Gene Therapy in Inherited Retinal Diseases: Current Approaches and Future Perspectives

Hüseyin Baran Özdemir[1], *Şengül Özdek*[1]

ABSTRACT

Inherited retinal diseases (IRDs) comprise a genetically and phenotypically heterogeneous group of disorders that can cause irreversible vision loss. The approval of voretigene neparvovec-rzyl for RPE65-associated retinal dystrophy has advanced retinal gene therapy from experimental research to clinical practice. This review summarizes adeno-associated virus vector technologies, capsid engineering, and preclinical model systems and evaluates current clinical evidence across major gene-specific programs for IRDs. CRISPR/Cas-based gene editing, antisense oligonucleotides, RNA-based therapies, optogenetics, cell replacement, and nonviral delivery systems are also discussed. Available evidence indicates that functional improvement or disease stabilization may be achieved in genetically eligible patients when sufficient viable target cells remain. However, variable efficacy, procedure-related risks, immune responses, ongoing retinal degeneration, cost, and limited access remain major challenges. Early molecular diagnosis, standardized functional endpoints, improved vector targeting, and long-term follow-up with real-world outcome monitoring will be central to broader clinical implementation.

Keywords: Retinal Dystrophies; Genetic Therapy; Genetic Vectors; CRISPR-Cas Systems; Optogenetics

INTRODUCTION

Inherited retinal diseases (IRDs) are a heterogeneous group of rare disorders associated with more than 280 different genes and constitute one of the most important inherited causes of vision loss. This group includes phenotypes such as retinitis pigmentosa, Leber congenital amaurosis, congenital achromatopsia, Stargardt disease, Usher syndrome, X-linked retinoschisis, Bardet-Biedl syndrome–associated retinal degeneration and choroideremia.[1] Most of these diseases begin at an early age, cause progressive vision loss, and, until now, have lacked a curative treatment option.[2]

The inability to treat IRDs limited clinicians to supportive approaches for many years. However, advances in molecular genetics, cloning of target genes and the development of safe vector technologies have brought gene therapy to the forefront.[3] The eye is highly suitable for gene transfer because it is an anatomically isolated organ, a high clinical effect can be achieved with a low volume, and it can be closely monitored using noninvasive imaging methods.[4]

The aim of gene therapy is to correct the genetic defect caused by a pathogenic mutation through gene augmentation, gene silencing, gene editing, or functional bypass methods.[5] Voretigene neparvovec-rzyl

1 Gazi University Faculty of Medicine, Department of Ophthalmology, Besevler, 06500, Ankara, Türkiye

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Correspondence author:
Hüseyin Baran ÖZDEMIR
Email: baranozdemir@gmail.com

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(Luxturna®), developed for patients with Leber congenital amaurosis and retinitis pigmentosa caused by *RPE65* gene mutations, received FDA approval in 2017 and EMA approval in 2018 and entered clinical practice as the first intraocular gene therapy based on gene replacement.[6] In the following years, phase I–III clinical studies were initiated for many diseases, including X-linked RP associated with *RPGR* mutations, X-linked retinoschisis associated with *RS1* mutations, Stargardt disease associated with *ABCA4* mutations, achromatopsia associated with *CNGA3/CNGB3* mutations, RP associated with *MERTK* mutations, Leber hereditary optic neuropathy (LHON) associated with *ND4/ND1* mutations, and Bietti crystalline dystrophy associated with *CYP4V2* mutations.[7-9]

The aim of this review is to comprehensively evaluate, from a clinical perspective, the carrier and model systems, current clinical evidence, safety profile, and next-generation approaches of retinal gene therapy.

Vector Technologies and Model Systems

Adeno-Associated Virus (AAV) Serotypes

Adeno-associated virus (AAV) is a small and harmless DNA virus found in nature. It does not normally cause disease in humans and requires another helper virus (e.g., adenovirus) to replicate. Owing to this feature, it can be used as a gene carrier without posing a risk of pathogenicity.

AAV vectors used in gene therapy are re-engineered in the laboratory. The virus's own replication genes are removed. In their place, a healthy copy of the gene that is missing or defective in the target disease is inserted. In this way, when AAV enters the cell, it neither replicates nor causes disease. Instead, it delivers the gene's DNA into the cell nucleus. The cell then begins to produce the required protein using the instructions encoded by this gene.

The fact that AAV is not naturally pathogenic and that the gene can be expressed for months to years after a single injection are its most important advantages. The retina is highly suitable for AAV-based gene transfer because it is relatively isolated from the immune system, a high effect can be achieved with a low volume, and treatment can be monitored directly using noninvasive imaging.

Many AAV serotypes have been identified in nature. They differ in their capacities to bind to different cells and in their transduction efficiencies (Table 1).

Table 1. *Major AAV serotypes used in retinal gene therapy and their clinical characteristics*

AAV serotype	Principal retinal tropism/ feature	Clinical or research example	Route of administration and current status
AAV2	Provides strong transduction in RPE cells and photoreceptors.	Voretigene neparvovec-rzyl (Luxturna®) for *RPE65*-associated retinal dystrophy.	Administered subretinally. It is the first ocular gene therapy platform approved by the FDA in 2017 and the EMA in 2018.
AAV5	Suitable for photoreceptor transduction.	Botaretigene sparoparvovec for *RPGR*-associated X-linked retinitis pigmentosa.	Administered subretinally. Although functional improvement signals were reported in early-phase studies, the phase 3 LUMEOS trial did not meet its primary visual mobility endpoint; the treatment remains investigational.
AAV8	Can efficiently target photoreceptors, particularly cone cells.	Gene replacement studies for *CNGA3*-associated achromatopsia.	Administered subretinally. Safety and cone-function outcomes have been evaluated in clinical studies.
AAV9	Has broad tissue tropism; its potential to reach different cell types in the retina is being investigated.	AXV-101 for *BBS1*-associated retinal degeneration	It is being investigated particularly for intravitreal administration and broad retinal distribution; its ocular use remains experimental.

Capsid Engineering

Although natural AAV serotypes have achieved important successes in retinal gene therapy, several biological barriers limit clinical efficacy. The principal barriers are the internal limiting membrane (ILM), insufficient cell type-specific transduction, and the host immune response. To overcome these problems, molecular modifications are made to the capsid, the outer protein shell of AAV.

Capsid engineering is performed using two main strategies:

1. Rational design: Specific amino acid regions in the natural AAV capsid are deliberately modified. This can increase binding capacity to cell-surface receptors or eliminate antibody-recognition sites.

2. Directed evolution: Thousands of random capsid variants are generated, after which those that best transduce retinal cells are selected. The AAV2-7m8 variant discovered using this method was able to cross the ILM barrier and reach photoreceptors after intravitreal injection.[5] Intravitreal rAAV2tYF-CB-hRS1, used for X-linked retinoschisis, was found to be safe in early clinical data.[10]

Preclinical Models

Before proceeding to clinical trials, the safety and efficacy of gene therapies are tested in laboratory and animal models. Given the complex structure of the retina and the genetic diversity of human IRDs, different model systems play complementary roles in research.

Mouse models provide a rapid and low-cost platform for genetic manipulation, mechanistic studies, and initial efficacy assessment; *RPE65* and *RPGR* models have been instrumental in this regard.[6] However, their low cone density and lack of a macula reduce their predictive value for macular diseases. Briard dogs with *RPE65* mutations played a critical role in the translation of voretigene neparvovec-rzyl because of their eye size and natural disease phenotype.[2] Pigs and rabbits are used in studies of surgical technique, subretinal blebs, and distribution, whereas nonhuman primates are used to evaluate foveal anatomy, intravitreal penetration, and immunogenicity.[5]

Retinal organoids generated from patient-derived induced pluripotent stem cells (iPSCs) enable investigation of the effect of a patient-specific mutation in human cells, comparison of capsid tropism, and validation of gene-editing candidates. Correction of a *PROM1* variant in iPSC lines is one example of this approach.[11] Human retinal explants, prepared from donor retinas, enable short-term analysis of vector penetration and expression within the native layered architecture. Because organoids do not fully reflect the vascular and immune microenvironment, explants have a short lifespan, and animal models have species-specific differences, the most reliable translational approach is to use these systems in a complementary manner.[5, 12]

Clinical Applications and Current Studies

Approved Gene Therapy

a) Voretigene Neparvovec-rzyl, AAV2-RPE65 (Luxturna®)

Voretigene neparvovec-rzyl is the first ocular gene therapy approved by the FDA in 2017 and the EMA in 2018. Its demonstration of the clinical feasibility of AAV2-based gene transfer in the human retina accelerated the development of programs for other inherited retinal diseases.[2]

The treatment is indicated for patients with retinal dystrophy associated with biallelic RPE65 variants who have sufficient viable retinal tissue. RPE65 enzyme deficiency disrupts the conversion of all-trans-retinyl esters to 11-cis-retinal, leading to impairment of the visual cycle and progressive photoreceptor degeneration. Voretigene neparvovec-rzyl delivers a functional *RPE65* gene subretinally to RPE cells via an AAV2 vector, thereby aiming to restore enzyme production and reactivate the visual cycle.[6]

Phase 1/2 studies reported improvements particularly in visual function under low-light conditions, light sensitivity, navigation performance, and microperimetry.[13] In the phase 3 randomized controlled trial involving 31 patients, the primary endpoint, the multi-luminance mobility test (MLMT) score, improved significantly in the treatment group, whereas changes in visual acuity and visual field were more limited.[14] Functional gains were shown to be largely maintained at two- and five-year follow-up, and functional magnetic resonance imaging studies demonstrated increased visual cortex activation.[15-17]

Although the treatment's safety profile is generally acceptable, retinal tear or detachment, subretinal

hemorrhage, and cataract may develop due to vitrectomy and subretinal injection.[14] Perifoveal chorioretinal atrophy has been reported in treated areas, and these atrophic areas have been shown to enlarge over time in some cases.[18-20] Serious complications such as bilateral exudative retinal detachment are rare.[21] Although no serious systemic immune reaction has been reported, perioperative corticosteroid therapy is administered to control the vector-related inflammatory response.[15]

Gene-Specific Therapies Under Clinical Investigation

Most gene-specific therapies for inherited retinal diseases remain investigational, with programs ranging from early-phase safety and dose-escalation studies to phase 3 trials. Representative clinical programs are summarized in Table 2.

a) Choroideremia (CHM)

Choroideremia is an X-linked progressive chorioretinal degeneration caused by pathogenic variants in the *CHM* gene. *REP1* deficiency disrupts intracellular vesicular transport, causing progressive loss in the RPE, photoreceptors, and choroid. The disease usually begins in males with night blindness and constriction of the peripheral visual field; central vision is also affected at advanced stages.

Gene therapy aims to deliver a functional *CHM* gene subretinally to the RPE and photoreceptors using an AAV2 vector and to restore *REP1* expression. Choroideremia has become one of the IRDs in which clinical gene replacement studies have reached the most advanced stage after *RPE65*-associated retinal dystrophy.[8]

Early-phase studies reported stabilization or partial improvement of visual acuity and improvement in microperimetric retinal sensitivity in some patients.[22] However, the visual acuity-based primary endpoint was not met in the phase 3 trial; the results were considered potentially influenced by the area of preserved retina at baseline, surgical targeting, and the endpoints used. Long-term data indicate that efficacy varies among patients and that disease progression is not completely halted.[8]

Although the safety profile is generally acceptable, complications related to subretinal surgery, including retinal detachment, cataract, and local inflammation, have been reported. Current findings demonstrate that gene transfer is feasible; however, appropriate patient selection and disease-specific functional endpoints are required to demonstrate clinical efficacy.

b) X-Linked Retinitis Pigmentosa (RPGR)

RPGR-associated X-linked retinitis pigmentosa is one of the most severe forms of RP, with early onset and rapid progression. The *RPGR* protein contributes to the structural and functional integrity of the photoreceptor cilium; loss of function causes degeneration first of rods and then of cones. The rapid natural course of the disease and the limited therapeutic window created by an adequate photoreceptor reserve have made *RPGR* a priority target for gene therapy.[4] The treatment aims to deliver a functional *RPGR* gene subretinally to photoreceptors using AAV5 or AAV8 vectors, restore ciliary function, slow degeneration, and preserve existing visual function.[23] In the phase 1/2 study of AAV5-based botaretigene sparoparvovec, signals of improvement in retinal sensitivity and microperimetry were reported, whereas changes in visual acuity remained more limited and heterogeneous.[23] Studies of AAV8-based cotoretigene toliparvovec also showed increased retinal sensitivity in some patients; however, a consistent functional benefit could not be demonstrated across the entire cohort.[24]

More recently, the phase 3 LUMEOS trial involving 95 patients did not meet its primary endpoint based on the visual mobility assessment.[25] However, improvements were reported in secondary measures, including retinal sensitivity, low-luminance visual acuity, and patient-reported visual function. In 2026, Meira GTx reacquired botaretigene sparoparvovec and announced plans to pursue regulatory submissions; nevertheless, the treatment remains investigational.[25]

Safety concerns are predominantly retinal detachment, cataract, and transient inflammation related to subretinal surgery. Clinical outcomes are thought to be influenced by baseline photoreceptor reserve, the location of the treatment area, dose, and transgene expression. Therefore, future studies should focus on patients at an early stage, sensitive functional measures, and standardization of surgical targeting.

Table 2. *Selected ongoing gene, RNA, and optogenetic therapy trials in inherited retinal diseases*

Disease/target gene	Therapeutic candidate and platform	Route of administration	Phase	Current recruitment status	ClinicalTrials.gov number
RP (*RHO*-associated and gene-agnostic cohort)	OCU400; NR2E3 modifier gene therapy	Subretinal	Phase 3	Active; not recruiting	NCT06388200
Bietti crystalline dystrophy (*CYP4V2*)	VGR-R01; gene replacement	Subretinal	Phase 3	Active; not recruiting	NCT06699108
LCA10 (*CEP290* c.2991+1655A>G)	Sepofarsen; antisense oligonucleotide	Intravitreal	Phase 3	Recruiting	NCT06891443
X-linked retinoschisis (*RS1*)	ATSN-201; AAV.SPR-hGRK1-hRS1syn gene replacement	Subretinal	Phase 1/2/3	Recruiting	NCT05878860
X-linked RP (*RPGR*)	AGTC-501 (laruparetigene zovaparvovec); rAAV2tYF-GRK1-hRPGRco	Subretinal	Phase 2/3	Active; not recruiting	NCT04850118
RP (*USH2A* exon 13)	Ultevursen; antisense oligonucleotide	Intravitreal	Phase 2b	Active; not recruiting	NCT06627179
Stargardt disease (*ABCA4*)	SB-007; AAV-based gene therapy	Subretinal	Phase 1/2	Recruiting	NCT06942572
Stargardt disease (*ABCA4*)	ACDN-01; AAV-based ABCA4 RNA exon editor	Subretinal	Phase 1/2	Recruiting	NCT06467344
RP (*RHO*)	ZVS203e; rAAV8/SauriCas9-based gene editing	Subretinal	Phase 1/2	Recruiting	NCT06952842
Advanced rod-cone dystrophy (gene-agnostic)	SPVN06; AAV-RdCVF/RdCVFL	Subretinal	Phase 1/2	Active; not recruiting	NCT05748873
RP (*PDE6A*)	rAAV8.hPDE6A; gene replacement	Subretinal	Phase 1/2a	Active, not recruiting; one-year results published[43]	NCT04611503
RP (*CNGA1*)	VG901; AAV2.NN-CNGA1 gene replacement	Intravitreal	Phase 1	Recruiting	NCT06291935
Advanced RP or choroideremia	RTx-015; optogenetic gene therapy	Intravitreal	Phase 1	Active; not recruiting	NCT06460844
AIPL1-associated IRD	LX107; gene therapy	Subretinal	Early phase 1	Recruiting	NCT07063030
RDH12-associated retinopathy	PUMCH-E101; gene therapy	Intravitreal	Early phase 1	Recruiting	NCT06749639
Usher syndrome type 1B (*MYO7A*)	AAVB-081; dual-AAV8 gene replacement	Subretinal	Phase 1/2	Enrollment completed; follow-up ongoing	NCT06591793
Stargardt disease (*ABCA4*)	AAVB-039; dual-AAV8 ABCA4 gene therapy	Subretinal	Phase 1/2	Recruiting	NCT07161544
BEST1-associated retinal disease	OPGx-BEST1; AAV-based gene replacement	Subretinal	Phase 1b/2a	Recruiting	NCT07185256

Note: Data were obtained from ClinicalTrials.gov records on August 21, 2026. The table includes representative studies that are recruiting or under active follow-up and is not a comprehensive list. Recruitment statuses may change over time.
Abbreviations: AAV, adeno-associated virus; ASO, antisense oligonucleotide; RdCVF, rod-derived cone viability factor; RP, retinitis pigmentosa.

c) Congenital X-Linked Retinoschisis (RS1)

Congenital X-linked retinoschisis is an IRD caused by pathogenic variants in the *RS1* gene and characterized by reduced central vision and foveal schisis in males. Loss of the retinoschisin protein disrupts cellular adhesion between the retinal layers and communication between photoreceptors and bipolar cells. The potential occurrence of complications such as vitreous hemorrhage and retinal detachment makes the disease an important target for gene replacement.[4] The treatment approach is based on delivering a functional *RS1* gene to retinal cells. The intravitreal rAAV2tYF-CB-hRS1 vector was developed to provide broader retinal distribution and reduce the need for subretinal surgery. Tyrosine-to-phenylalanine modifications in the capsid aim to increase outer retinal penetration by reducing intracellular degradation.[10]

No serious systemic safety signal was detected in the phase 1/2 study; however, responses in visual acuity, microperimetry, and OCT measures remained limited and heterogeneous. Although partial improvement in foveal structure was observed in some patients, a consistent gain in visual function could not be demonstrated across the entire cohort.[10] More recently, a phase 1 study of subretinal scAAV8-hRS1 in 12 patients aged 5–18 years showed closure of the macular schisis cavity in all treated eyes by week 13 and a mean BCVA gain of 10.8 letters at week 52. No grade 3 or higher adverse events or ocular inflammation were reported; however, one patient developed a macular hole, and no clinically meaningful improvement was observed in retinal sensitivity or electroretinographic function.[26]

Transient intraocular inflammation, changes in intraocular pressure, and vitreous opacities are the principal ocular events. Anti-AAV antibodies and cellular immune responses are also important limitations of intravitreal administration. Future studies need to optimize capsid penetration, the dose–immune response balance, and age-appropriate functional and structural endpoints for children.[4, 10]

d) Stargardt Disease (ABCA4)

Stargardt disease is an inherited maculopathy, most commonly caused by biallelic *ABCA4* variants, that is characterized by macular photoreceptor-RPE loss. Loss of *ABCA4* function leads to accumulation of bisretinoids in photoreceptor outer segments, RPE toxicity, and progressive macular atrophy. The fact that the *ABCA4* gene exceeds the carrying capacity of AAV has necessitated the development of alternative vector systems.[27]

Clinical studies have used the EIAV-based lentiviral vector SAR422459, which can carry full-length *ABCA4* cDNA. Subretinal gene transfer was intended to restore *ABCA4* expression, reduce toxic bisretinoid accumulation, and slow degeneration.[27] The phase 1/2a study evaluated the feasibility and safety of treatment for up to three years. However, no consistent and clinically meaningful efficacy signal was demonstrated in visual acuity, microperimetry, OCT, or fundus autofluorescence measures. Progression of RPE atrophy was observed in some eyes; whether this change was related to the natural course of the disease, surgery, or the vector could not be determined conclusively.[27]

Although current experience demonstrates that large genes can be delivered using lentiviral vectors, it has also shown that target-cell transduction and expression efficiency are important limitations. Dual or split AAV systems, gene editing, and combinations with pharmacologic therapies that reduce bisretinoid formation are major areas of future research.[27]

e) Achromatopsia (CNGA3/CNGB3)

Achromatopsia is a cone dysfunction characterized by photophobia, nystagmus, severe color vision impairment, and reduced visual acuity and is most commonly associated with biallelic *CNGA3* or *CNGB3* variants. Dysfunction of the cone-specific cyclic nucleotide-gated channel impairs phototransduction. The potential anatomical preservation of target cells has made the disease a suitable candidate for cone-specific gene replacement.[28]

Treatment aims to deliver the missing *CNGA3* or *CNGB3* subunit subretinally to cone photoreceptors via AAV and reactivate cone phototransduction. AAV8-based vectors containing cone-specific promoters have been used in clinical programs.[28] Early clinical studies found safety to be generally acceptable and reported partial improvements in contrast sensitivity, photophobia, and some cone-specific psychophysical measures. In contrast, gains in visual acuity remained limited and variable among patients.[28]

Complications are mainly local retinal injury related to creation of the subretinal bleb, retinal tear or detachment,

cataract, and transient inflammation. Age at treatment, foveal cone integrity, bleb location, and the developmental plasticity of the visual cortex may affect the clinical response. Future studies need to focus on cone-specific functional measures and the early therapeutic window.[28]

f) MERTK-Associated Retinitis Pigmentosa

The MERTK protein plays a fundamental role in the phagocytosis of photoreceptor outer segments by RPE cells. Loss of *MERTK* function causes accumulation of outer-segment debris and secondary photoreceptor degeneration, resulting in an early-onset and rapidly progressive RP phenotype.[29] In gene replacement, functional *MERTK* cDNA is delivered subretinally to RPE cells using an AAV vector. The aim is thereby to reactivate RPE phagocytosis, slow photoreceptor loss, and preserve existing visual function.[29]

In the phase 1 study, the treatment was feasible and generally safe. Signals of improvement in visual acuity and other functional measures were observed in a limited number of patients, whereas stabilization predominated in the others. The response is thought to be more pronounced, particularly in early-stage eyes with adequate outer retinal integrity.[29] Safety issues are predominantly events related to subretinal surgery, such as transient local retinal detachment, hemorrhage, cataract, and inflammation. Although current data support the validity of the biological target, they indicate that larger studies, appropriate patient selection, and standardized functional endpoints are required to confirm efficacy.[29]

g) Bietti Crystalline Dystrophy (CYP4V2)

Bietti crystalline dystrophy is a chorioretinal dystrophy caused by biallelic *CYP4V2* variants and characterized by progressive loss of the RPE and photoreceptors as a result of impaired lipid metabolism. The disease is characterized by difficulty with night vision, visual-field constriction, and progressive central vision loss.[30]

Treatment aims to deliver functional *CYP4V2* cDNA subretinally using an AAV vector, correct lipid metabolism, reduce toxic accumulation, and slow retinal degeneration.[30] Nonrandomized early clinical studies reported signals of improvement in visual acuity and retinal sensitivity within 6–12 months in some patients. OCT and fundus autofluorescence measures were suggested to show possible slowing of atrophy progression; however, responses remained heterogeneous across the cohort.[30, 31]

More recently, a phase 1/2 dose-escalation study of subretinal ZVS101e in 11 patients reported no dose-limiting toxicities or drug-related serious adverse events. The low-dose group showed a mean BCVA gain of 14.0 letters at one year, whereas inflammation occurred mainly in the medium- and high-dose groups and was controlled with corticosteroids.[32] Treatment generally showed an acceptable safety profile; complications were largely limited to transient retinal separation, local detachment, cataract, and manageable inflammation related to subretinal surgery. Although the findings are promising, efficacy and durability need to be confirmed in larger, longer-term randomized controlled studies.[30, 31]

h) AIPL1-Associated Severe Retinal Dystrophy

AIPL1-associated severe retinal dystrophy is an autosomal recessive, rapidly progressive early-onset rod-cone degeneration that commonly presents in infancy with nystagmus, profoundly reduced vision, and severely attenuated or undetectable electroretinographic responses. *AIPL1* is a photoreceptor-specific molecular chaperone required for the stability and function of phosphodiesterase 6. Biallelic pathogenic variants lead to early photoreceptor loss, resulting in a narrow therapeutic window in which intervention before substantial structural degeneration is likely to be essential.[33]

In a first-in-human study, four children aged 1.0–2.8 years received unilateral subretinal rAAV8.hRKp.AIPL1. At a mean follow-up of 3.5 years, visual acuity in the treated eyes improved from an equivalent of 2.7 to 0.9 logMAR, whereas vision in the untreated eyes became unmeasurable. One child developed cystoid macular edema, with no other safety concerns reported.[33]

i) Bardet-Biedl Syndrome–Associated Retinal Degeneration (BBS10/BBS1)

Bardet-Biedl syndrome is an autosomal recessive multisystem ciliopathy in which progressive rod-cone degeneration frequently causes severe visual impairment during childhood or early adulthood. *BBS10* and *BBS1* are among the most common causative genes. In a *Bbs10* knockout mouse model, subretinal gene augmentation

delayed photoreceptor loss, preserved retinal function, and partially restored cone responses.[34] Building on these findings, three pediatric patients received investigational *BBS10* gene therapy in the United Kingdom in 2026 under the MHRA Specials program. This physician-led program primarily evaluates safety and feasibility and should not be considered a registered clinical trial.[35] For *BBS1*-associated retinal degeneration, AXV-101 is an AAV9-based subretinal gene-replacement candidate. A first-in-human, open-label, early phase 1 dose-escalation trial (AXIS; NCT07269665) has been registered in children with biallelic *BBS1* variants but was not yet recruiting at the latest update.[36] Both approaches remain investigational, and early molecular diagnosis is likely to be important because treatment cannot restore photoreceptors that have already been lost.

j) Leber Hereditary Optic Neuropathy

Leber hereditary optic neuropathy (LHON) is an optic neuropathy that affects retinal ganglion cells, is most commonly caused by mitochondrial *MT-ND4*, *MT-ND1*, or *MT-ND6* variants, and is characterized by acute or subacute central vision loss. The disease frequently occurs in young men and may become bilateral within a short period.[37]

Because of the difficulty of direct gene transfer to mitochondrial DNA, allotopic expression is used. An *ND4* or *ND1* transgene optimized for nuclear codons is delivered intravitreally to ganglion cells using an AAV2 vector; the protein synthesized in the cell nucleus is then directed to the mitochondria.[37, 38] Baseline visual level, mutation type, and the symptom-to-treatment interval are the main factors affecting the clinical response.[39]

Lenadogene nolparvovec has been evaluated in the REVERSE, RESCUE, and REFLECT phase 3 programs. Improvement in visual acuity in the untreated fellow eye as well as in the treated eye has complicated interpretation of the studies but has also been one of the distinctive features of the method.[9, 38] More pronounced gains have been reported in patients treated within the first six months after symptom onset, and follow-up extending to five years has shown that visual improvement is maintained to some extent.[9, 40, 41] Early studies with AAV2-ND1 also suggest that allotopic expression may be applied to mitochondrial targets other than *ND4*.[37]

Mild intraocular inflammation and transient elevation of intraocular pressure are the principal ocular events; no serious systemic or ocular safety signal has been detected during long-term follow-up.[9] The relationship between structural and functional responses is incomplete; RNFL and ganglion cell layer measurements may help determine the therapeutic window.[42] Although current data support the clinical feasibility of allotopic gene transfer, the treatment has not yet been approved.

Next-Generation and Gene-Agnostic Approaches

CRISPR/Cas9-Based Gene Editing

AAV-mediated gene replacement exerts its effect by adding a functional gene copy; however, its use is constrained by vector carrying capacity and may be unsuitable for dominant-negative disease mechanisms. By contrast, mutation-specific genome- or RNA-targeted strategies may be used to address pathogenic deep-intronic and splice-altering variants. CRISPR/Cas systems enable disease-causing sequences to be disrupted, excised, or corrected at the DNA level. Although the postmitotic nature of retinal cells may support the long-term persistence of gene-editing effects, it also limits homology-directed repair.[1]

Gene editing may involve the creation of a double-strand break to disrupt the mutant allele, excise a pathogenic region, or facilitate sequence correction. Base editing and prime editing can correct selected nucleotide changes without generating a double-strand break, whereas targeted exon excision, reframing, or splice correction may restore a partially or fully functional protein in selected disorders.[5] CRISPR components are commonly delivered to the retina using subretinal AAV vectors, although nonviral delivery systems, including lipid nanoparticles, are also being investigated.[43]

EDIT-101, developed for *CEP290*-associated LCA10, is one of the first in vivo CRISPR programs administered to the human retina. Subretinally administered Cas9 and guide RNA were intended to eliminate the aberrant splicing caused by the pathogenic variant in intron 26. Early clinical data demonstrated the feasibility of the approach and showed that functional improvement could be achieved in some patients.[44]

Beyond clinical in vivo editing, patient-derived iPSC models provide an important platform for the individualized preclinical evaluation of gene-editing strategies. Correction of a pathogenic *PROM1* variant in patient-derived iPSC lines has demonstrated the feasibility of variant-specific editing in a human cellular model.[11] For rare disorders such as *RDH12*-associated retinopathy, representative disease models, robust natural history data and sensitive outcome measures remain particularly important before emerging molecular therapies can be translated into clinical studies.[12]

The principal safety concerns are off-target genetic changes, permanent genotoxicity, immune responses to the Cas protein, and surgical complications related to subretinal administration.[2] Therefore, although gene editing has strong clinical potential, its long-term genomic safety requires meticulous evaluation.

Antisense Oligonucleotides (ASOs)

Antisense oligonucleotides (ASOs) bind to target RNA to correct defective splicing, promote skipping of the pathogenic exon, or trigger degradation of the mutant transcript. Because they do not cause permanent changes in the DNA sequence, the treatment dose can be adjusted, and treatment can be discontinued when necessary. In contrast, their transient effects generally require repeated intravitreal injections.[1]

ASOs are particularly suitable for splicing defects and dominant-negative mutations. Approaches targeting *USH2A* exon 13 have demonstrated the feasibility of intervention at the transcript level in large genes; more durable AAV-mediated exon-skipping strategies have also been developed for the same target.[45] Splice modification targeting intronic variants in CEP290-associated *LCA10* is an important example of RNA-level therapy.[43] In dominant RHO variants, the aim is allele-specific suppression of the mutant transcript.[3]

The ability to design ASOs rapidly and in a variant-specific manner is an important advantage. However, the need for repeated dosing, the burden of intravitreal injections, risk of inflammation, cost, and patient adherence are the principal limitations of long-term use.

Other RNA and Gene-Agnostic Therapies

RNA-based therapies aim to regulate protein production without permanently altering the DNA sequence. mRNA administration can provide temporary synthesis of the missing protein, whereas siRNA or microRNA can suppress pathogenic transcripts. These approaches are less affected by gene size and are reversible; however, RNA stability, efficient delivery to the target cell, and short duration of action are the principal technical problems.[43] Suppression of the mutant transcript using siRNA is being investigated preclinically in dominant *RHO* variants.[3]

The clinical success of RNA-based therapies depends on increasing intracellular stability of the molecules, developing target-specific carriers, and safely implementing repeated dosing.

Gene-Agnostic Therapies

Gene-agnostic therapies do not correct a specific disease-causing variant. Instead, they aim to preserve residual retinal cells or restore visual function through mutation-independent mechanisms. These approaches may therefore be applicable to broader groups of patients with genetically heterogeneous inherited retinal diseases.

a) Neuroprotective Approaches

Neuroprotective strategies aim to delay photoreceptor loss, which represents a common final pathway in many inherited retinal diseases. *SPVN06* is an AAV-based gene-agnostic therapeutic candidate designed to support cone survival through the expression of rod-derived cone viability factors. By targeting mechanisms shared across different genetic forms of retinal degeneration, this approach has the potential to benefit a broader population of patients with retinitis pigmentosa.[4]

b) Optogenetic Therapies

Optogenetic therapy is a gene-agnostic restorative strategy intended primarily for patients with advanced retinal degeneration who no longer have sufficient viable photoreceptors for conventional gene replacement or gene editing. Light-sensitive opsin genes are delivered to surviving retinal ganglion or bipolar cells, enabling these inner retinal cells to respond to light even after substantial photoreceptor loss.[3]

In the first human studies, limited visual functions, including object perception and orientation, were achieved in some patients with advanced retinitis pigmentosa using AAV-

mediated opsin delivery combined with image-enhancing goggles.[1] The principal advantage of optogenetic therapy is its potential applicability in advanced disease regardless of the underlying genotype. Its current limitations include low visual resolution, the need for high-intensity light or external equipment, and the requirement for visual rehabilitation.

Recent clinical findings have strengthened the translational position of optogenetics. In the open-label phase 2 STARLIGHT study involving six patients with Stargardt disease, a single intravitreal injection of MCO-010 was well tolerated, with no serious adverse events and a mean BCVA improvement of 5.5 ETDRS letters at week 48.[46] However, the small sample size and absence of a control group limit the interpretation of efficacy. A rolling BLA submission for MCO-010 in advanced retinitis pigmentosa was initiated in 2025; however, the treatment remains investigational.[47]

Cell Replacement Therapies

Cell replacement therapy is also independent of the underlying genotype but is biologically distinct from gene-agnostic gene therapy. Rather than modifying the function of surviving retinal cells, it aims to replace photoreceptors or RPE cells that have already been lost. Stem cell- or induced pluripotent stem cell-derived photoreceptors and RPE cells are transplanted into the subretinal space with the aim of restoring photoreceptor function or metabolic support provided by the RPE. Preclinical studies have demonstrated partial functional restoration; however, integration into the appropriate retinal layer, formation of synaptic connections, long-term cell survival, immune rejection, and tumorigenicity remain fundamental unresolved challenges.[43]

Optogenetic therapy may provide limited but functional vision in the nearer term, whereas cell replacement aims to achieve more comprehensive tissue regeneration. Both approaches may expand treatment options for patients with advanced retinal degeneration who can no longer benefit from conventional gene replacement.

Nanotechnology and Nonviral Carriers

The approximately 4.7-kb carrying capacity of AAV vectors, their immunogenicity, and the difficulty of redosing have increased the need for alternative carrier systems. Lipid, polymeric, and inorganic nanoparticles aim to deliver DNA or RNA to retinal cells without using a viral capsid.[43]

Lipid nanoparticles are particularly prominent for their ability to carry RNA and their chemical customizability. Polymeric systems offer higher carrying capacity, whereas inorganic nanoparticles can be directed to a target through surface modifications. The principal advantages of nonviral systems are their ability to carry large genes, their lower susceptibility to anti-AAV antibodies, and their suitability for redosing.

In contrast, penetration into the outer retina, cell-specific targeting, adequate expression, biodegradability, and long-term toxicity remain unresolved. Rather than completely replacing AAV in the near term, these platforms are expected to play a complementary role in delivering large genes and repeated RNA therapies.

Future Perspectives and Challenges

Durability and Safety

Achieving long-term transgene expression with a single administration does not mean that clinical efficacy will continue indefinitely. Although gene therapy can improve the function of existing cells, the underlying degenerative process may not be completely halted. Therefore, functional gain and anatomical disease progression should be evaluated separately.[6]

Although gains in visual function can be maintained for a long period in RPE65-associated retinal dystrophy, outer retinal degeneration has been shown to continue during four- to five-year follow-up.[14, 16] In choroideremia, visual function and retinal sensitivity were stabilized in some patients, but disease progression could not be completely prevented.[22] In LHON, improvements in visual acuity have been reported to persist for up to five years after lenadogene nolparvovec treatment.[9]

The safety profile varies according to the route of administration, vector, dose, and target cell. Subretinal injection can lead to surgical complications such as retinal tear or detachment, hemorrhage, and, rarely, exudative retinal detachment.[21] Development and progression of chorioretinal atrophy in areas treated with voretigene neparvovec have been reported in different series.[18, 20] Although intravitreal administration is less invasive, outer

retinal penetration is lower and the anti-AAV immune response may be more pronounced. Although inflammatory reactions can generally be controlled with corticosteroids, redosing remains an important limitation.[2]

In studies to date, serious systemic toxicity has been rare, and systemic distribution of the vector has generally been limited.[15] Nevertheless, small patient groups cannot exclude rare or late complications. Preclinical rAAV.hPDE6A studies also demonstrate the importance of vector- and dose-specific long-term ocular toxicology assessment.[48]

Long-term follow-up is required in gene therapy programs to evaluate late genotoxicity, immunologic complications, and persistence of efficacy. Follow-up of patients for up to 15 years in the Luxturna clinical program is one example of this approach.[6] Postmarketing registries and real-world data will play a fundamental role in evaluating rare adverse events and clinical durability.

Overall, retinal gene therapies can provide meaningful functional benefit in the short and medium term; however, it should be considered that anatomical degeneration may continue and that responses vary among patients. Long-term success depends on the combined optimization of early patient selection, appropriate dose, safe administration, control of the immune response, and disease-specific endpoints.

Personalized Medicine and Targeted Approaches

The clinical success of retinal gene therapy depends on identifying the right patient at the appropriate stage of disease. Integration of molecular diagnosis into routine practice will enable patients to be identified before irreversible photoreceptor loss develops and allow more effective use of the potential therapeutic window. A better understanding of genotype-phenotype relationships and the natural history of disease may allow the treatment platform, dose, target retinal area, and follow-up strategy to be planned for each patient.[43]

Artificial Intelligence and Imaging-Based Monitoring

OCT, fundus autofluorescence, microperimetry, and other functional tests are fundamental tools for patient selection and assessment of treatment response. Artificial intelligence-assisted analyses may enable earlier and more reproducible detection of outer retinal integrity, atrophy progression, and structural changes after treatment. These technologies may increase the sensitivity of endpoints in clinical studies while also contributing to the standardization of real-world follow-up.[49]

Access, Cost, and Regulatory Processes

The high development, manufacturing, and administration costs of gene therapies are among the main barriers to treatment access. Sustainable financing for small, genetically defined patient groups may require outcome-based payment models, national patient registries, and intercenter collaboration. Long-term outcome monitoring through patient registries and real-world data collection will be integral to the regulatory evaluation of both the persistence of clinical efficacy and rare or delayed adverse events.[6]

Integration of New Technologies

In the future, a single platform is not expected to be sufficient for all IRDs. Gene replacement and gene editing may have different roles in patients with a sufficient number of viable target cells; RNA therapies in specific transcript and splicing defects; and optogenetics and cell replacement in advanced photoreceptor loss. The development of nonviral carriers may contribute to overcoming the problems of delivering large genes and redosing. For these approaches to enter clinical use, long-term safety, manufacturing standardization, and feasibility, as well as efficacy, must be demonstrated.

Conclusion

Gene therapy for inherited retinal diseases moved from an experimental approach into clinical practice with the approval of voretigene neparvovec-rzyl. This development has demonstrated that treatment directed at the molecular cause is possible in patients with an appropriate genotype and sufficient viable retinal tissue. However, most gene-specific therapies other than *RPE65* remain under clinical investigation and reported efficacy outcomes are largely limited or heterogeneous.

Current evidence indicates that clinical success depends not only on the vector and transgene but also on early molecular diagnosis, appropriate patient selection, preservation of the target tissue, safe administration, and disease-specific endpoints. The possibility that anatomical degeneration

may continue despite long-term transgene expression demonstrates the continuing importance of structured post-treatment follow-up.

In the future, gene replacement, gene editing, RNA therapies, optogenetics, and cell replacement may become complementary options according to disease stage. The principal goal should be not merely to move more technologies into clinical trials, but to match the right patient with the appropriate treatment platform at the right time and preserve the resulting benefit without compromising long-term safety, accessibility, and sustainability.

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