MEDXCHANGE LIVE™ SPECIAL EDITION

ADVANCES IN INHERITED RETINAL DISEASES: Symptoms, Diagnosis, and Management

Inherited Retinal Diseases: A Group of Rare, Genetic, Degenerative Diseases with Varying Prevalence

Inherited retinal diseases, also known as inherited retinal dystrophies, are a group of rare, degenerative diseases of the retina that have marked and genetic heterogeneity.[1-3] These disorders are caused by mutations in 1 of more than 317 mapped genes, and as a whole, inherited retinal diseases affect around 5 to 6 million people worldwide.[4] Over the next few decades, severe vision impairment and blindness in the global population is predicted to increase with the growth of the aging population.[5] Most inherited retinal diseases primarily effect the retina and may result in vision impairment and ultimately blindness, but possible signs and symptoms vary for each individual disorder.[6] There are many types of inherited retinal diseases, with the most common including retinitis pigmentosa, choroideremia, achromatopsia, Stargardt disease, cone-rod dystrophy, and Leber congenital amaurosis.[7] It has been estimated that 1 in 2,000 people have inherited retinal diseases,[6,8-11] but estimated prevalence rates for each of the inherited retinal diseases vary widely. Prevalence of common inherited retinal diseases can be seen in the **Figure**.[7]

Prevalence of Common Inherited Retinal Diseases[7]

Achromatopsia	~1 out of 30,000 people
Choroideremia	1 out of every 50,000 to 100,000 people
Cone-rod dystrophy	1 in 30,000 and 1 in 40,000 people
Leber congenital amaurosis	2 to 3 out of every 100,000 newborns
Retinitis pigmentosa	~1 in 4,000 people
Stargardt disease	1 out of every 8,000 to 10,000 people

Source: https://www.webmd.com/eye-health/inherited-retinal-dystrophy

Varied Symptoms Associated with Inherited Retinal Diseases

Inherited retinal diseases encompass a large, heterogenous group of monogenic diseases exhibiting autosomal dominant or recessive, mitochondrial, and X-linked inheritance patterns.[6] Possible signs and symptoms vary within the group of inherited retinal diseases.[6] Common presenting symptoms among patients with inherited retinal diseases include night blindness, color blindness, and tunnel vision.[1] Inherited retinal disorders usually lead to severe vision impairment and are a leading cause of blindness.[1,2]

Biallelic mutations in the *RPE65* gene cause the most severe forms of inherited retinal diseases, Leber congenital amaurosis and early onset retinal dystrophy.[12] Clinical manifestations of *RPE65* mutation-associated inherited retinal diseases include a concentrically constricted visual field, night blindness, and reduced best-corrected visual acuity, with the progressive, irreversible loss of retinal pigment epithelial (RPE) and retinal photoreceptor cells eventually leading to severe visual dysfunction and complete blindness.[13,14] The **Table** shows the varied signs and symptoms associated with five of the most common inherited retinal diseases—retinitis pigmentosa, achromatopsia, choroideremia, Stargardt disease, cone-rod dystrophy, and Leber congenital amaurosis.[7] Symptoms range from color blindness to total loss of vision.[15-24]

> Possible signs and symptoms vary within the group of inherited retinal diseases. Symptoms range from color blindness to total loss of vision.

Varied Symptoms Associated with Common Inherited Retinal Diseases

Inherited Retinal Disease	Associated Symptoms
Achromatopsia[15]	Partial or total absence of color vision; photophobia; nystagmus; reduced visual acuity; hyperopia
Choroideremia[16]	Progressive atrophy of the outer retina and inner choroid; nyctalopia in early childhood; progressive loss of peripheral visual field and visual acuity; blindness (for all patients—commonly in late adulthood)
Cone-rod dystrophy[17]	Decreased visual acuity; photophobia; loss of color vision; scotomas; loss of peripheral vision; legal blindness by mid-adulthood
Leber congenital amaurosis[18]	Vision loss (at birth to early infancy); photophobia; nystagmus; hyperopia; keratoconus; Franceschetti's oculo-digital sign (eye poking, pressing, and rubbing)
Retinitis pigmentosa[19-22]	Nyctalopia; blind spots; tunnel vision; loss of central vision, rapid progression of vision loss; legal blindness; early nyctalopia
Stargardt disease[23,24]	Slow, progressive loss of central vision; nyctalopia; color blindness

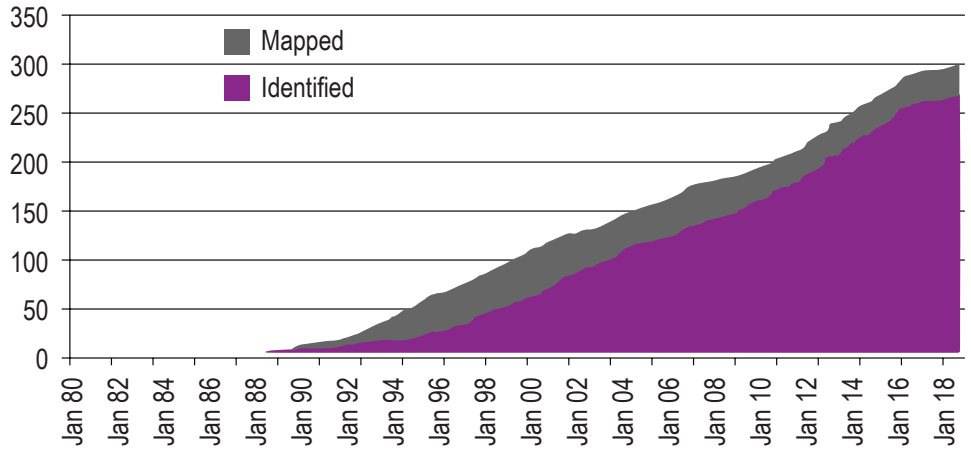
Genes Related to Inherited Retinal Diseases

Inherited retinal disorders are caused by mutations in 1 of more than 317 mapped genes as seen in the **Figure**.[4] Each of the over 300 causal genes discovered to-date has numerous variants associated with diseases that range from point mutations to large changes, such as deletions and duplications.[25-27]

Mapped and Identified Inherited Retinal Disease Genes[26]

317 Disease-causing genes mapped to date

281 Disease-causing genes identified to date



Source: https://web.sph.uth.edu/RetNet/sum-dis.htm?csrt=9939195897742936975#D-graph

A study of 4,415 patients with inherited retinal diseases diagnosed through genetic testing showed that approximately 43% had variants in one of the five most commonly seen inherited retinal disease genes (*ABCA4, USH2A, RPGR, PRPH2,* and *BEST1*); however, of the 20 most prevalent variants identified, five were not included in the most common genes seen (*CNGB3*, *BBS1*, *TIMP3*, *EFEMP1*, and *RP1)*.[28] Genes associated with five of the most common inherited retinal diseases—retinitis pigmentosa, achromatopsia, choroideremia, Stargardt disease, cone-rod dystrophy, and Leber congenital amaurosis are as follows:

Achromatopsia can affect any of six genes that are linked to achromatopsia that help cones respond to light.[29] Up to 90% of achromatopsia cases in patients are due to mutations in *CNGA3* and *CNGB3*.[29] *ATF6, GNAT2, PDE6C,* and *PDE6H* are the other known achromatopsia genes.[29]

Choroideremia is an X-linked genetic condition.[30] The gene that causes choroideremia is on the X chromosome.[30] Choroideremia is caused by mutations in the *CHM* gene.[30]

Cone-rod dystrophy is linked to more than 30 genes that help the rods and cones in the retina work.[31] The four most common disease-associated genes are *GUCA1A, PRPH2, ABCA4* and *RPGR*.[31]

Leber congenital amaurosis is associated with changes to any one of at least 24 different genes.[32] The most common variants are *CEP290* and *GUCY2D* followed by *NMNAT1*.[32] Those patients with *AIPL1, CEP290, GUCY2D, LCA5,* and *NMNAT1* gene mutations exhibit the most severe visual dysfunction.[32]

Retinitis pigmentosa is found in patients with a mutation to any of 60 different associated genes.[33] Some of these genes are autosomal dominant.[33] The most common genes associated with retinitis pigmentosa are *PRPF31, PRPH2, RDH12, RHO, RPE65, ABCA4, MAK, MERTK, NR2E3, PDE6B,* and *RPGR*.[33]

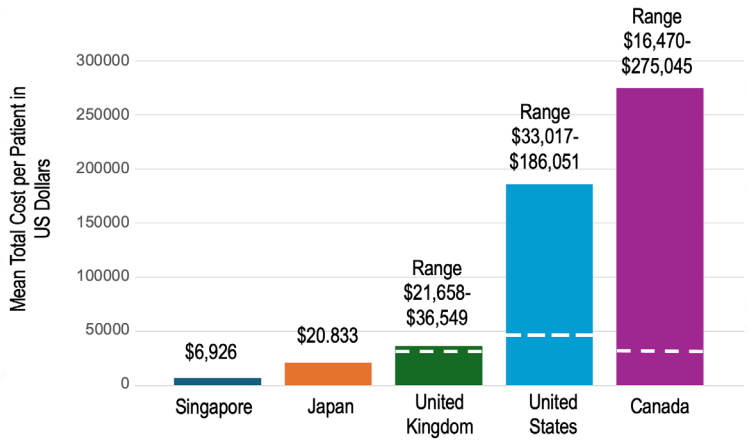
Stargardt disease occurs from a mutation in the *ABCA4* gene.[34] Changes to *ABCA4* cause lipofuscin to build up in and damage the macula.[34]

The most common genes associated with retinitis pigmentosa are *PRPF31, PRPH2, RDH12, RHO, RPE65, ABCA4, MAK, MERTK, NR2E3, PDE6B,* and *RPGR.*

Cost-of-illness Associated with Inherited Retinal Diseases Worldwide

A significant disease burden is associated with inherited retinal diseases.[35-37] The mean total cost of inherited retinal diseases per patient worldwide is approximated to range from $6,926 US per year in Singapore up to $275,045 US per year in Canada as seen in the **Figure**.[35] The costs associated with inherited retinal disease have a significant impact on society, with the costs associated with the diagnosis, treatment, and management of the diseases being considerable, including costs associated with physician visits, genetic testing, diagnostic imaging, mediations, surgeries, low vision aids, rehabilitation, and lifelong monitoring.[9,36,37] Non-health costs related to inherited retinal diseases, such as wellbeing costs (i.e., disability-adjusted life years), productivity loss (i.e., loss in productivity due to illness or disability), and deadweight losses (i.e., loss of economic efficiency occurring when equilibrium for a good/service is not achieved) made up most of the overall costs compared with actual healthcare costs.[35] Therefore, inherited retinal diseases impose a disproportionate societal burden outside of the health care system.[35] For that reason, societal costs should be incorporated in the evaluation of cost-effectiveness inherited retinal disease treatments, including genomic testing and targeted gene therapies.[35]

Inherited Retinal Diseases: Mean Total Cost per Patient in US Dollars[35]



Cost of Gene Therapies May Offset Cost-of Illness

Effective, novel gene therapies are being used as targeted therapies for the effective treatment of some inherited retinal diseases, but these treatments are associated with large, one-time payments, as is the case with voretigene neparvovec (Luxturna)—a novel gene therapy medication used to treat a specific form of inherited retinal disease called Leber congenital amaurosis or retinitis pigmentosa caused by mutations in the RPE65 gene.[38] Voretigene neparvovec offers an effective treatment for a disease that was previously thought to be medically untreatable, but it costs approximately $425,000 US per eye[39] depending on insurance coverage and available financial assistance programs.[40] In a randomized, controlled clinical trial, 65% of participants receiving voretigene neparvovec passed multi-luminance mobility testing at the lowest luminance level tested, while no control participants did.[41] These improvements in functional vision and visual function were sustained in majority of the patients even up to 4 years.[42] When considering the benefit versus cost-effectiveness of novel gene therapy treatments, societal costs should be incorporated into the evaluation for inherited retinal disease treatments, since the societal costs associated with inherited retinal diseases are so high.[35,43] The cost of gene therapies may offset the cost of illness while improving patient quality-of-life.[35,43]

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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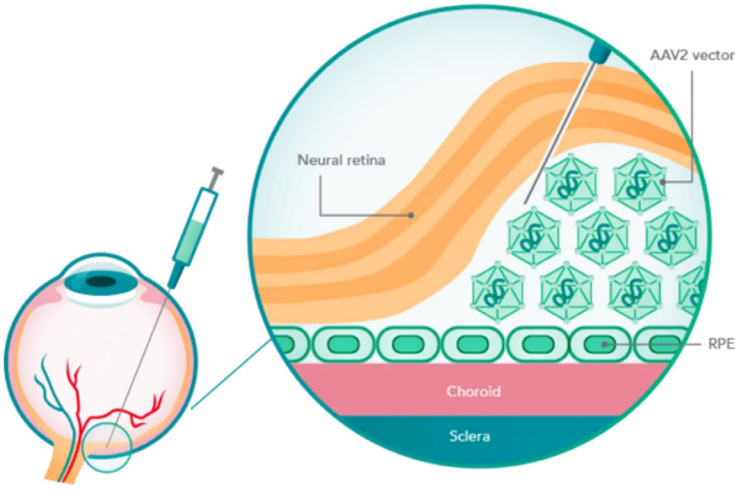
Voretigene Neparvovec Gene Therapy: Effectiveness and Safety Demonstrated in Pivotal Trials, Real-World Experience, and Prospective Data

Voretigene neparvovec (Luxturna) is the first approved ocular gene augmentation therapy in patients with visual impairments, due to biallelic *RPE65* gene mutation-associated inherited retinal disorders, who have sufficient viable retinal cells.[38] Voretigene neparvovec uses the adeno-associated viral vector serotype 2 (AAV2) to carry a functional copy of the *RPE65* gene into the retinal pigment epithelial (RPE) cells to compensate for the *RPE65* mutation.[42] Successful clinical studies resulted in the approval of voretigene neparvovec by the US Federal Drug Administration (FDA) in 2017 and the European Medicines Agency (EMA) in 2018 for the treatment of *RPE65*-associated retinal dystrophy.[44-46] The current evidence on the safety and efficacy of voretigene neparvovec comes from three clinical trials that included a total of 41 patients.[47] The results of these studies were promising, with an acceptable safety profile and the majority of patients reporting improvements in functional visions/visual function with persistence of therapeutic effect lasting up to 4 years.[42,44,47,48] Real-world data after FDA and EMA approval has demonstrated functional improvements following voretigene neparvovec treatment in routine clinical practice, which are consistent with the published clinical trial results.[49,50] As an ongoing, post-authorization, prospective, multicenter, registry-based observational study, PERCEIVE is the largest study assessing the real-world, long-term safety and effectiveness of voretigene neparvovec in routine clinical practice.[51] Overall, the outcomes of the PERCEIVE study are consistent with the findings of voretigene neparvovec clinical trials.[51] Data from 103 patients treated with voretigene neparvovec according to local prescribing information (mean age 19.5 years) showed that 34% of patients experienced ocular treatment-emergent adverse events, including intraocular inflammation and/or infection related to the procedure.[51] The mean changes from baseline in full-field light-sensitivity threshold testing (white light) ranged from −16.59 dB (n=51 eyes) at month 1 to −13.67 dB (n=13 eyes) at year 2.[51] There were no meaningful changes in BCVA and mean foveal thickness reported up to year 2.[51] In addition to being consistent with clinical trial results, the results from PERCEIVE are similar to the published real-world data.[51-54] As an ongoing study, PERCEIVE will continue to collect data and provide evidence on the long-term safety and effectiveness of gene therapy in the clinical setting.[51]

Voretigene Neparvovec: First Approved Ocular Gene Therapy

Voretigene neparvovec uses the adeno-associated viral vector serotype 2 (AAV2) to carry a functional copy of the *RPE65* gene into the retinal pigment epithelial (RPE) cells to compensate for the *RPE65* mutation



Source: https://luxturnahcp.com/about-luxturna/mechanism-of-action/

Delayed Diagnosis for Patients with Inherited Retinal Diseases

Rare diseases affecting the eyes have been found to have a greater diagnostic delay than those rare diseases affecting other body systems.[55] A study was conducted to evaluate the experience of 1,000 patients with inherited retinal diseases during their diagnostic journey.[55] The mean time between symptoms onset and diagnosis for patients was 6.4±9.1 years.[55]

- **57%** of patients waited more than 1 year for a diagnosis.
- **46%** of patients had more than 5 clinician visits until the diagnosis was made; 28% had 1 or 2 clinician visits; and 26% had 3 or 4 visits.
- **77%** of patients had 1 or 2 different diagnoses until receiving the correct one, and 23% had more than 3 diagnoses.
- **78%** of patients reported having their diagnosis clearly explained to them.

The diagnosis of a rare disease is a significant event in a patient's life.[55] There are areas of opportunity to improve the patient journey.[55] Improved accessibility to genetic testing and the development of networks of specialized doctors may optimize the diagnostic pathway for individuals with inherited retinal diseases.[55]

Delay in Access to Genetic Testing and Genetic Counseling in Inherited Retinal Disorders

In an online survey to assess the accessibility and timeliness of genetic testing for patients with inherited retinal disease from over 30 countries worldwide, patients (N=410) demonstrated going through a long and difficult journey to access genetic testing.[56] Of the patients surveyed, 40% had to visit more than 5 physicians, 27% had to visit more than 5 clinics, and 57% had to wait for more than 3 years before obtaining a genetic diagnosis.[56] Furthermore, 46% of respondents reported not receiving genetic counseling prior to undergoing genetic testing, and 39% reported not receiving genetic counselling after undergoing genetic testing.[56] Greater awareness regarding inherited retinal diseases and the benefits of genetic testing and counseling are needed for earlier diagnosis in an effort to improve patient outcomes.[56]

Genetic Counseling: An Essential Part of Inherited Retinal Disease Management

Genetic counselors are critical for patient understanding of genetic information, which may have prognostic, systemic, family planning, and therapeutic implications for patients and their families.[57] Recently, both access to genetic testing for inherited retinal disorders and the number of genes associated with inherited retinal disorders has increased.[4] Improvements in genetic testing have greatly enhanced the complex process of determining gene variants that cause various inherited retinal diseases in an effort to establish a molecular diagnosis for patients.[58] Genetic counseling is essential to help patients and their family members and caregivers understand inherited retinal diseases, the potential risk for future or current offspring, patient prognosis for the diagnosis, and potential treatment options, including gene therapy an clinical trials.[58] Psychological support for patients and caregivers through genetic counseling is important throughout all stages of diagnosis and treatment, and is an essential component of the multidisciplinary approach to inherited retinal disease management.[58] Effective communication throughout the diagnostic and treatment journey is essential to patient success, and the patient and caregivers' needs and expectations must be acknowledged and discussed throughout with genetic counselors.[58] Genetic counseling allows community-based retina specialists to partner with genetic counselors to assist in disclosing key test results to patients and to manage difficult conversations associated with complex genetic results and potential risks to the patient's family members.[59] It is important for patients to understand through genetic counseling that receiving genetic testing does not guarantee that they will receive a molecular diagnosis for their inherited retinal disorder, and that a positive genetic test result will not necessarily qualify them for a clinical trial or novel therapy.[60] In addition, it should be understood that not all of the genes and variants associated with inherited retinal diseases have been identified, and therefore testing may not detect the disease-causing variant for all patients.[60]

Genetic Testing Is Standard for Making a Precise Diagnosis in Inherited Retinal Diseases

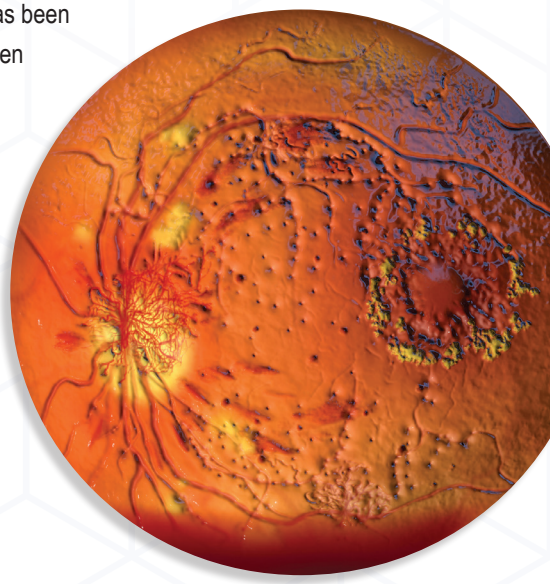
Genetic testing has become the standard for reaching a more precise diagnosis in inherited retinal disorders because of the genetic heterogeneity of the disorders, with a single gene being associated with multiple phenotypes.[6,25-27,61-63] With targeted therapies becoming available for specific inherited retinal disorders, a more accurate diagnosis from genetic testing can assist physicians to use a novel therapy, enroll a patient in a clinical trial, or choose the best therapy for patients with a specific inherited retinal disorder.[6,64,65] Clinical assessment and genetic testing should be interpreted together to ensure accuracy of diagnosis.[63] In addition, knowing the precise genetic cause of vision loss or impairment provide a better prognostic understanding of how vision may change over time and any potential health impacts that may occur in addition to problems with vision and the eye.[63,66] Genetic testing is the standard for making a precise diagnosis,[6] with the American Academy of Ophthalmology recommending genetic testing for most patients with a suspected inherited retinal disease.[63] It has been shown that genetic testing can assist in making a precise diagnosis in most patients by identifying and confirming the genetic cause of vision loss or impairment.[63] In most cases with genetic testing, a pathogenic variant is found.[59] In cases where genetic testing results are negative for pathogenic variants, genetic reevaluation should be considered every 2 to 5 years because it is often the case that if the variant is not found, that the molecular cause of the disease has not yet been identified.[59] In those patients having a genetic retest conducted, it is important to assess whether the testing used will be substantially different than the previous analyses, because it is possible that the patient may harbor variants in regions of known genes not identified using the previously used genetic testing method.[59]

BENEFITS OF GENETIC TESTING

- Confirm inherited retinal disease diagnosis
- Know how vision loss might progress
- Identify risk to other family members
- Determine treatment
- Confirm eligibility for clinical trials
- Understand inheritance

Secondary Macular Neovascularization in Inherited Retinal Diseases

Macular neovascularization may be a presenting feature or occurs as a late-stage complication in several inherited retinal diseases.[67] Secondary macular neovascularisation, in patients with many inherited retinal diseases, has been variably treated with intravitreal antivascular endothelial growth factor, steroids, laser, and surgery. Given that inherited retinal diseases are a large group of heterogenous conditions driven by specific genetic variants that affect retinal structure and function in different ways, the pathogenesis of macular neovascularization in inherited retinal disorders is likely to be influenced by the causative genetic variant in many patients.[68] Those with late-onset Stargardt disease may be seen as exudative age-related macular degeneration when macular neovascularization is the presenting feature.[67] Macular neovascularization is a rare complication in choroideraemia and rod-cone dystrophies.[67] The prevalence of macular neovascularization in retinitis pigmentosa is variable among studies.[68] Better clarification of genotype–phenotype correlations in inherited retinal diseases along with an increased understanding of disease mechanisms associated with retinal health and function might help clinicians to better understand which patients with inherited retinal disorders are at increased risk of secondar macular neovascularization development.[67,68] There is currently no consensus on the management of macular neovascularization secondary to inherited retinal diseases.[67,68]



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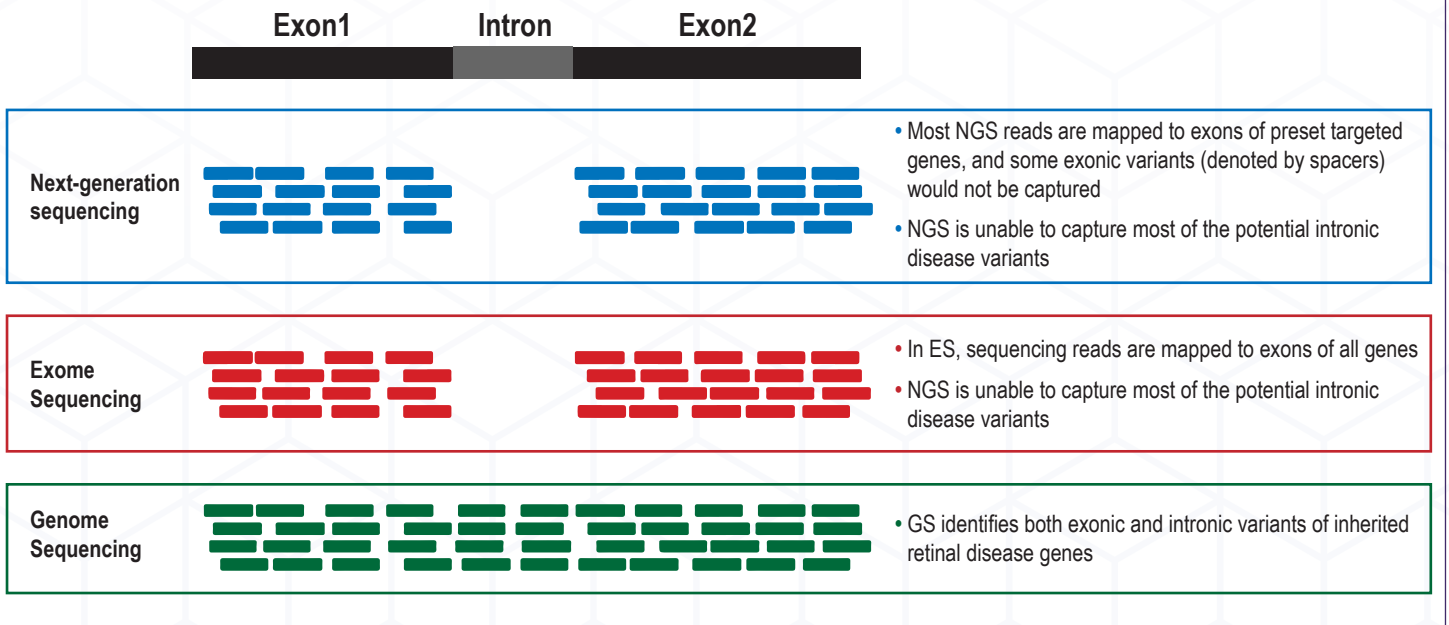
Types of Genetic Testing for Inherited Retinal Disorders

With the advent of an effective gene therapy for biallelic *RPE65* variants implicated in Leber congenital amaurosis, knowledge of the specific disease-causing genetic variants in patients plays an increasingly important role in the diagnosis and management of disease.[69] Genetic testing options for inherited retinal diseases include a phenotype-driven next-generation sequencing (NGS) panel of preselected genes, exome sequencing (ES), and comprehensive genome sequencing (GS) as seen in the **Figure**.[70] A tiered testing strategy, starting with NGS panel-based testing, is commonly done to reduce cost and false genotype rate, but in some patients, ES or GS is recommended as a first line genetic test for patients with intellectual disability or multiple congenital anomalies or complex phenotypes for which the differential diagnosis is broad.[69] NGS panel-based testing is the most commonly used approach for the genetic diagnosis of inherited retinal disease.[69] NGS panels are custom designed to target exons and flanking intronic regions of genes implicated in inherited retinal diseases, and is an economical method of focusing sequencing capacity in smaller genomic regions, which maximizes the coverage of clinically relevant genes.[69] ES approaches can capture all coding regions from gene panels and can aid in diagnosis of complex monogenic phenotypes.[69] GS approaches are superior in detecting a wider spectrum of genetic changes, including large structural variations, non-coding variants excluded from targeted NGS analysis regions, and variants in genes excluded from targeted capture, but the cost is approximately five times higher for GS on a per-sample basis than NGS and ES.[69] Genetic testing is traditionally started with panel-based testing due to lower costs and minimized rates of to reduce cost and minimize the rates of false genotyping.[69-71] Panel-based testing focuses on smaller genomic regions and maximizes the coverage of clinically relevant genes. Panel-based NGS techniques, the most commonly used, have a detection rate of 60% to 70%.[71] If NGS panel is negative, ES is conducted, while GS is mostly reserved for research. ES and GS cost more than NGS and entail time-consuming analysis.[69] A next step to improve the field of genetic testing for inherited retinal disorders may include the more widespread use of GS.[69]

Types of Genetic Testing for Inherited Retinal Disease[69]



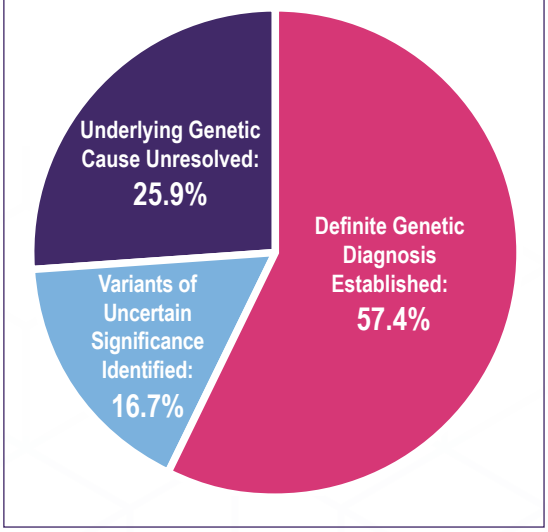
ES=exome sequencing; GS=comprehensive genome sequencing; NGS=next-generation sequencing.

Genome Sequencing Improves Diagnostic Yield in Inherited Retinal Diseases

Genome sequencing (GS) is expected to reduce the diagnostic gap in rare disease genetics.[72] In a study, PCR-free short-read GS was performed in 1,000 consecutive patients with inherited retinal diseases as a routine diagnostic test, and a definite genetic diagnosis was established in 57.4% of the patients as seen in the **Figure**. For another 16.7%, variants of uncertain significance were identified in known inherited retinal disorder genes, while the underlying genetic cause remained unresolved in 25.9% of patients.[72] The results of this important study demonstrated that GS is viable in routine clinical practice outside of clinical trials and reliably identifies causal variants in a substantial percentage of patients with inherited retinal diseases.[72] GS extends the diagnostic yield to rare non-coding variants and enables precise determination of structural variants for fast, effective diagnosis in inherited retinal diseases.[72]

GS enables precise determination of structural variants for fast, effective diagnosis in inherited retinal diseases.

GS Performed on Patients with Inherited Retinal Diseases[72] (N=1,000)

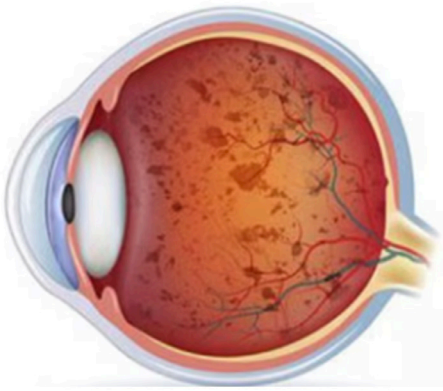


Additional Studies of Potential Therapies for Retinitis Pigmentosa Following the Approval of Voretigene Neparvovec

Since the approval of voretigene neparvovec (Luxturna), there has been an increase in gene augmentation therapeutic strategies for patients with retinitis pigmentosa caused by mutations in the *RPE65* gene and has led to increased interest in developing additional gene therapy treatments targeting other genetic forms of inherited retinal disease.[38,73] Gene size, gene function, and the large number of patients that are not genetically diagnosed are some of the issues that present challenges for developing additional individual gene replacement/augmentation-based therapies.[74] Three different approaches are currently being studied for the treatment of retinitis pigmentosa.[73-75] One is to knockdown the mutant RHO by replacing with a wild-type RHO.[73] Another is to overexpress wild-type RHO to overcome the mutant protein effect.[75] The third is to overexpress *NR2E3*, the upstream regulator of RHO.[74] Future studies will also evaluate promoter specificity and potency, dosage studies, and combination therapies to determine optimal efficacy.[74] The main focus of most ongoing clinical trials for inherited retinal diseases is novel gene therapy, which has demonstrated efficacy for halting/reversing the progression of some inherited retinal diseases.[76] Continued research and clinical trials are essential to fully harness the potential of gene therapies in treating inherited retinal diseases and enhancing patients' lives.[76] Other ongoing clinical trials include treatment with retinal cell replacement, neuroprotection, pharmacological interventions, and optogenetics.[76] While these experimental therapies hold great potential, they are associated with challenges such as timing optimization, standardized assessment criteria, inflammation management, and vector refinement.[76]

Three treatment approaches currently being studied for retinitis pigmentosa:

- Replacing mutant RHO with wild-type RHO
- Overexpressing wild-type RHO
- Overexpressing *NR2E3*



Impacts on Activities of Daily Living and Quality-of-Life in Patients with Retinitis Pigmentosa and Leber Congenital Amaurosis

Inherited retinal diseases can cause severe and progressive loss of peripheral visual field, nyctalopia, and ultimately loss of central vision, all of which are associated with severe impairment in activities of daily living and quality-of-life.[77] Retinitis pigmentosa and Leber congenital amaurosis are rare inherited retinal diseases, both associated with visual impairments that can have significant impacts on patients' vision-dependent activities of daily living and health-related quality-of-life.[78] Across various retinitis pigmentosa and Leber congenital amaurosis genotypes, night blindness, reduced peripheral vision, vision in very bright lighting and light/dark adaptation were the most frequently reported visual function symptoms impacting patients' activities of daily living and mobility.[78] In addition, impacts on health-related quality-of-life were identified, including impacts on social functioning, work and school, emotional wellbeing, and financial impacts.[78] These results are supported by previously reported areas of quality-of-life affected by vision loss, including independence, mental health, and the ability to engage socially with others.[77-81] The impact on patient quality-of-life and activities of daily living leaves patients with inherited retinal diseases, including retinitis pigmentosa and Leber congenital amaurosis, with feelings of helplessness and frustration.[77-81]

Retinitis pigmentosa and Leber congenital amaurosis are rare inherited retinal diseases, both associated with visual impairments that can have significant impacts on patients' vision-dependent activities of daily living and health-related quality-of-life.

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