MEDXCHANGE LIVE™ SPECIAL EDITION

Inherited Retinal Diseases

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Inherited retinal diseases (IRDs) are a highly heterogeneous group of diseases, with unequaled phenotypic and genotypic variability, and are caused by mutations in one of several hundred genes.[1,2] Approximately 1 in 2,000 people worldwide are affected by this group of disorders, and 2.7 billion people are healthy carriers of at least one likely disease-causing variant linked to autosomal recessive IRDs.[3–5] IRDs, which are a leading cause of blindness, are typically characterized by photoreceptor dysfunction, followed by retinal cell death and include rod-cone, cone-rod, isolated cone and macular dystrophies, and cone and rod dysfunction syndromes.[2,6–10] IRDs can be classified as panretinal pigmentary retinopathies, in which pigmentary clumping occurs secondary to photoreceptor death; macular dystrophies with only central retinal involvement; stationary conditions in which the photoreceptors do not function but do not die; optic nerve disease primarily due to involvement of ganglion cells; and other less frequent diseases such as vitreoretinopathies.[11,12] There are many types of IRDs identified and others yet to be discovered.[1] Some of the most common IRDs are detailed in Table 1. Other IRDs, such as geographic atrophy, affect the ability to accomplish everyday tasks such as reading, driving, or cooking.[13] As the global population grows and ages, the number of people with vision loss will also increase.[14] Treatments for IRDs remain as an unmet medical need, but the huge disease burden caused by IRDs and the advancements in retinal genetics, imaging, and molecular biology, have led to improved diagnosis and the development of clinical trials of novel therapeutics.[14–19]

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Table 1. Most Common Inherited Retinal Diseases

RETINITIS PIGMENTOSA[20–22]	• Most frequent IRD • Progressive hereditary retinal dystrophy in which degeneration of retinal photoreceptors causes nyctalopia and progressive visual field defects • Caused by variations in 60 genes that affect the retina; depending on gene affected • Can appear during childhood or adulthood • X-linked retinitis pigmentosa represent some of the most severe forms of retinitis pigmentosa, resulting in early onset in childhood and rapid progression to blindness by the time patients reach 20 to 30 years old
CHORIORETINAL DSYTROPHY[23–28]	• Characterized by a diffuse, progressive atrophy of the choroid, retinal pigment epithelium, and retina • Structural alterations of the central retina in the early stage of the disease • Exact pathogenesis not completely understood • Remarkable for chronic progressive visual loss, including early onset night blindness and peripheral visual field reduction, with patients usually retaining good central visual acuity into their 50s
STARGARDT MACULAR DYSTROPHY[3,29–31]	• Associated with progressive central vision loss • Genetically and clinically heterogeneous disease • Leading cause of adolescent/young adult vision impairment
ACHROMATOPSIA[32,33]	• Rare inherited autosomal recessive disease • Caused by mutations in either CNGB3 or CNGA3 • Prevents cone photoreceptors from functioning • Patients legally blind from birth and usually suffer from severely reduced visual acuity of 20/200 or worse; a disabling sensitivity to light, or photophobia; total color blindness; and involuntary back and forth eye movements, or nystagmus
AGE-RELATED MACULAR DEGENERATION (AMD); NEOVASCULAR AMD, AND GEOGRAPHIC ATROPHY[5,13,34]	• Most common cause of blindness in developed countries, accounting for 8·7% of all blindness worldwide • Patients often have low levels of CD59, a protein that protects the retina from damage caused by an essential part of the body's natural immune response called complement • Sight loss from advanced AMD occurs either as neovascular (or “wet”) AMD or geographic atrophy • Geographic atrophy, which affects around 5 million people globally, and is one of the leading causes of blindness in people over age 50; 1 in 4 people over 90 are affected
LEBER CONGENITAL AMAUROSIS[35–38]	• Primarily affects the retina • People typically have severe visual impairment beginning in infancy • Considered one of the most severe Inherited Retinal Diseases • One of the most common IRDs (>5% of all IRDs) • A monogenic autosomal recessive disease that affects ~1:30,000 newborns
PROGRESSIVE CONE AND CONE-ROD DYSTROPHIES[7,39,40]	• Clinically and genetically heterogeneous group of IRDs, with at least 30 genes implicated • Characterized by cone photoreceptor degeneration, which may be followed by subsequent rod photoreceptor loss • People typically present with progressive loss of central vision, color vision disturbance and photophobia • Estimated incidence ranges from 1:20,000–100,000

THEIR GENES GAVE THEM BUTTON NOSES, BROWN HAIR, AND VISION LOSS

To date, science has discovered more than 270 genes related to **inherited retinal diseases**.[1] With the evolution of genetic testing comes the ability to more precisely diagnose your patients.

More answers may uncover more possibilities for active clinical trials, emerging treatments, and even identifying underlying conditions beyond vision issues.

MOVE FORWARD WITH MORE ANSWERS

Scan to find more answers about genetic testing and retesting at **EyesOnGenes.com**.

Reference: 1. Branham K, Schlegel D, Fahim AT, Jayasundera KT. Genetic testing for inherited retinal degenerations: triumphs and tribulations. *Am J Med Genet C Semin Med Genet.* 2020;184(3):571-577.

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Genetic Testing for Inherited Retinal Diseases

Extensive progress has been made towards understanding the pathophysiology of IRDs through advances in genetic testing with more than 3,000 mutations being identified in more than 300 genes, and that number is constantly increasing due to greater access to next-generation sequencing (NGS).[7,43] A retrospective analysis demonstrated that genetic testing was conducted in only approximately 10% of patients with IRDs between 1986 and 2014.[42] Over the past decade, gene-based classification of IRDs is becoming the standard of care for patients with IRDs, with lower costs making DNA sequencing more accessible.[44] A cornerstone in the diagnosis of inherited retinal dystrophies is molecular genetic testing, with a case series confirming that NGS is a useful genetic test for most patients with IRD.[41,45–56] In advanced cases of IRDs, where the exact phenotype cannot be determined due to widespread retinal degeneration, genetic testing may still assist in obtaining a specific diagnosis.[41] Genetic testing can also result in the correction of an initial clinical diagnosis, may uncover an unexpected diagnosis, and may guide further investigations if the IRD suggests a syndromal condition.[41,57] Identification of the molecular cause through genetic testing can not only provide information regarding the potential disease course or inheritance, but is also essential in light of potential disease-specific therapeutic options (Figure 1).[41,44] In addition, a definitive diagnosis using genetic testing is an important step to facilitate identification of patients acceptable for enrollment and participation in clinical trials.[18,44]

In advanced cases of IRDs genetic testing may still enable a specific diagnosis.

Figure 1. Genetic testing Provides Information Regarding Diagnosis and Treatment for Patients with Inherited Retinal Diseases

Genetic testing identifies the specific gene mutation behid a patient's vision loss or impairment. It is important to know the gene mutation to determine treatment eligibility.

Diagnosis of Inherited Retinal Diseases

Across the group of IRDs, there is vast variability in degree of visual impairment, burden of disease, progression of disease, and patient suitability to therapeutic intervention; therefore, an early, precise diagnosis is critical for improved patient outcomes.[41] Diagnosis is often delayed due to unspecific clinical signs, multiple clinical manifestations, and genetic heterogeneity of the underlying molecular defects.[42] Therefore, a structured diagnostic process would greatly reduce diagnostic delays.[42] The diagnosis and characterization of IRDs should include the possibility of IRD into the differential diagnosis of visual loss or visual field defect with undefined causes as part of a detailed medical and family history, a clinical examination with testing of visual function, multimodal retinal imaging, and molecular genetic testing to confirm the initial clinical diagnosis (Table 2).[41,42] A thorough and effective patient examination may assist in distinguishing between different IRDs, as well as a differentiation from mimicking diseases or monogenic systemic diseases with retinal involvement.[41] The goals of the detailed examination are to establish the specific clinical diagnosis, to determine the most appropriate treatment plan, and to connect the patient and family members to necessary supportive services.[41]

> An early diagnosis of inherited retinal or optic nerve disorders is often delayed due to unspecific clinical signs

Table 2. Steps in Efficient Diagnostic Testing for Inherited Renal Diseases

PATIENT HISTORY
• Ophthamologists first make inquiries about patient history, which should include questions about current vision issues, patient medical history, current medications, and past medication use
FAMILY HISTORY
• Constructing a family medical history to show the genetic relationships and medical disorders that occur in a family. From the family medical history, patterns of familial disorders and how diseases were passed down may emerge. This, in turn, leads doctors to a clear diagnosis of the genetic disorder and allows assessments for family members who may also be at risk for the disorder
CLINICAL EXAMINATION
• The eye examination may include the following testing: dilation, visual acuity, slit lamp, indirect ophthalmoscopy imaging (retinal photographs, optical coherence tomography, fundus/infrared autofluorescence, visual field testing, electroretinography), and genetic testing

Clinical Trials of Gene Therapies in Inherited Retinal Diseases

The immune-privileged characteristics of the eyes and the continuous identification of causative genes indicate that gene therapy may hold great promise for the treatment of patients with IRDs.[58] Gene supplementation, gene editing, antisense oligonucleotides, optogenetics, and stem cell-based therapies are some of the techniques currently being tested to improve eyesight and/or reduce the rate of disease progression in patients with IRDs.[1,6,7,8,9,17,18,19] Gene therapy has overcome many barriers to evolve from fundamental science to clinical development and has proved to be relatively safe in multiple clinical trials.[44] Currently, there are over 40 gene therapy clinical trials for IRDs, ranging from phases I to III, with varying results.[43,44,58] *Clinicaltrials.gov* (www.clincaltrials.gov)[59] is a useful resource when searching for IRD clinical trials, which are dynamic and constantly changing (Table 4).[43,44] To date, clinical trials are mostly gene augmentation therapies that deliver the correct gene to the retina to restore its function.[58] The approval of the first gene therapy (voretigene neparvovec) for patients with Leber's congenital amaurosis, due to mutations in the RPE65 gene, was just the beginning with additional novel therapies likely becoming available through clinical trials.[19] For instance, gene therapies for choroideremia and X-linked RP are currently in the late stages of clinical development.[58,60–63] An investigational phase 1 gene therapy, HMR59, administered as a one-time, outpatient, intravitreal injection and designed to increase the ability of retina cells to make CD59, is being tested in the aim of preserving vision in patients with geographic atrophy and wet age-related macular degeneration. Six-month data from a phase 1/2 clinical trial of an investigational gene therapy for X-linked retinitis pigmentosa demonstrated promising results, with low and intermediate doses of the investigational adeno-associated virus retinitis pigmentosa GTPase regulator being generally well-tolerated and indicating significant improvement in vision. The development of gene augmentation therapy has created a highly promising avenue for treating a range of IRDs, which will greatly impact patient's health-related quality-of-life.[43]

Table 4. Clinical Trials of Gene Therapies in Inherited Retinal Diseases Listed in *ClinicalTrials.gov* [58,59]

Inherited Retinal Disease	Number of Trials	Trial Phase(s)	Estimated End Range	Patients Enrolled, N (Range)	Gene Target(s)
Achromatopsia	1	I/II	2027	14	CNGA3
Age-related Macular Degeneration	5	I/II	2015–2024	453 (9–300)	anti-VEGF, GAA
Choroideremia	9	I/II, II, III	2017–2023	322 (6–170)	REP1, CHM
Leber Congenital Amaurosis	14	I, I/II. III	2014 – 2029	224 (3–36)	RPE65, CEP290 p.Cys998X, CEP290 Intron 26 (IVS26)
Retinitis Pigmentosa (and Advanced and Autosomal Dominant)	6	I/II	2021–2035	175 (9–35)	PDE6B, RLBP1, USH2A, PDE6A, ChR2, RHO
X-linked Juvenile Retinoschisis	2	I/II	2023	51 (24–27)	RS1
X-linked Retinitis Pigmentosa	5	I/II, III	2020–2026	349 (37–50)	RPGR

CEP290=Centrosomal Protein 290; CHM=Choroideremia; ChR2=Channelrhodopsin-2; PDE6A=Phosphodiesterase 6A; PDE6B=Phosphodiesterase 6B; REP1=Rab escort protein 1; RHO=Rhodopsin; RLBP1=Retinaldehyde-binding protein 1; RPE65=Retinal pigmented epithelium-specific protein with molecular mass 65 kDa; RPGR=Retinitis pigmentosa GTPase regulator; RS1=Retinoschisin; USH2A=Usherin.

Treatment for Inherited Retinal Diseases

The use of genetic testing, the irreversible progress of visual impairment, and lack of effective treatments highlight the need for innovative therapeutic strategies.[58] At present, not all IRDs have proven treatments that halt progression or restore lost vision.[7] Therefore, current management consists of symptomatic alleviation, including refractive correction, use of tinted spectacles/contact lenses for photophobia, and low vision aids.[7] After an interpretation of molecular genetic testing results involving geneticists, ophthalmologists, and potentially additional disciplines, patients with an IRD should receive treatment in a multidisciplinary approach given the complicated nature of these diseases and their care; medical professionals in the team approach to care usually include an IRD specialist, a genetic counselor (for patients and families), a low-vision specialist, and a social worker.[41,44] All of these professionals play essential roles in patient care.[41,44] Some therapies that are under investigation aim to halt disease progression, to return some degree of sight to patients, or seek to actively simulate sight through a device called a "retinal prosthetic" (Table 3). Among the innovative therapeutic options, gene augmentation therapy has shown great promise by delivering healthy copies of the defective gene to the target tissue.[43] The eye is an advantageous organ for such interventions due to its immune-privilege status and small enclosed structure allowing the use of a small amount of the vectors.[43] In the case of targeting photoreceptor cells or the retinal pigment epithelium, subretinal injection allows the vectors to be directly delivered to the location of the target cells with no epithelial barriers or anatomical barriers.[43] This is an exciting time for IRD patient care, with healthcare professionals being able to provide treatments that can potentially prevent blindness for some patients.[44]

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Table 3. Types of Treatments Under Investigation for Inherited Retinal Diseases

NEUROPROTECTIVE AGENTS
• Works to prevent cell death; designed to slow degeneration of cones and rods
RETINAL PROSTHETIC
• Works to restore vision for patients with certain inherited retinal diseases using a microchip that converts images collected by a camera worn by the patient into impulses sent wirelessly to the brain
GENE THERAPY
• Replaces a faulty gene/adds a new gene to stop, cure disease, or improve your body's ability to fight a disease; currently only available for treating inherited retinal diseases related to a specific gene

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