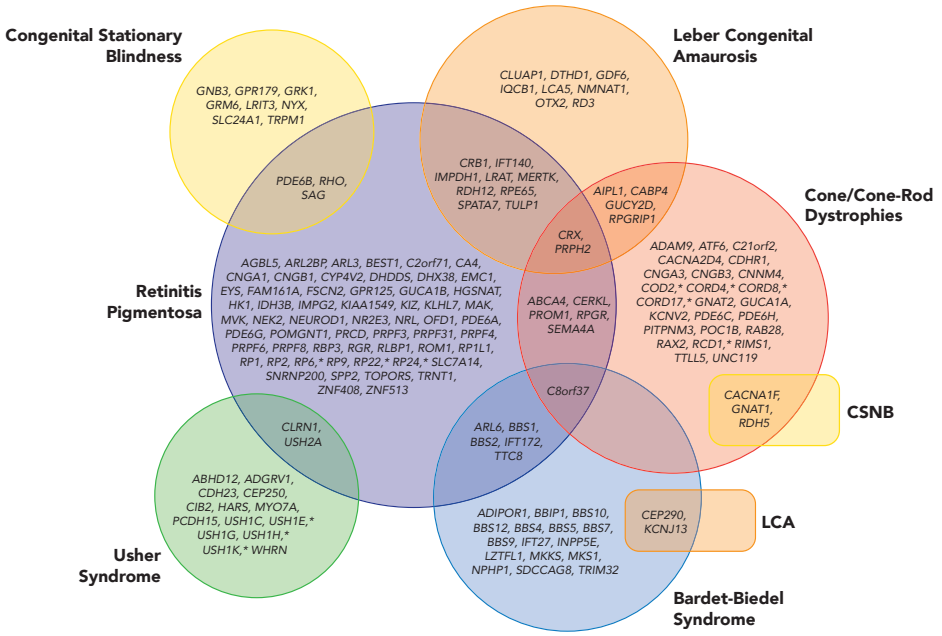
The Spectrum of Inherited Retinal Disease



While a genetic diagnosis is now recommended for all IRDs, the clinical description remains an important first step in focusing genetic testing. As current gene screening techniques often identify multiple potentially causative changes, these always need to be interpreted in a clinical context. Consequently, it is essential that clinicians recognize the various categories of IRDs. However, the complexity of clinical diagnoses (**Table 1**) may be overwhelming to most physicians, especially considering that IRDs are rare. The

FIGURE 2

Genetic and Clinical Diversity of Mutations Associated with Retinitis Pigmentosa



gene most commonly mutated is the *ABCA4* gene. Biallelic mutations in this gene cause Stargardt disease, with an estimated 400 new cases per year in the US.[15] In comparison, mutations in most other IRD-associated genes cause fewer than 100 new cases per year.[15] The majority of patients experiencing visual impairment due to an undiagnosed IRD are initially seen by a pediatrician, optometrist, or general ophthalmologist.[16,17] Most of these physicians have little or no direct experience with the diagnosis or management of IRDs, which leads to multiple rounds of referrals and variable patient access to specialist services.[16] As a result, rare-disease patients such as these see up to 8 physicians and receive 2 to 3 misdiagnoses over the course of 5-7 years before receiving a correct diagnosis.[8] Eliminating or reducing this delay in reaching an accurate and complete diagnosis may prevent irreparable vision loss, lost opportunities to receive current and emerging treatments and access to early intervention services, and harm to a patient's general health and development if the IRD is associated with a systemic

TABLE 1

Clinical Classification of Inherited Retinal Disease

Retinal Degeneration
Abnormal Full Field ERG

Progressive

Nonsyndromic RP
- Rod-cone Dystrophies
- Cone-rod Dystrophies
- Cone Dystrophies

Leber Congenital Amaurosis
SECORD/Jevenile RP
X-Linked RP
AR RP
AD RP

Syndromic RP
Ciliopathies
- Usher Syndrome
- Bardet-Biedl Syndromes
- Joubert Syndrome
- Senior Loken Syndrome
- Alström Syndrome

Mitochondrial Disorders
- Kearns-Sayre Syndrome, etc.

Peroxisomal Disorders
- Zellweger Spectrum, etc.

Lysosomal Storage Disorders
- Hurler, Hurler-Scheie, Scheie Disease, etc.

Spinocerebellar Ataxia 7
Neuronal Ceroid Lipofuscinoses
- *CLN3*-Related, etc.

Choroidal Degenerations
Choroideremia
Gyrate Atrophy
Bietti Crystalline Dystrophy
Late Onset Retinal Dystrophy

Stationary

Cone Dysfunction Syndromes
- Achromatopsia
- Oligocone Trichromacy
- Blue Cone Monochromacy
- Enhanced S-cone Syndrome
- Bradyopsia

Rod System Function Disorders
- Congenital Stationary Night Blindness
  - **ERG Patterns**
    Schubert-Bornschein, Riggs, etc.
  - **Genes**
    AD: *GNAT1, RHO, PDE6B*
    XL: *NYX , CACNA1F*
    AR: *GRM6, TRPM1, LRIT1*, etc.
- Fundus albipunctata (*RDHS*)
- Oguchi Disease (*ARR, GRK1*)

X-Linked Retinoschisis

Fleck Dystrophies
- Benign Familial Flecked Retina
- Retinitis Punctata Albescens
- Alport

Macular Degeneration
Normal Full Field ERG

Progressive

***ABCA4* Spectrum**
Stargardt/Fundus Flavimaculatus
- Macular Dysfunction
- Peripheral Cone
- Peripheral Rod/Cone

Bestrophinopathies *(BEST1)*
- AD Best Vitelliform Macular Dystrophy
- AR Best Vitelliform Macular Dystrophy
- AR Bestrophinopathy
- AD VitreoRetinoChoroidopathy

***PRPH2* Spectrum**
- Pattern Dystrophy
- Central Areolar Choroidal Dystrophy

***EFEMP1* Spectrum**
Dominant Drusen
Doyne Honeycomb Dystrophy
Malattia Levintenese

Sorsby Macular Dystrophy

Occult Macular Dystrophy

Stationary

North Carolina Macular Dystrophy

Isolated Foveal Hypoplasia

Albinism
- Oculocutaneous Albinism
- Ocular Albinism

syndrome. In addition, significant reduction in anxiety is the result of an early diagnosis. For this reason, we present a simplified approach to evaluation of these diseases.

Photoreceptor Diseases

Nearly two-thirds of IRDs are photoreceptor diseases.[15] Classically, these were described as rod-mediated and cone-mediated diseases, but this sharp distinction has been discarded. Some conditions are progressive and are called dystrophies, while others are mostly stationary.

In most, if not all, photoreceptor dystrophies, the function of both rod and cone systems is compromised, sometimes in the early stages of the disease. Photoreceptor dystrophies comprise a spectrum of diseases, ranging from predominantly rod dystrophies to predominantly cone dystrophies, with disorders intermediate between the two having varying involvement of both systems.[18] Therefore, these are more properly called generalized photoreceptor IRDs of the rod-cone, cone-rod, or cone types.[18]

The most common clinical subgroup among all generalized, progressive photoreceptor IRDs is RP, a diverse group of peripheral retinal dystrophies affecting photoreceptors and the retinal pigment epithelium (RPE). In general, RP is characterized by reduced sensitivity to light resulting in night blindness—causing difficulty navigating in moderately low light—and delayed dark adaptation, followed by a progressive loss of peripheral visual fields (VFs), and, eventually, reduction of best-corrected visual acuity (BCVA) in many cases. Patients with RP lose 5%-10% of their remaining VF every year once the disease process has begun,[19-21] approximately 50% every 5 years. RP is also the most genetically diverse subgroup of IRD, with disease-causing mutations in more than 100 genes despite similar clinical presentations (**Figure 2**).[1,13] Likewise, mutations in one of these genes may cause a range of clinical presentations, as demonstrated in a recent natural history study reporting over 20 distinct clinical diagnoses for autosomal recessive *RPE65* mutations.[2] In fact, the clinical findings of most IRDs are rarely pathognomonic of a single genetic mutation, with few exceptions. This lack of genotype-phenotype correlations is one of the most critical factors driving change in the IRD diagnostic pathway. Clinical descriptions, such as RP, are no longer considered final diagnoses; they are now merely the first step toward a definitive genetic diagnosis via molecular testing.

Retinal vs. Macular Classification

It is helpful to use practical, broad categories based on clinical presentation. For example, does the IRD primarily affect the entire retina or only the macula? One study at a tertiary care IRD subspecialty practice reported that 65% of IRDs are generalized photoreceptor diseases and another 28% are localized, macular dystrophies.[15] The ocular history is useful for differentiation here, as the vast majority of retinal IRD is of the rod-cone type,[15] typically presenting with night blindness (nyctalopia) and constricted VFs. On the other hand, macular IRDs present with reduced central vision, color vision abnormalities, and variable degrees of photophobia and nystagmus.

Family history is also very useful to learn, whether other family members have had similar symptoms, at what age, and whether these were progressive.

Fundus appearance may be helpful, such as the bone-spicule appearance classically associated with retinal IRD such as RP, or the pisciform flecks associated with the most frequent macular IRD, *ABCA4*-related Stargardt disease (**Figure 3**). However, it is important to know that many IRD cases do not have these classic textbook findings, so one must be aware of more subtle fundus abnormalities. In fact, some cases of IRD have no visible fundus abnormalities at all in the early stages. For this reason, any patient suspected of having an IRD must undergo further workup, including additional imaging and functional testing.

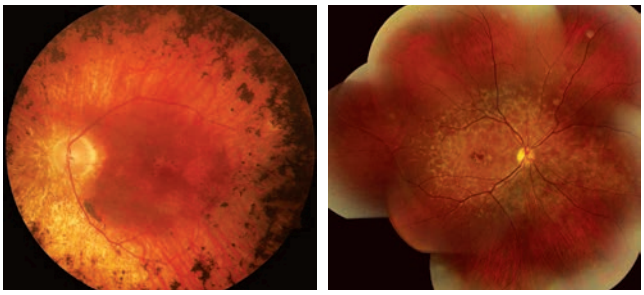
Useful forms of imaging for the evaluation of IRD include color fundus photos, spectral domain ocular coherence tomography (SD-OCT), fundus autofluorescence, and reflectance imaging with blue and near-infrared light. In addition, formal VF testing—including kinetic fields, microperimetry, and, in some cases, static VF evaluation—is essential whenever possible. Electroretinography (ERG) is particularly important in differentiating forms of IRD. The full-field flash ERG will be abnormal in generalized retinal disease, but not in disease limited to the macula. Many forms of IRD have a distinct pattern on ERG, making this test indispensable in the evaluation of these patients. However, an ERG must be performed according to internationally accepted International Society for Clinical Elec-

LACK OF GENOTYPE-PHENOTYPE CORRELATIONS IN IRD

- Clinical findings of most IRDs are rarely pathognomonic of a particular genetic mutation.
- A given genetic mutation may result in a variety of clinical IRD presentations.
- One phenotype may be caused by mutations in a variety of genes.

FIGURE 3

Differentiation of Retinal and Macular IRD



A. Bone-spicule fundus appearance in RP, a generalized photoreceptor IRD

B. Fundus changes due to *ABCA4*-related Stargardt macular dystrophy

trophysiology of Vision (ISCEV) standards and interpreted properly for accurate results.[22] While detailed knowledge of each subcategory of IRD and the associated test results is commendable, it is not necessary for most eye care professionals. Instead, the best way to ensure optimal outcomes for these patients is to consider the possibility of an IRD, order a workup commensurate with your expertise and availability of tests, and, most importantly, make a prompt referral to an IRD specialist for further evaluation, genetic testing, and potential treatment.

Progressive vs. Non-Progressive IRDs

As mentioned above, it is important to distinguish whether an IRD is progressive or stable. Some IRDs, such as congenital stationary night blindness (CSNB) and achromatopsia, are either non-progressive or only minimally progressive, and therefore have a better prognosis than IRDs that inexorably progress to complete blindness. However, their clinical presentations often mimic those of progressive IRDs, making it challenging to distinguish progressive from non-progressive diseases.[12] For example, CSNB is characterized by night blindness similar to a rod-cone IRD, and achromatopsia is often mistaken for a progressive cone-rod dystrophy. In addition, progression of high myopia in some IRDs may be mistaken for progression of the disease, adding to the confusion. Misdiagnosis is particularly common in cases where an ERG has not been performed or has been misinterpreted, resulting in unnecessary anguish for patients and their parents who have been told to prepare for eventual blindness. This is another crucial reason for consulting an IRD specialist as soon as an IRD is suspected, so that progressive IRDs may be differentiated from non-progressive conditions with rod and/or cone system dysfunction.

Chorioretinopathies

Another category of IRD involves the choroid in addition to the retina. Chorioretinopathies often have distinct appearances with loss of choroidal vessels and RPE, although this is not always the case, especially early in the disease course. For example, choroideremia is often mistaken for RP. However, choroideremia is an X-linked disease while RP may be autosomal recessive, autosomal dominant, or X-linked. Misdiagnosis may therefore have implications in terms of family planning.

Age of Onset

Historically, age of onset has been a major feature in the clinical classification of IRDs. For example, in the spectrum of rod-cone dystrophies, infants presenting with nystagmus, failure to fix and follow, and non-recordable ERGs were diagnosed with Leber congenital amaurosis (LCA) while adults with nyctalopia, peripheral VF loss, peripheral retinal abnormalities, and abnormal scotopic ERGs were diagnosed with RP. Children with similar signs and symptoms received a diagnosis of early onset RP. However, the clinical classifications have progressively lost importance with the advent of the molecular era.

ENSURING OPTIMAL OUTCOMES FOR PATIENTS WITH IRD

- Awareness of IRD clinical spectrum
- Order workup
  - Commensurate with local physician's expertise
  - Based on local availability
- Prompt referral to IRD specialist for further evaluation, genetic testing, and potential treatment

Indeed, mutations in one of several genes, including *RPE65*, *LRAT*, *MERTK*, *SPATA7*, and *TULP1* may cause rod-cone dystrophy with onset from birth to early adulthood (**Figure 2**), limiting the usefulness of age of onset for diagnosis.[23-28] While a clinical classification is not completely out of date, a more modern one is based on genotypes, accommodating the diversity of phenotypes related to mutations in genes implicated in IRD. For example, in a retrospective natural history study of 70 patients with biallelic *RPE65* mutations, over 20 distinct clinical diagnoses were used at the patients' first visits, which occurred from 1 to 43 years of age.[2] Nine patients had clinical diagnoses of both Leber congenital amaurosis (LCA) and RP over the course of their follow-up. Clearly, then, clinical diagnoses alone may be misleading, with genetic testing required for a more accurate diagnosis. Furthermore, genetic testing can distinguish LCA from achromatopsia, albinism, CSNB and syndromic disease, all of which may be clinically similar at their onset but have markedly different prognoses for visual function.[39]

Syndromic IRDs

The importance of recognizing systemic disease associated with a rod-cone IRD cannot be overstated. Again, it is the genetic analysis that will help in making an early, specific diagnosis. In general, genetic mutations that result in abnormalities of cellular organelles common to retinal and non-ocular cells cause syndromic IRDs. For example, Usher syndrome, familiar to all eye care professionals, describes a group of autosomal recessive conditions characterized by rod-cone dystrophy and partial or complete congenital sensorineural hearing loss.[40] In some subtypes, vestibular function is also abnormal. The affected organelles are the specialized cilia in the photoreceptors and in the hair cells of the inner ear.

Usher syndrome is now recognized early because many, if not all, children with congenital sensorineural hearing loss are screened for mutations in genes involved in genetically determined deafness. At a minimum, they are screened for retinal involvement annually. However, an IRD may be the first presenting feature of other ciliopathies, including Joubert syndrome and Senior-Loken syndrome, requiring magnetic resonance imaging (MRI) of the brain and kidney function testing. Likewise, Bardet-Biedl syndrome is another ciliopathy that causes renal insufficiency. Therefore, it is imperative to reach a conclusive genetic diagnosis as quickly as possible to

guide systemic evaluation and treatment.

Peroxisomal disorders are another category of syndromic IRD, with severe deficiency of one or more of nearly 50 biochemical reactions that take place in peroxisomes. Peroxisomal syndromes range from the severe systemic involvement and infant mortality of Zellweger syndrome to single protein or enzyme abnormalities such as adult-type Refsum disease, associated with serious neurologic and cardiac dysfunction in adulthood.[41] Some aspects of peroxisomal disorders, such as the accumulation of phytanic acid in Refsum disease, are managed with dietary modifications, while others, like the adrenal insufficiency associated with X-linked adrenoleukodystrophy, are treatable with medications.

While some IRD-associated syndromes present with dysmorphic features that signal a systemic disorder, many present only as an IRD. For example, *CLN3*-related neuronal ceroid lipofuscinosis, previously known as Batten disease, is often only recognized after an initial diagnosis of a retinal dystrophy. In this syndrome, vision loss is often the first presenting symptom, and patients are frequently misdiagnosed with Stargardt disease, although ERG may differentiate between the two. Subsequent progressive mental and neuromotor degeneration follow, very often ending in early death.[42] However, isolated retinal dystrophies due to specific mutations in *CLN* genes have recently been described, further illustrating the need for accurate genotyping. Therefore, the best method of detecting or ruling out systemic involvement is through early, appropriate genetic testing, as the majority of genetic mutations mediating syndromes have been identified.

Genetic Testing Is Required for Accurate, Complete IRD Diagnosis

As discussed, a variety of clinical diagnoses may be used to describe a single genetic mutation (e.g., *ABCA4* and *RPE65*), and numerous mutations may cause a "single" clinical diagnosis (e.g., RP) due to a lack of strict genotype-phenotype correlations.[1,12,43] For this reason, genetic testing is the only accurate way to make a specific diagnosis. American Academy of Ophthalmology (AAO) guidelines now state that genetic testing is required to pinpoint the causative mutation of IRDs, thereby directing disease management, defining prognosis, informing genetic counselling and family planning, and helping identify those for whom gene-based or other therapies might be appropriate.[44-46] However, the outdated concept that IRDs are untreatable has presented a huge obstacle for patient access to genetic testing. With the availability of numerous clinical trials and the recent approval of voretigene neparvovec,[47] there is an urgent need to reduce the time from onset of symptoms to genotyping in order to identify patients who can benefit from gene therapy treatments.[48]

In IRDs without current options for gene-based treatments, genetic testing may still direct medical management in meaningful ways and help to better understand disease mechanisms in preparation for future therapy. For example, a genetic diagnosis may sometimes reduce the need for additional electrophysiologic testing, clarify the need for evaluation for syndromic disease, and determine when to change medications and supplements, such as the avoidance of supplemental vitamin A in *ABCA4*-macular dystrophy.[49] Furthermore, a genetic IRD diagnosis is irrefutable evidence to a school district that a child needs educational accommodations that may otherwise be denied. In addition, better insight into inheritance risk and family planning, including planning of prenatal or pre-implantation diagnosis, are directly dependent on an accurate genetic diagnosis.

GENETIC TESTING OPTIONS

- Single gene
- Gene panel, grouped by clinical diagnosis
- Whole Exome Sequencing (WES)
- Whole Genome Sequencing (WGS)

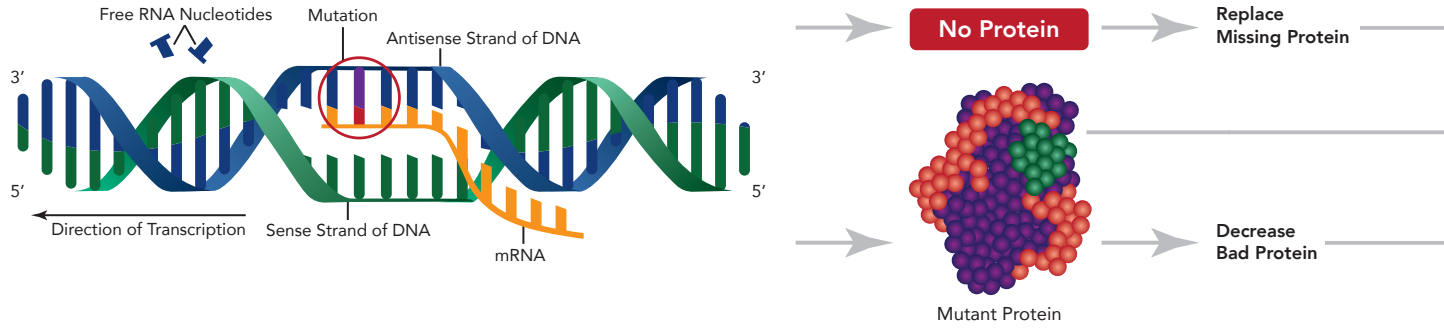
Genetic Testing Options: Selecting the Appropriate Genetic Test

After providing accurate clinical input to guide genetic testing, a clinician's diagnostic work is not finished. Selecting the appropriate test is the next step. However, genetic testing, particularly in a genetically diverse set of diseases such as IRD, is not as straightforward as ordering a complete blood count (CBC). In recent years, IRD genetic testing options have expanded to include numerous choices, including single-gene testing, gene-panel tests that include multiple IRD genes grouped by clinical diagnosis, whole-exome sequencing (WES, all coding portions of DNA sequenced), and whole-genome sequencing (WGS, all coding and non-coding DNA sequenced).[1,44] All of these options except single-gene testing employ next-generation sequencing (NGS), the use of parallel sequencing of millions of short segments of DNA that are then matched with a human reference genome using bioinformatics. Unexpected DNA variations are then reported. NGS has revolutionized genetic testing, reducing cost and time, so that it is now possible to sequence an entire human genome within a day.[50] However, NGS testing is not sensitive at picking up large deletions or duplications, so some alleles can be missed.

Experts recommend ordering the most specific test available given the patient's clinical findings to avoid the financial and emotional cost of discovering unrelated IRD-causing mutations and so-called variants of unknown significance (VUS).[46,51] To avoid this and simultaneously control costs, some researchers have developed algorithms for tiered testing guided by clinical diagnosis, although this can prolong the wait for results.[12,15,51] On the other hand, in patients with clinically hard-to-distinguish cases, sequencing a larger set of retinal disorder-related genes can increase the chance of identifying the genetic cause.[52] This should be reserved for times when an IRD expert cannot pinpoint the phenotype well enough to order a narrower panel, for an important reason: WES may

FIGURE 4

What is Gene Therapy?



reveal several potential inherited eye disease-causing mutations per patient, challenging even the most experienced IRD specialist to make a diagnosis when interpreting these results. Furthermore, whole-exome results may reveal other mutations with serious health implications, such as predisposition to cancers or neurodegenerative disease.[48] Therefore, although WES is certainly gaining traction as the go-to technology, interpretation of its results often requires input from an IRD expert. For the same reasons, genetic counseling may be extremely helpful for these families. Additionally, testing may be determined by the patient's insurance and by what the family can afford. When comprehensive testing is financially prohibitive for some families in the US, initial research testing may be an affordable option to help identify a gene of interest, since only confirmation testing of mutation(s) in a single gene is required.

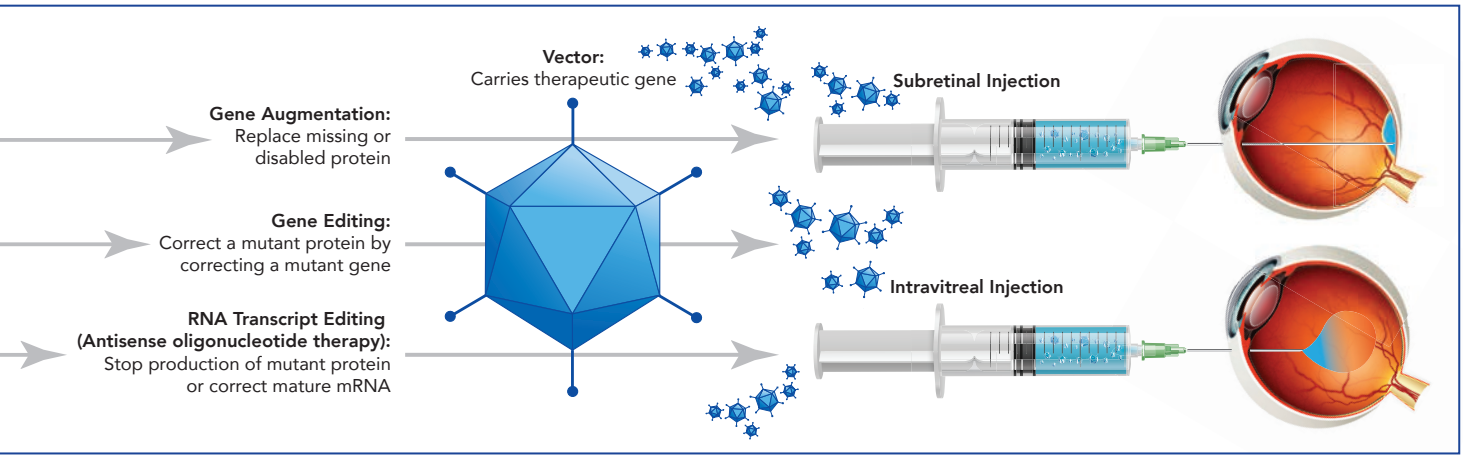
The vast majority of ophthalmologists do not have training in choosing among these genetic testing options. A medical geneticist, a genetic counselor with expertise in ocular disease, and/or an IRD specialist can help determine the best genetic test to use, based on current test methodology, the number of genes to be tested, detection rate, price of the test, and potential insurance reimbursement. IRD specialists are best positioned to provide this service in concert with genetic counselors, but there are only 68 members of the International Society of Genetic Eye Disease and Retinoblastoma worldwide.[53] Therefore, it becomes incumbent upon every ophthalmologist and optometrist to familiarize themselves with genetic testing for IRDs, if only to expedite referral to one of these experts. It is also important to identify genetic counselors with the appropriate expertise to assist in managing these patients, and for genetic counselors themselves to expand their knowledge of IRD genetic testing options. The Genetic Testing Registry website (**https://www.ncbi.nlm.nih.gov/gtr/**) is a helpful resource for identifying available genetic tests and associated laboratories for IRDs as well as other genetic conditions.

Interpretation of Genetic Test Results

Unlike the straightforward interpretation of most lab tests, genetic test results—the genotype—must always be carefully evaluated in the context of the clinical phenotype to avoid errors in diagnosis.[15,16] Results may be inconclusive, often revealing sequence VUS that may or may not be pathogenic. Terminology describing these variants has been confusing, prompting recommendations for classifying and labeling them.[54] In these inconclusive cases, interpretation requires a level of expertise that is lacking in most ophthalmologists because only a few US board-certified ophthalmologists are also board certified as medical geneticists by the American Board of Medical Genetics.[16,55] While a brief CME program could never substitute for a one- or two-year fellowship in medical genetics, it is critical to recognize the sometimes-inconclusive nature of genetic test results and the related need to identify appropriate ocular geneticists and genetic counselors for consultation. Otherwise, ophthalmologists risk misdiagnosis, which can cause irreparable harm to patients. A causative mutation can be identified in up to 60%-80% of patients with IRDs.[15,44]

Genetic Counseling in IRD

Genetic counseling should be provided before IRD genetic testing is ordered and after results are obtained, according to the AAO Recommendations on Clinical Assessment of Patients with Inherited Retinal Degenerations 2016, AAO Recommendations for Genetic Testing of Inherited Eye Diseases 2014, and others.[44,46,55] This can take place in the physician's office if the physician employs a genetic counselor or is qualified to provide this service (although few are). Otherwise, a referral to a clinical geneticist or an in-person or telephone-based genetic counselor with expertise in genetically determined eye disorders is required. Prior to genetic testing, genetic counselors collect detailed family histories, draw pedigrees, provide genetic and prognostic counseling, and review molecular testing options, implications, and limitations with patients. Genetic counselors review genetic variants in test reports and research their potential contribution to disease. Following genetic testing, genetic counselors may coordinate additional testing of family members, enroll the patient in research or patient registries and discuss clinical trials.[44] They may also provide support for pa-



tients who are disappointed to learn that the test results are negative, meaning that treatment is not available to them currently.[49]

As we have seen, most ophthalmologists are not qualified to offer these complex and time-consuming services, and therefore need to collaborate with a genetic counselor trained in ocular genetics and/or an ocular geneticist. A recent study showed that 92% of patients with RP desire genetic counseling, demonstrating its value to patients.[56] However, lack of access to a qualified genetic counselor due to availability or insurance coverage is a significant barrier to proper diagnosis and management of IRDs.

Gene Therapy for IRD

The ultimate purpose of genetic testing is not only accurate diagnosis, prognosis, family planning, research, etc., but also treatment. Prior to the possibility of gene therapy, physicians were taught to avoid the potential harm of ordering genetic testing for untreatable diseases. For this reason, the growing availability of treatment for IRDs will be the most powerful motivating factor for the widespread adaptation of genetic testing of these diseases.

As gene mapping for IRDs has exploded, the possibility of gene therapy has become a reality. Many patients with these monogenic diseases are excellent candidates for gene therapy. The most advanced gene therapy, voretigene neparvovec, has been approved by the US Food and Drug Administration (FDA) as the first gene therapy for an inherited disease (*RPE65* mutation-associated IRD).[47] Numerous other gene therapies are also under development for IRDs such as Stargardt disease, Usher syndrome Type 1B, *RPGR*-related X-linked RP, LCA, X-linked retinoschisis, choroideremia, Leber hereditary optic neuropathy (LHON), and achromatopsia.[28] As these treatments become available in clinical trials and commercially, there is an urgent need to reduce the time from onset of symptoms to accurate diagnosis with genotyping in order to identify patients who would benefit from gene therapies.

Before discussing gene therapy programs for individual IRDs, it is useful to understand the concepts of gene therapy itself. This is not a one-size-fits-all approach to treatment, but rather, a number of highly diverse technologies that address strategies for gene augmentation, antisense oligonucleotides (AON), gene silencing, and genome editing. Each type of therapy has its own distinct mechanism, and the availability of clinical safety and efficacy data is highly variable. With the wide array of gene therapy technologies being developed and the rapid pace at which genomic medicine is advancing, it is critical to understand that each genetic therapeutic, even within the same category (e.g., gene augmentation therapy), is unique.

In order to understand gene therapy, a brief review of basic genetics is in order. DNA contains the coding sequences, or genes, for every protein needed in the body, arranged in 23 pairs of chromosomes found in every human cell. When a protein is needed, DNA unwinds and is transcribed into messenger RNA (mRNA), which subsequently undergoes maturation through splicing (the cellular mechanism of cutting out non-coding sequences called introns and keeping the needed coding sequences, called exons). Mature mRNA then carries the "sense" genetic instructions to ribosomes, where the protein is produced (**Figure 4**). A mutation is an error in a gene, usually resulting in production of an abnormal protein that has one of two consequences: loss of function or gain of function. Most biallelic mutations, in autosomal recessive conditions, result in loss of function, either through decreased protein production or production of a malfunctioning protein. On the other hand, heterozygous mutations in autosomal dominant disease may cause gain of function, or may interfere with the function of the normal protein encoded by the normal allele (a "dominant negative" mutation).

Gene therapy may be used to address mutations in several ways, as shown in **Figure 4**: to replace the missing or disabled protein by supplying a normal copy of the gene that remains separate from the target cell's DNA (gene augmentation), to correct the genetic code for the protein within the target cell's native DNA (gene editing), to stop production of a harmful mutant protein by preventing the translation of mRNA (RNA transcript editing via AON therapy), or to correct abnormal intron splicing in mature mRNA via AON. The use of AON therapy is described in more detail below.

While gene augmentation therapy may be com-

TABLE 2

Comparison of Recombinant Viral Vectors Used in Gene Therapy[57-60]

	Adenovirus	Adeno-Associated Virus (AAV)	Lentivirus (retrovirus)
Pathogenic	Low	No	No
Integration Into Target Cell Genome	No	No*	Yes
Immunogenicity	High	Very low with subretinal delivery; Higher with intravitreal delivery	Low
Infects Dividing Cells	Yes	Yes	Yes
Infects Non-dividing Cells	Yes	Yes	Yes (with less efficiency)
Transgene Expression	Transient	Prolonged (Transient or stable)	Prolonged (Transient or stable)
Relative Viral Titer	Very High	High	High
Carrying Capacity	7.5 kb	4.5-4.9 kb	8 kb

*Native AAV will integrate, but recombinant AAV rarely does

pared with administering a medication, gene editing has been described as genome surgery.[61] In this technique, the defective gene is corrected directly, using molecular scissors called endonucleases to cut certain sequences of DNA. The mutated gene may be cut and revised, cut and removed, or cut and replaced. Earlier versions of gene editing have been largely replaced by Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) technology, an adaptation of a Streptococcus pyogenes endonuclease guided to the mutated gene by RNA. Researchers hope to begin the first Phase 1 trial of a potential CRISPR gene-editing treatment for *CEP290*-mediated IRD this year.[61,62]

Another potential approach to treating inherited diseases is the use of gene editing to correct a mutation in a patient's own stem cells, followed by transplantation of those cells into the affected tissue. However, this approach to IRD is in very early preclinical stages.[61]

The last gene therapy strategy, AON, stops the translation of harmful, abnormal proteins by blocking a segment or correcting intron splicing of mRNA. Recall that one strand of DNA is the "sense" strand, containing the actual genetic instructions for proteins, and the other is the "antisense" strand (**Figure 4**). During transcription, so-called pre-messenger RNA, containing exons and introns and that is complementary to the antisense strand, is produced, so that the mRNA contains the correct sense sequence. Before the latter is translated into a protein, splicing ensures that introns are correctly spliced out and all exons are combined. However, if the DNA contains a mutation, the mRNA carries an incorrect sequence and an abnormal protein will result. A small antisense RNA segment, an "antisense oligonucleotide," can be sent to bind with the mutated sense mRNA message and either correct splicing or block protein synthesis altogether. This technology is only designed to block one single, specific mutation at a time, so that a different mutation in the same gene causing the same IRD will not be addressed. AON therapy is currently under study for *CEP290*-mediated IRD.[63]

An Overview of Vectors for Gene Therapy

Regardless of the gene therapy modality used, the therapeutic DNA or RNA must be delivered into the target cell. Only AONs do not require vectors. The vehicle used to deliver the therapeutic gene is called a vector and may be designed to target specific cells. Several viruses have been used as vectors including adenovirus, adeno-associated virus (AAV2, AAV8), and lentivirus. Differences among the types of viral vectors include packaging capacity, stability, level of immune response, infectivity of dividing or non-dividing cells, and DNA integration into chromosomes (integrating) vs. remaining extrachromosomal (episomal), as shown in **Table 2**.[64] Since gene therapy is delivered to specific target cells and not reproductive cells, the resulting changes cannot be passed to offspring.

A vector carries the transgene (therapeutic gene) along with helper plasmids. In addition, vectors may contain an enhancer, responsible for cell-specific gene regulation, and a promoter, a coding sequence that initiates transcription of the therapeutic gene.

AAV is a nonpathogenic virus incapable of causing infection in the host. In addition, it is an episomal vector, meaning that its DNA remains separate from the host cell's DNA and therefore does not disturb the normal expression of host genes under typical conditions. For these reasons, it is considered a safer approach than other viral vectors.[64] Furthermore, AAV has a low potential to cause an immune response in the subretinal space and is durable.

AAV2, the best characterized and most commonly used AAV, targets the RPE cells in the eye, as well as the central

nervous system and kidneys. AAVs have a limited carrying capacity of 4.5-4.9 kb, thereby limiting the size of the gene carried. While some genes, including *RPE65*, are appropriately sized for this vector, others like *ABCA4* and *MYO7A* are too large. For these larger genes, the carrying capacity of lentivirus (such as equine infectious anemia virus [EIAV]) may be more appropriate, although lentivirus has proven less efficient at transducing photoreceptor cells than RPE cells. Furthermore, lentiviruses are retroviruses, inserting themselves into host DNA randomly, with a consequent small risk of cancer or other serious mutations.

Packaging parts of large genes such as *MYO7A*, *ABCA4*, and *ALMS1* into dual or even triple AAV, with inserts recombining after delivery into the target cell, is an alternative strategy that is currently being studied.[65-67]

In addition to viral vectors, liposomal nanoparticle vectors are under development, with the intention of compacting DNA or RNA and packaging it to travel across cell membranes.[68] Liposomal nanoparticle vectors may have the capacity to deliver genes that are too large to be carried by lentiviruses.

Once the building blocks of the vector have been designed, gene therapy manufacturing can take place in cells acting as biological factories. For example, voretigene neparvovec is an AAV2 vector manufactured using human-derived HEK293 (human embryonic kidney) cells. The manufacturing process includes multiple purification steps to reduce the number of empty capsids, maximizing the potential for full capsids containing *RPE65* to be delivered to the RPE target cells.[69] A surfactant is added at the end of the manufacturing process to help prevent adherence of the product to the inside of vials or syringes.

It is critical to note that gene therapies using the same gene and targeting the same tissue, even with the same or similar vector capsid, can vary in multiple important ways, including helper sequences, purification of empty capsids, final formulation, dose optimization, surgical delivery procedure, and adjuvant immunomodulatory therapy. This may explain why various *RPE65* gene therapy trials, with different administration procedures, gene constructs, vector formulations, and/or surgical approaches, showed improvements in retinal function but variable durability of effect.[64,70-74]

Vector Administration

Even the best-designed, most efficient vector must ultimately be delivered to the appropriate target cell. In systemic diseases, this may be accomplished through an intravenous infusion. As with all systemic medications, the concentration of vector that ultimately reaches the target cell is limited as the treatment travels through the body's circulation. In contrast, the eye is an ideal site for gene therapy for several reasons. First, its small size and enclosed compartment require only relatively small amounts of vector to achieve the necessary concentration, limiting local toxic reactions. The eye's transparent media allow direct visualization during examination and during surgical procedures. The ability to perform non-invasive tests, such as fundus photography, OCT, fluorescein angiography, and autofluorescence, further facilitate assessment of efficacy and safety.[64,75] In addition, the eye's immune privilege makes systemic circulation of the vector less likely, reducing the risk of a harmful immune response.[64]

MEANINGFUL CLINICAL TRIAL ENDPOINTS MUST:

- Reflect the real-life effect of an IRD on functional vision and visual function
- Consider the expected rate of disease progression relative to the endpoint

Gene therapy may be delivered to the retina via intravitreal (IVT) injection or subretinal injection (**Figure 4**). IVT injection is very familiar to retina specialists due to widespread, frequent use of vascular endothelial growth factor inhibitors in retinal vascular diseases. In adults, this is an in-office procedure, with relatively low risk of complications. However, IVT injection with the most common viral vectors has been shown to achieve only limited transduction efficiency, confined to cells in the inner retinal layers. Furthermore, extra-ocular distribution and shedding of vector after IVT injection is measurable, resulting in a systemic humoral immune response.[75,76] Nevertheless, the ease of administration with IVT may outweigh these concerns, certainly if sufficient immunosuppression is applied.

Subretinal injection, on the other hand, delivers vector to the outer retinal layers, including photoreceptors and RPE cells, over a localized area. Unlike IVT injection, this technique requires pars plana vitrectomy in an operating room under retrobulbar or general anesthesia. While the subretinal injection technique is not as ubiquitous as IVT injection, it is nevertheless within the skill set of retina surgeons. Risks of this technique are those of vitrectomy, including infection, cataract, as well as macular holes or retinal detachment.[27,77] In addition, thinning of the outer nuclear layer has been reported, although this has been determined to be clinically nonsignificant.[78]

Subretinal injection is preferred when the outer retinal layers or RPE are the target, causing the minimal immune response associated with localized vector. On the other hand, IVT injection is useful when inner retinal layers and wide areas of the retina are to be treated, especially when retinal structural damage from underlying disease would prevent successful subretinal injection, and where no major concerns over systemic shedding and off-target transduction are present.[75]

IRD Gene Therapy Clinical Trials

Ideally, a clinical trial for any IRD treatment is designed with endpoints measuring aspects of visual function and functional vision affected by the pathophysiology of that particular IRD. Measures of visual function, such as BCVA and VF, are familiar clinical trial endpoints (**Table 3**). On the other hand, measures of functional vision, often described as the ability to integrate multiple aspects

TABLE 3

Photoceptor-Associated Impairments and Visual Function Assessments

	Associated Impairment	Visual Function Assessment
Rods	Decreased light sensitivity/night blindness	• Full-field light sensitivity threshold (FST) • ERG--rod response
	Poor adaptation to changing light levels	Dark adaptometry
	Decreased peripheral visual field	Dark-adapted perimetry
Cones	Poor central vision	Visual acuity
	Impaired color vision	Specialized color vision testing
	Overall cone function	• Full-field light sensitivity threshold (FST) with chromatic stimuli • ERG—cone response
	Decreased peripheral visual field	Peripheral visual field testing
	Photophobia	Light discomfort test
	Central scotoma	Central visual field testing, including microperimetry

of visual function to conduct visually dependent activities of daily living, are less often included in clinical trial design despite their importance to overall quality of life. Examples of functional vision are reading and mobility or navigation. When evaluating clinical trial results, one must consider whether the endpoints are meaningful to the disease and treatment being studied. For example, BCVA is of interest in any ocular clinical trial. However, this measure of cone-mediated, foveal visual function is much more relevant to a cone, cone-rod, or macular dystrophy than to a predominantly rod-mediated rod-cone dystrophy that often leaves the macula intact until later stages of disease. Likewise, VF testing is typically done under photopic conditions, thereby measuring only cone function. As a result, the extent of rod-mediated VF constriction affecting navigational ability at night is not measured with standard VF testing. Furthermore, the clinical manifestations of an IRD, such as very limited retinal and macular function with photophobia or nystagmus, often of congenital or early onset, may limit the ability to perform certain evaluations. One of the unique challenges in IRD clinical trial design, then, is to select measurable endpoints that reflect the real-life visual impact of the disease.

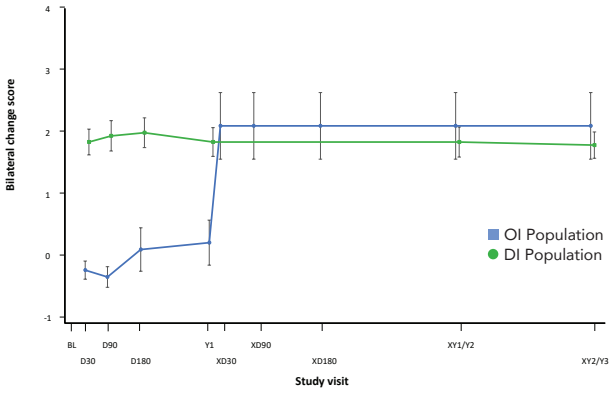
Knowledge of disease progression relative to an endpoint is also essential when selecting meaningful outcome measures. This is the founding principal behind ProgSTAR, the largest natural history study of Stargardt disease, which is caused by autosomal recessive *ABCA4* mutations. The ProgSTAR study group is dedicated to understanding disease progression and determining the best outcome measures to accelerate evaluation of emerging treatments.[5] For example, BCVA, as a measure of foveal, cone-mediated function, would appear to be an ideal endpoint for a macular dystrophy like Stargardt disease, but annual change in BCVA in these patients has been found to be too small to be a sensitive outcome measure for *ABCA4* treatment trials of 1 year's duration.[79] This may be due to a ceiling or floor effect in the data. On the other hand, microperimetry has been identified as an important outcome measure for future *ABCA4* clinical trials,[80,81] and incidence of definitely decreased fundus autofluorescence (DDAF) may serve as a monitoring tool for interventional clinical trials that aim to slow disease progression.[82] A similar natural history study called RUSH2A is underway for patients with Usher syndrome type 2 caused by *USH2A* mutations.[83]

Without an available appropriate functional vision outcome measure for a rod-cone dystrophy like *RPE65* mutation-associated IRD, researchers in the voretigene neparvovec gene therapy trials developed a novel endpoint to measure change in rod- and cone-mediated functional vision. The Multi-Luminance Mobility Test (MLMT) was developed to measure functional, ambulatory vision at light levels encountered during activities of daily living.[84] This mobility course with 12 standardized configurations was designed to be performed by children as young as age 3. Subjects were evaluated for accuracy and speed on the MLMT at 7 standardized light levels, ranging from 1 to 400 lux, where 1 lux is comparable to the light level of a moonless summer night or a nightlight and 400 lux is equivalent to a brightly lit office. A normally sighted ambulatory person would be able to complete the course at 1 lux with no or minimal errors, while someone with *RPE65* mutation-associated IRD or other rod-cone dystrophy would have significant challenges at the 1 to 10 lux range. In this way, changes in MLMT performance were designed to correlate with changes in real-world, clinically meaningful functional vision. Subjects passed at a given light level if they succeeded in both accuracy and time assessments. The corresponding lux score was recorded for the lowest

FIGURE 5

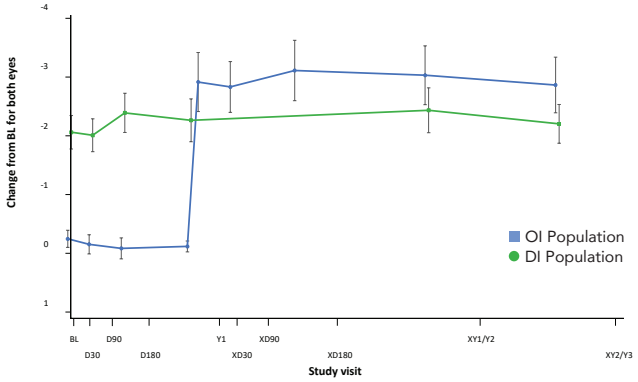
Results from Phase 3 Voretigene Neparvovec Trial

A. Mean Bilateral MLMT Change Scores Over Time



Data presented as mean ± SE. For the DI group, change is relative to injection baseline after year 1.

B. Mean Change in FST White Light Over Time



Data presented as mean ± SE. log10(cd.s/m2), log 10 (candela second per meter squared).

light level at which the subject had passed.[84] In addition to change in MLMT score, full-field light sensitivity (FST) threshold (a test of rod photoreceptor function measuring the lowest illumination detectable over the entire retina) and visual acuity (VA) were other endpoints used in voretigene neparvovec clinical trials.[70] Variations of MLMT are currently used in several gene therapy trials.

Gene Therapy Phase 3 Clinical Trials

Voretigene Neparvovec for RPE65 *Mutation-Associated IRD*

The phase 3 open-label, randomized, controlled study of gene augmentation by sequential, bilateral, subretinal administration of voretigene neparvovec (VN) for *RPE65* mutation-associated IRD was the first phase 3 trial of a gene therapy for IRD.[70] Biallelic *RPE65* mutation is responsible for 8% to 16% of LCA cases, presenting with profoundly impaired vision and nystagmus in infancy, and about 1% to 3% of RP cases, presenting with nyctalopia and peripheral VF loss in childhood or young adulthood.[23,85-89] As previously discussed, due to its variable phenotype, patients with *RPE65* mutation-associated IRD have been given a number of other clinical diagnostic labels.[2]

The primary efficacy endpoint of the phase 3 VN trial was the change in bilateral MLMT performance (change in lux score for the lowest passing light level) at 1 year relative to baseline. A positive change score indicates passing the MLMT at a lower light level. Thirty-one subjects with biallelic *RPE65* mutations comprising the intent-to-treat (ITT) group were randomized 2:1 to the intervention group and the control group, respectively. One subject from each group withdrew prior to receiving VN, leaving 20 intervention and 9 control subjects in the modified ITT (mITT) population and safety analysis populations.

At 1 year, the mean bilateral MLMT change score for the ITT population was 1.8 in the original intervention group and 0.2 in the control group, a statistically significant difference (P=0.0013, **Figure 5A**).[70] This average change of almost 2 light levels for the intervention group reflects a gain of functional vision allowing independent navigation over a wider range of illuminance levels encountered in daily life. On average, the intervention group moved from passing the MLMT at the level of 50 lux, comparable to light found in an indoor stairwell or train station at night, to passing at the level of 4 lux, or light associated with holiday lights or an outdoor parking lot at night. Thirteen (65%) of the 20 mITT intervention subjects passed MLMT at the lowest luminance level tested (1 lux) at 1 year, demonstrating the maximum MLMT improvement possible. By contrast, no control subjects passed MLMT at 1 lux at 1 year. A change of 1 light level in passing the MLMT was considered clinically significant, especially against the backdrop of the progressive nature of this condition. The design of the MLMT with 7 steps of predetermined light levels precluded evaluation of subjects at illuminance lower than 1 lux, creating a ceiling effect that limited the ability to measure the true scale of improvement in some subjects. In addition, the MLMT change score does not reflect the full extent of improvement, including the speed with which subjects complete the course.

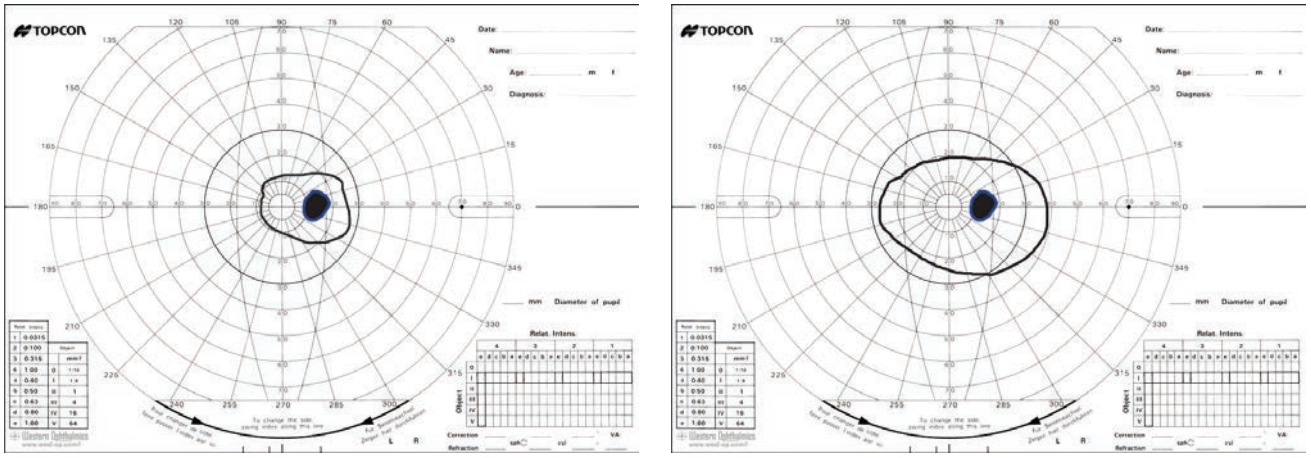
Increased light sensitivity, as expressed by MLMT scores, was further corroborated by mean FST (white light [reported as log10(cd.s/m^2)] averaged over both eyes) in the intervention group, which showed a rapid 1.89 log unit improvement by day 30 in light sensitivity that increased to over 2 log units by 1 year (**Figure 5B**).[70] The control group showed no meaningful change in this measure over 1 year. The difference of −2.11 between the ITT intervention and control groups was significant (P=0.0004).

Mean Goldmann VF III4e nearly doubled compared with baseline after treatment with VN (**Figure 6**), increasing by 92% in the intervention group and decreasing by 16% in the control group. Mean BCVA averaged over both eyes improved by 8.1 letters from baseline for the intervention group and 1.6 letters for the control group, which was not statistically significant.[70]

No harmful immune responses associated with VN

FIGURE 6

Representative Goldmann Visual Field III4e Before and After Treatment With VN



were observed. The most frequently reported ocular treatment-emergent adverse events among phase 3 subjects were consistent with vitrectomy and the subretinal injection procedure, including transient mild ocular inflammation, transient elevated intraocular pressure, cataract, and intraoperative retinal tears treated with laserpexy. One subject experienced loss of VA.[70]

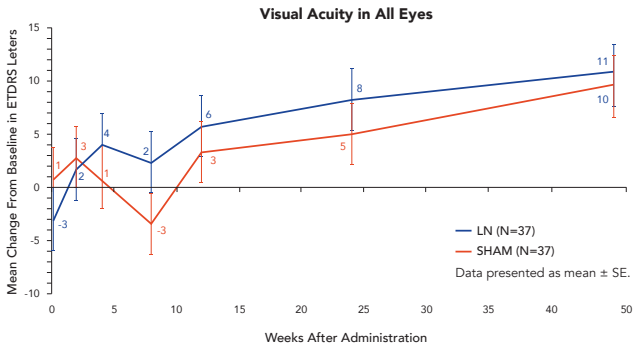
After one year, phase 3 control subjects crossed over to receive treatment with VN. These delayed intervention subjects had similar results to those of the original intervention group.[90] Improvements in MLMT and FST have remained durable for 3 years in phase 3 subjects (**Figure 6**), as have improvement in VF and stabilization of VA.[91]

Lenadogene Nolparvovec for ND4 *Mutation-Associated Leber Hereditary Optic Neuropathy*

Three ongoing phase 3 studies of lenadogene nolparvovec (LN) are investigating its efficacy and safety in subjects with vision loss duration of ≤6 months (RESCUE trial), >6 months to 1 year (REVERSE), and <1 year (REFLECT) in Leber Hereditary Optic Neuropathy (LHON) due to the 11778G>A mutation in *ND4*. LHON is the most commonly recognized mitochondrial disease, presenting most frequently in young men as painless, acute, profound vision loss in one eye, followed within weeks or months and sometimes years by similar manifestations in the other eye. LHON is caused by mutations in mitochondrial genes, with the most severe and common mutation occurring in the *ND4* gene (11778G>A). These mutations cause death of the retinal ganglion cells, leading to optic atrophy.[92] LN is a recombinant AAV2 containing DNA encoding human mitochondrial ND4 protein that includes a mitochondrial targeting sequence. The protein is assembled in the ganglion cell cytoplasm and then imported into the mitochondria.

FIGURE 7

Mean Change from Baseline in the REVERSE Lenadogene Nolparvovec Trial



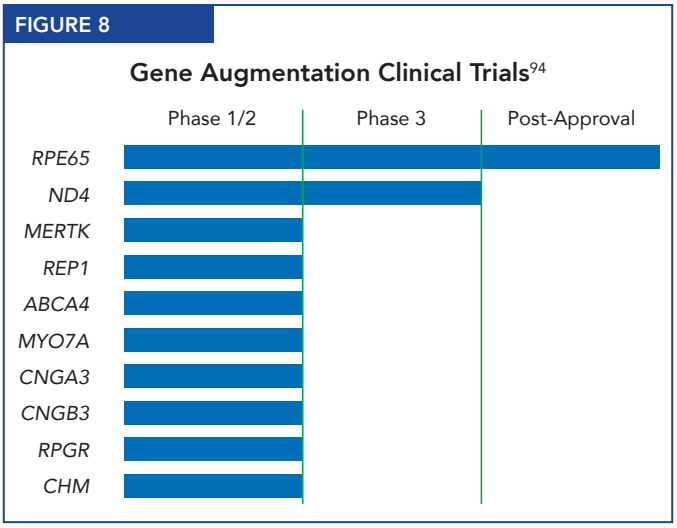
Topline results from the REVERSE randomized, double-masked, sham-controlled trial, in which one eye received IVT injection of LN and the contralateral eye received a sham injection, were recently released.[93] The primary efficacy endpoint was change in BCVA at 48 weeks post-injection. Treated eyes (n=37) had a mean improvement of 11 letters as compared with baseline. Unexpectedly, untreated contralateral eyes (treated with a sham injection) also showed a similar improvement of 10 letters (**Figure 7**). Due to this improvement in untreated eyes, the trial did not meet its primary endpoint.

Mean change in retinal ganglion cell macular volume measured on SD-OCT from baseline demonstrated a statistically significant difference (P=0.0189) between LN-treated eyes and sham-treated eyes, with untreated eyes losing 0.038 mm^3 of macular ganglion cell volume while the ganglion cell volume of treated eyes was essentially unchanged (-0.003 mm^3).[93]

Mean change in thickness of the temporal quadrant and papillomacular bundle of the retinal nerve fiber layer from baseline demonstrated a statistically significant difference (P=0.0359) between LN-treated eyes and sham-treated eyes, with untreated eyes showing a loss of 3.4 µm compared with a loss of 0.6 µm in treated eyes.[93]

Ocular treatment-emergent adverse events among phase 3 subjects were related to the injection procedure and to LN itself. Specifically, intraocular inflammation,

FIGURE 8



accompanied by elevation of intraocular pressure in some patients, was reported, and was responsive to conventional treatment without sequelae.[93]

Topline data for the RESCUE trial are expected later in 2018, while the REFLECT trial has just begun.[95,96]

Emerging Gene Therapy Treatments

Other emerging gene therapy trials are summarized in **Figure 8**. Clearly, gene therapy is on the horizon for many IRDs, from the breakthrough of VN for *RPE65* mutation-associated IRD to the promise of LN for *ND4* mutation-associated LHON to many other promising investigational treatments.

Members of a focus group including patients with RP, LCA, Stargardt macular dystrophy, and Usher syndrome mentioned their concern that patient access to clinical trials is dependent on the awareness of an individual's doctor.[97] Patients want to be informed of, and participate in, new and ongoing research efforts for their otherwise untreatable diseases, but lack of physician knowledge regarding investigational gene therapy is a barrier to patient access.[16] For this reason, it is imperative that physicians identify and consult IRD specialists who are up to date in their knowledge of potential treatments and clinical trials.

Conclusion

Clinicians must be vigilant for IRDs, able to describe them well enough to give them a preliminary clinical classification, and make prompt referrals to IRD specialists and genetic counselors for definitive workup including genetic testing. They must also remain aware of developments in gene therapy—which are unfolding almost weekly—including how to find available treatments or clinical trials for their IRD patients. In most cases, optimal care will be given by an IRD specialist, aided by genetic counselors and low vision specialists. In this brave new world of gene therapy, we can finally offer hope of improvement in visual function and functional vision to patients who would have otherwise become blind.

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