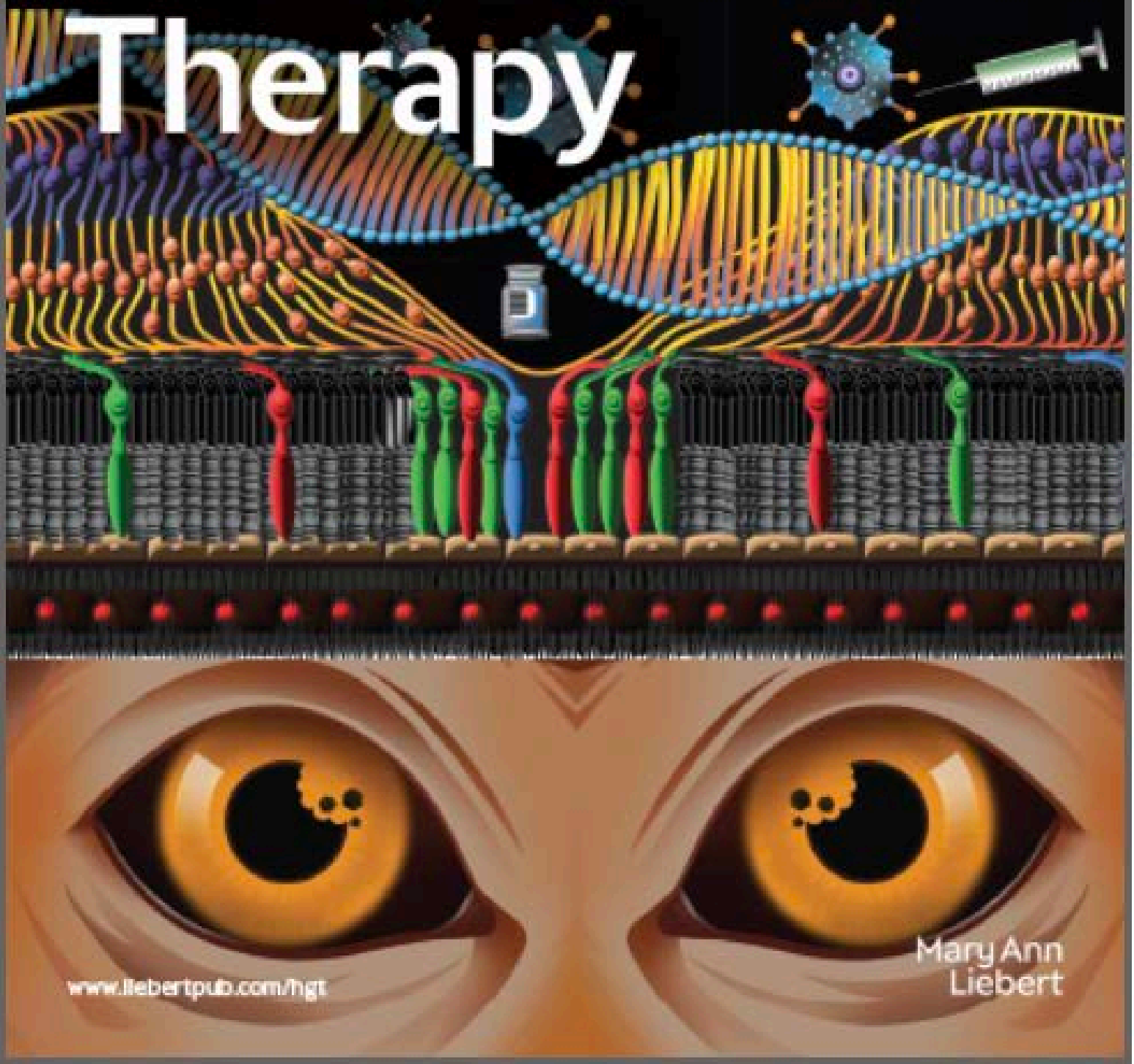
VOLUME 36, NUMBERS 19 AND 20, OCTOBER 2025

ISSN: 1043-0342

Human Gene Therapy

Special Issue:
Ocular Gene Therapy



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Update on Gene Therapy Clinical Trials for Eye Diseases

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Inherited and complex retinal degenerative diseases, such as retinitis pigmentosa, age-related macular degeneration, and glaucoma, represent a significant global burden of irreversible vision loss. Due to immense genetic and clinical heterogeneity and complex underlying mechanisms, these diseases still lack safe and effective disease-modifying treatments. This review summarizes the current landscape of gene therapeutic approaches to develop novel treatments for these blinding conditions. Specifically, we provide an update on several ongoing or completed clinical trials on gene-specific or gene-agnostic approaches, including recombinant adeno-associated viral vector-mediated delivery of the full gene or gene editing and antisense oligonucleotide components into the eye. We also discuss the initial clinical trial results of the use of the different approaches to ocular delivery, including subretinal, intravitreal, and suprachoroidal delivery. While long-term clinical trial data and refined clinical endpoints are essential to assess the efficacy, safety, and durability of these strategies, the data so far underscore the immense potential of gene therapy to revolutionize the management of retinal diseases in patients living with these debilitating conditions.

Keywords: retina, retinal degeneration, age-related macular degeneration

INTRODUCTION

The retina is a neurosensory tissue located in the back of the eye. It consists of several types of neurons and Müller glia. The neurons in the retina are arranged in multiple layers: photoreceptor layer, inner nuclear layer (houses inner neurons, such as bipolar cells, horizontal cells, and amacrine cells), and ganglion cell layer (extends the axons to the brain via the optic nerve). In addition, there are two synaptic layers (outer plexiform layer, connecting photoreceptors to bipolar cells, and inner plexiform layer, connecting the inner neurons to the ganglion cells). Photoreceptors are the most abundant cell types in the retina and are the first responders to light. They are also in direct contact with the overlaying retinal-pigmented epithelium (RPE), which participates in maintaining photoreceptor homeostasis and in the visual cycle to renew the chromophore for the phototransduction cascade.[1,2] The Müller cells are the major glial cells of the retina and provide morphological support to the retina. The cell bodies of the Müller cells reside in the inner nuclear layer and emanate processes that encompass the outer and inner plexiform layers. They are involved in neuronal metabolism, waste removal, controlling retinal homeostasis, and supplying chromophores for cone visual function.[3]

There are two types of photoreceptors: rods and cones. The rods are highly sensitive to light and function at very low light intensities (starlight vision). The photopigment rhodopsin present in the rods is bleached at higher light intensities. Cones, in contrast, respond to higher light intensities and are responsible for our daytime vision. The human retina contains 95 – 97% rods and only 3 – 5% cones. In primates, most of the photoreceptors are concentrated around the central retina in a region called the macula. It also houses >90% of the cones in its center in a region called the fovea. The fovea, therefore, is responsible for high acuity vision.[2]

Given the interplay between the different cell types of the retina, any perturbations in the development or function of photoreceptors, RPE, or ganglion cells due to genetic or environmental insults result in vision-threatening disorders. They range from retinitis pigmentosa (RP) to age-related macular degeneration (AMD) and glaucoma.[4] Considerable progress has been made in tackling these disorders. In this review, we will focus on the recent

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DOI: 10.1177/10430342251379824

advances in gene therapy approaches to develop therapeutic modalities for these blinding disorders.

Most inherited retinal dystrophies (IRDs) are caused by mutations in photoreceptor cell-expressed genes. If the mutated gene is not exclusively expressed in the retina, the condition can manifest as syndromic disease affecting also other tissues (*e.g.,* Bardet–Biedl syndrome[5]: *BBS2*, *BBS4*, *BBS6*, *CEP290*; Joubert syndrome[6]: *CEP290*; Senior–Loken syndrome[7]: *NPHP5*, *CEP290*; Meckel–Gruber syndrome[8]: *CEP290*; Usher Syndrome[9]: *MYO7A*; *USH2A*). Different mutations in the same gene can cause a range of clinical diseases (*e.g., CEP290*), whereas the same pathology can be caused by mutations in different genes, complicating the genotype-to-phenotype correlation and making IRDs one of the most heterogeneous disease groups in humans. IRDs are monogenic and follow a Mendelian inheritance pattern. X-linked mutations manifest with a wide range of heterogeneity in males, whereas, in females, pathologies are generally milder, if present at all, but can also be variable due to random X-chromosome inactivation.

The IRDs are a spectrum of disorders that vary by age of onset and location (peripheral or central retina involvement) and severity (age of onset and rate of progression) of the pathology.[10–12] Leber congenital amaurosis (LCA) is a childhood blindness disorder and is characterized by early onset IRD. RP is a relatively slower-progressing IRD and mainly affects rod-mediated vision, followed by cone cell loss. Cone-rod dystrophy is characterized by the loss of cone function followed by rod dysfunction and degeneration. Some photoreceptor dystrophies can also be caused by genes expressed in RPE, such as LCA2, since RPE cells are important for maintaining retinal homeostasis. Finally, there are a few atypical forms of IRDs. Stargardt disease is a condition that primarily affects the foveal cones. The disease is caused by mutations in the photoreceptor-specific protein ABCA4 (ATP-binding cassette, subfamily A, and member 4)[13] or the photoreceptor-enriched protein ELOVL4 (elongation of very long chain fatty acid-like 4).[14] Mutations in these genes also cause secondary RPE pathologies,[15,16] which is atypical for mutations in photoreceptor-expressed genes. Retinoschisis,[17] choroideremia,[18] and Leber hereditary optic neuropathy (LHON)[19] are examples of IRDs that are caused by genes and also expressed in cell types other than photoreceptors.

Remarkable progress has been made in developing gene therapies for IRDs. This review article has been compiled to provide an update on the outcomes of clinical trials that have recently been completed and of the new clinical trials that have been initiated to tackle these blinding diseases (Supplementary Table S1).

Monogenic

Achromatopsia. Achromatopsia is an autosomal recessive cone dysfunction affecting 1 in 30,000 people. It is a genetically heterogeneous disease with mutations in six known genes. Of these, mutations in two cone cyclic nucleotide-gated (CNG) channel subunit genes, *CNGA3* (MIM 600053) and *CNGB3* (MIM 605080), account for most cases. Patients start showing symptoms at birth or early infancy with reduced visual acuity, photophobia (sensitivity to bright light), nystagmus (involuntary eye movements), and loss of color vision.[20]

As of June 2025, there are five registered gene therapy clinical trials for achromatopsia. The study center STZ eye trial initiated the first Phase I/II clinical trial for CNGA3 achromatopsia in 2015 (NCT02610582). The gene therapy vector was delivered via unilateral subretinal injection without substantial safety findings after 12 or 36 months, resulting in modest improvement in visual acuity and contrast sensitivity.[21,22] However, these improvements were not found to be statistically significant when compared with the fellow untreated eye. An updated clinical trial is currently in progress, involving a bilateral injection of the test article. Patients who received treatment in one eye under the original protocol received an injection in the fellow eye. The study aims to evaluate additional benefits in treating children and adolescents (NCT02610582), who may exhibit greater cortical plasticity, for a better outcome by limiting the impact of the disease on the development of the visual cortex.[23,24] Comprehensive results from this longer follow-up are expected in 2027.

MeiraGTx recently completed two open-label, dose-escalation Phase I/II clinical trials for both CNGA3 and CNGB3 gene augmentation therapies for patients with achromatopsia (NCT03758404 and NCT03001310). AAV8-hCARp.hCNGB3, delivered subretinally, was safe and generally well tolerated in adult and pediatric participants.[25] Adverse events, and in particular intraocular inflammation, appeared to be more severe at higher doses but were manageable. There was no consistent efficacy observed after 24 weeks; however, changes in some participants indicated positive trends in color vision and photoaversion. Results from a separate long-term follow-up study for patients who participated in AAV2/8-CNGB3 or AAV2/8-CNGA3 retinal gene therapies (NCT03278873) are not yet available.

At the time of our last review,[26] two other clinical trials in Phase I/II from Applied Genetic Technologies Corp (AGTC) targeting both CNGA3 and CNGB3 achromatopsia with subretinal injections (NCT02935517 and NCT02599922) reported favorable safety profiles, with improved photosensitivity in some individuals for CNGB3. Following the acquisition of AGTC by Beacon Therapeutics, the development of these two achromatopsia adeno-associated virus (AAV) candidates is currently on hold.[27]

To date, these studies have reported evidence of an excellent safety profile for the subretinally injected AAV2/8-CNGA3 and potential signs of light responsiveness by

the treated cones. The limited cohort size as well as potential impact of visual deprivation and amblyopia could preclude further interpretation of the results of this gene augmentation therapy.

X-linked retinoschisis. X-linked retinoschisis (XLRS; MIM 312700) is a clinically heterogeneous recessive disease and the leading cause of juvenile macular degeneration affecting 1 in 15,000–35,000 males annually. The disease mainly manifests in the first decade of life, although patients as young as 3 months of age have also been identified. XLRS is caused by mutations in the RS1 (Retinoschisin) gene located on the X chromosome. It encodes the Retinoschisin protein. This protein is secreted primarily by photoreceptors and is localized to the extracellular surface of photoreceptors and bipolar cells. Defects in Retinoschisin expression, structure, and secretion result in significant vitreo-retinal dystrophy, characterized by the splitting of inner retinal layers, retinal holes, reduced electroretinogram b-wave amplitudes, and vitreous humor alterations. Schisis in the peripheral retina increases the risk of extensive retinal separations and occasional retinal detachment.

The fragility of the retina in XLRS poses challenges for gene-based therapies. Most AAV gene therapies for retinal disorders that affect photoreceptor cells involve subretinal vector administration, which requires local retinal detachment—a method considered risky for XLRS patients. This has led to the development of new viral delivery methods.

Multiple clinical trials have been evaluating gene therapies for XLRS. An intravitreal (IVT) injection of a modified AAV2 from AGTC *(now Beacon Therapeutics)* delivering *Retinoschisin* (RS1) at three different doses failed to demonstrate a significant therapeutic effect (NCT02416622). Similarly, another Phase I/II trial initiated by the National Eye Institute showed no significant functional improvement 18 months posttreatment of an AAV8 vector delivered intravitreally (NCT02317887).[28] Of note, one patient in the highest dose cohort had retinal cavities closed transiently, suggesting sign of retinal biological activity. After a pause due to the COVID-19 pandemic, the original trial is now being continued by VegaVect Therapeutics. Dose-dependent ocular inflammation was observed in both trials, a risk that might be increased due to the baseline immune function in patients with XLRS[29] and which might limit transduction efficacy.

Atsena Therapeutics has developed a novel capsid (AAV.SPR) for subretinal injection that spreads laterally beyond the bleb margins.[30] This allows for gene delivery to large areas of the retina, including foveal photoreceptors, diminishing the risk of foveal detachment from blebs around the fovea. This is of particular interest for XLRS patients who present schisis cavities (splitting of retinal layers) in the central retina, increasing the risk of retinal detachment. Atsena Therapeutics recently received Orphan Drug Designation from the Food and Drug Administration (FDA) for ATSN-201 to treat XLRS in nine patients. No serious adverse events were reported in any of the three dose levels, and seven of nine patients showed foveal schisis closure. Improvement in best corrected visual acuity (BCVA) and low-luminance visual acuity was also reported (NCT05878860).[30,31] Other trials using IVT or subretinal injections of gene therapies registered on ClinicalTrials.gov are currently recruiting XLRS patients, with limited information available[32] (NCT06289452, NCT06066008, and NCT06345898). Preclinical *in vivo* studies and clinical trials have provided significant new knowledge to develop not only new delivery vectors but also next-generation gene augmentation therapies to rescue the phenotype.

Choroideremia. Choroideremia (MIM 303100) is a rare X-linked chorioretinal disorder affecting approximately 1 in 50,000 individuals. The condition manifests as progressive degeneration of photoreceptors, RPE, and choroid. It is caused by mutations in the Choroideremia (*CHM*) gene, which encodes the Ras-related GTPase Rab escort protein 1 (REP1). REP1 is essential for regulating intracellular trafficking and secretion of proteins and organelles through lipid prenylation to Rab proteins. Although the precise mechanism of the disease is not fully understood, CHM gene mutations likely lead to the progressive degeneration of the choriocapillaris, RPE, and photoreceptor layer, resulting in significant peripheral vision loss and tunnel vision.

Given the slow progression of retinal degeneration and the packageable size of the *CHM* coding sequence, gene augmentation therapy using AAV vectors has emerged as a promising treatment strategy. Initially, subretinal delivery of the virus was the primary approach. However, given their limited outcomes, recent therapies have focused on improving delivery capsids and administration routes for *CHM* gene augmentation. These advancements aim to address the safety concerns associated with subretinal delivery of gene therapy vectors, while simultaneously exploring delivery routes such as IVT or suprachoroidal routes that may offer broader transduction and better therapeutic efficacy.

Several clinical trials for choroideremia using gene therapy as a treatment have been conducted. Unfortunately, the delivery of the *CHM* gene has shown mixed results. Biogen's AAV2 vector timrepigene emparvovec (BIIB111 or AAV2-REP1, acquired from NightStaRx) was used in a Phase III clinical trial (Luna) with 161 randomized male participants completing the study (NCT03496012) and an acceptable safety profile[33] seen also in other trials[34–36] (NCT01461213, NCT02553135, NCT02671539, NCT02077361, NCT03507686, and NCT02407678). However, the trial did not meet its primary endpoint, a ≥15-letter improvement from baseline in

BCVA at 12 months as measured by the Early Treatment of Diabetic Retinopathy Study Chart.[33] Nonetheless, four patients in the treated group had significant improvement from baseline in BCVA and mean gain in vision.

Another Phase I/II clinical trial using a similar AAV2 construct for *CHM* did not show evidence of efficacy[37] (NCT02341807). Due to the nature of some inherited retinal diseases, treatment is not always expected to improve vision but rather to slow or prevent disease progression. For diseases such as choroideremia, the slow progression of the disease with slow decline in central vision requires long-term follow-ups and optimized enrollment criteria with well-defined endpoints to understand the benefit of such therapies.[33,34,38] A combined Phase III long-term safety and efficacy follow-up for the treatment of choroideremia with BIIB111 and X-linked RP (XLRP) with BIIB112 (see sub-section XLRP) is set to be completed in June 2026 (NCT03584165). Overall, the clinical trials for choroideremia have provided insights into vector design, delivery, and patient inclusion/exclusion criteria, which will be important to improve the approach to treating CHM.

RP. RP (MIM 268000) is a group of clinically and genetically heterogeneous inherited retinal degenerative diseases. RP patients typically present with good central retinal vision with central cone photoreceptor preservation. Because most mutations affect rod photoreceptor-expressed genes, many patients exhibit night blindness.[10–12] The deterioration of rod photoreceptors outside the fovea eventually progresses to secondary cone photoreceptor loss, constricting the peripheral visual field until patients experience tunnel vision. While the disease can progress eventually to complete blindness, this occurs mainly in patients who experience tunnel vision at a younger age. RP is inherited in an X-linked, autosomal recessive, and autosomal dominant manner. Studies using animal models and clinical imaging show widespread photoreceptor degeneration in RP. The photoreceptors respond to light by initiating a cascade of events starting with activation of chromophore-bound rhodopsin, a G-protein-coupled receptor, leading to the activation of phosphodiesterases and culminating in the closing of the CNG channel. This generates a current that alters neurotransmitter release at the photoreceptor pedicle. The signal travels through bipolar cells to retinal ganglion cells (RGC), which relay the signal to the visual cortex of the brain through the optic nerve. This light transduction cascade is distinct from the visual cycle, which refers to the renewal of the visual chromophore and involves RPE and photoreceptor cells. In addition, the RPE also provides nutrient support to photoreceptors and phagocytizes the shed photoreceptor outer segments. Any perturbations in photoreceptor and RPE structure or function lead to some form of retinal degeneration that can progress to blindness.

XLRP. XLRP (MIM 312610) is a severe, early-onset retinal disorder predominantly affecting males, leading to photoreceptor degeneration.[39] Approximately 70% of XLRP cases are attributed to mutations in the RP GTPase Regulator (*RPGR*) gene.[40] These mutations typically result in rod-cone or cone-rod dystrophy, characterized by peripheral vision loss and progressing to complete blindness by the third decade of life. The RPGR protein plays a crucial role in regulating protein trafficking to the outer segments of photoreceptors.[41] The *RPGR* gene encodes two major isoforms in the retina: $RPGR^{1\text{-}19}$ and $RPGR^{ORF15}$. The latter includes exons 1–14 of the *RPGR* gene, followed by a unique C-terminal exon called open reading frame 15 (ORF15), which encodes a repetitive, purine-rich sequence highly prone to mutations.[42]

Gene augmentation has been the primary strategy for gene therapy; however, due to the presence of the purine-rich repeats in exon ORF15 of $RPGR^{ORF15}$, the cloning of this isoform has proven challenging.[43] Several gene therapies are advancing in clinical trials with the potential to improve or stabilize vision in patients with XLRP.

The first-in-human gene therapy from Biogen (NightStar acquisition) was injected subretinally, using an AAV8 capsid to deliver a codon-optimized human $RPGR^{ORF15}$ under regulation of a human G-protein coupled receptor kinase 1 (hGRK1; a photoreceptor-specific gene) promoter (NCT03116113). Although positive trends in secondary endpoints were observed, such as a measure of visual acuity under low light conditions, the Phase II/III study did not meet its primary endpoints.[44–46] Nonetheless, some patients at the high dose had improved outcomes with BIIB112, prompting a long-term follow-up study (NCT03584165) to compare the outcome with a natural history study for XLRP[45,47] (NCT04926129).

Beacon Therapeutics has also been using a photoreceptor-specific GRK1 promoter and a full-length cDNA sequence, along with a modified AAV2 capsid for subretinal injection. The Phase II SKYLINE trial (NCT06333249) 12-month interim safety and efficacy results suggest that the high-dose cohort showed notable improvement in visual function.[48] The company also presented 36-month interim results from their dose-escalation Phase I/II Horizon trial (NCT03316560) at the EURETINA Congress in 2024.[49] A follow-up Phase II/III randomized masked study comparing two doses with a control untreated group recently dosed its first patient (NCT04850118)[50] and their open-label Phase II DAWN trial in participants who have been previously treated in one eye is enrolling (NCT06275620).

4D Molecular Therapeutics is currently evaluating the safety and maximum-tolerated dose of an XLRP treatment in a Phase I/II study using their proprietary R100 capsid via IVT injection (NCT04517149). The FDA granted Fast Track Designation for 4D-125,[51] and the enrollment was completed in 2022. Program and clinical

data updates from the 14 patients that have been treated are expected for this year,[52] with interim results suggesting that the therapy was well tolerated in the first eight patients.[53] However, 4D has halted this trial due to prioritization of other clinical-stage programs.[54]

An early Phase I from Frontera Therapeutics (NCT05874310), along with a dose escalation and dose expansion Phase I/II (NCT06492850), has also commenced recruitment and subject dosing. The AAV5 capsid, which is delivered via subretinal injection, has been well tolerated in the first participants in China.[55] The company just announced that FT-002 has been cleared by the FDA for a Phase II clinical trial in the United States.[56]

MeiraGTx has started to treat patients in a Phase I/II clinical trial (NCT03252847) (sponsored by J & J) with a truncated form of the *RPGR* gene, also driven by the GRK1 promoter. This shorter sequence is considered less prone to instability and recombination errors. The AAV5 vector was safe and well tolerated, and data from this open-label, dose-escalation/expansion study suggest improved retinal sensitivity and function when compared with the control group after 1 year.[57] These data supported follow-up studies underway (NCT04671433, NCT04794101, and NCT04312672, Janssen Research & Development). The company recently reported that the Phase 3 trial failed to meet the primary endpoint of improving vision-guided mobility through the maze in XLRP patients. Nonetheless, initial signs of improvement in secondary endpoints, including patient-reported vision scores, were observed.[58]

PDE6. Phosphodiesterase 6 (PDE6; MIM 600827) RP is a rare, inherited disorder that leads to progressive vision loss. This condition arises from mutations in one of the four *PDE6* genes, which encode the rod cGMP PDE, a key regulator of the visual transduction cascade in PRs. Mutations in different subunits of the rod cGMP PDE6 complex can lead to autosomal recessive RP. A Phase I/II clinical trial sponsored by eyeDNA Therapeutics (a wholly owned subsidiary of Coave Therapeutics) supplied patients with the human beta subunit (PDE6B) via subretinal administration of an AAV2/5. The company recently reported at the Association for Research in Vision and Ophthalmology 2024 meeting on the 24-month follow-up of their investigational gene therapy HORA-PDE6b (NCT03328130). The study showed a good safety profile and suggested positive efficacy results, looking at BCVA and Goldmann Visual Field outcomes,[59] supporting the data observed at the 12-month follow-up.[60] Up to 5-year postinjection, data from the low-dose group suggest stabilization of BCVA of the treated eyes compared with the consistent decline in untreated eyes.[61]

STZ eyetrial has developed a subretinal gene therapy for patients with mutations in the PDE6A gene. However, 12-month data from the Phase I/II showed that two patients experienced foveal thinning and vision loss[62] (NCT04611503). Natural history of PDE6A-retinopathy might inform the design of trials and assess the risks and benefits of such a therapy.[62,63]

RLBP1. Retinaldehyde-binding protein 1 (RLBP1) retinal dystrophy (MIM 180090) is a rare disorder, with approximately 160 cases reported in the literature as of 2023. The RLBP1 gene encodes cellular retinaldehyde-binding protein (CRALBP), a key visual cycle protein that provides the 11-cis-retinal photosensitive chromophore to both rods and cones. In Müller cells, CRALBP supports a cone-specific visual pathway that allows cells to quickly adapt to a wide range of light intensities. Mutations in the RLBP1 gene are linked to autosomal recessive RD, including RP, retinitis punctata albescens, Bothnia-type dystrophy, Newfoundland rod-cone dystrophy, and fundus albipunctatus. RLBP1-RD is characterized by night blindness and delayed dark adaptation from early childhood, followed by a progressive decline in visual fields, visual acuity, and color vision. Dysfunction in CRALBP results in extremely prolonged dark adaptation, reduced light sensitivity, and progressive vision loss. As the disease advances, central retinal function deteriorates, leading to central vision loss and ultimately legal blindness.

A 3-year follow-up study on the treatment of RP caused by mutations in the RLBP1 gene has just been published.[21] Interim safety results of the dose-escalation trial (NCT03374657) suggest that the subretinal delivery of AAV8-RLBP1 (CPK850, Novartis Pharma AG) aimed at the retinal superior vascular arcade is overall well tolerated, with manageable dose-dependent inflammation observed. RPE atrophy without loss of function was noted as the dose-limiting toxicity concern. The treatment resulted in improved dark adaptation recovery in 11 out of 12 treated patients, with several reporting self-perceived quality of life, but not in secondary endpoints such as cone-mediated visual function. Interestingly, retinal white dot-like deposits characteristic of the early stages of the disease regressed in the treated eye of all three patients presenting this phenotype, extending even beyond the bleb margin.[64] For more benefits, the authors suggest treating younger patients in the future using doses from the current study that showed limited inflammation or atrophy.

Stargardt disease. Stargardt disease 1 (STGD1; MIM 248200), also known as Stargardt macular dystrophy or juvenile macular degeneration, is a prevalent inherited retinal disease, with an incidence of approximately 1 in 8,000 to 1 in 10,000 individuals. Typically detected in late childhood or early adulthood, STGD1 is progressive and varies in severity, with some individuals not noticing vision loss until later in life. This condition is inherited in an autosomal recessive manner and is caused by variants in the ABCA4 gene, which has a carrier frequency as high as 1 in 20.

In the normal visual cycle, the ABCA4 protein plays a crucial role by transporting N-retinylidene phosphatidylethanolamine (NrPE), a product of the visual cycle, across

the photoreceptor disc membrane. Dysfunction of the ABCA4 protein leads to the accumulation of NrPE and all-trans-retinal within the photoreceptor disc membrane, which condenses to form phosphatidyl-pyridinium bisretinoid (A2PE). A2E cannot be further metabolized, leading to its accumulation within the RPE and forming a major component of lipofuscin, which is toxic to the RPE and results in its degeneration and subsequent loss of photoreceptor cells.

Despite numerous pharmacological therapies for STGD1 being tested in clinical trials, targeting various aspects of the visual cycle to reduce lipofuscin accumulation, no approved therapies currently exist. Due to the ABCA4 gene's complexity, which includes 50 exons spanning 128 kb of genomic DNA and a large protein of approximately 250 kDa, gene therapy development has been particularly challenging.

Safety, tolerability, and preliminary efficacy tests of a gene therapy trial from Ascidian Therapeutics just started (NCT06467344). The unique approach uses an ABCA4 RNA editor that can post-transcriptionally replace multiple exons simultaneously, potentially allowing for treatment of up to 70% of patients carrying ABCA4 mutations[65]

Another approach to augment large genes is to use split AAVs. Several preclinical publications suggest the feasibility, and SpliceBio just announced FDA clearance of their SB-007 candidate.[66] Although information is limited, recently, a clinical trial sponsored by the West China Hospital and likely based on a split AAV8 ABCA4 expression[67] dosed its first patient[68] (NCT06300476).

LCA. LCA is a group of congenital retinal dystrophies that cause severe vision loss from birth or early childhood. Patients typically present with nystagmus, slow or nearly absent pupillary responses, significantly reduced visual acuity, photophobia, and high hyperopia. There are no established diagnostic criteria for LCA, with the first signs usually appearing before the age of 6 months. LCA is the second most common group of IRDs after RP, accounting for about 5% of all retinal dystrophies. Its estimated prevalence ranges from 1 in 33,000 to 1 in 81,000, making it responsible for about 20% of legal blindness in children.

Currently, mutations in 20 retinal genes are known to cause the LCA phenotype, accounting for approximately 70% of cases, whereas the genes responsible for the remaining 30% of patients are yet to be discovered. These known mutations affect genes encoding retinal proteins involved in the phototransduction cascade, retinoid cycle, retinal development, protein trafficking, photoreceptor structure, photoreceptor ion channels, and metabolic enzymes. Visual deterioration in LCA cannot yet be prevented or halted. However, several promising new treatments are currently being tested in human clinical trials, including gene augmentation, oral drug therapy, and intraocular drugs. Early and precise clinical and molecular genetic diagnosis is crucial for the appropriate management of these diseases.

LCA2. The first FDA-approved gene therapy in the United States was Luxturna[69] (voretigene neparvovecrzyl), for the treatment of patients with biallelic mutations in the *RPE65* gene, the causative gene for LCA 2 (MIM 204100). A long-term safety and efficacy assessment for 5 years after the subretinal AAV2 treatment was initiated in 2019 (NCT03597399). At 4 years, improvement in visual function is still present, including for patients with chorioretinal atrophy.[70] HuidaGene Therapeutics was granted both orphan drug designation and Rare Pediatric Disease designation by the FDA for its lower dose and injection volume of a new AAV9-hRPE65. First patients have been dosed in China and United States (NCT06088992, NCT05906953) and preliminary data suggest it may be safer and more efficacious.[71]

LCA5. LCA5 (MIM 604537) is a rare, IRD caused by biallelic mutations in the *LCA5* gene, which encodes for a photoreceptor ciliary transport protein, lebercilin. An open-label Phase 1/2a trial being conducted by Opus Genetics is currently underway for OPGx-LCA5 (NCT05616793). This is an AAV8-mediated subretinal delivery of *LCA5* under the control of chicken β-actin promoter in patients with biallelic mutations in *LCA5*. Interim 1-year analysis revealed no serious adverse events or dose-limiting toxicities. There were also early signs of improvement in visual acuity and visual function. The investigators have recently reported efficacy in three subjects receiving a dose of 1e10 vector genomes per eye. Improvement in cone-mediated vision and improvement in virtual reality orientation and mobility tests was observed.[72]

LCA1. In another first-in-human therapy, Atsena Therapeutics recently reported 12-month safety and efficacy data from the Phase I/II Clinical Trial of ATSN-101 in patients with LCA1 (MIM 204000), caused by mutations in the photoreceptor-specific guanylate cyclase 2D (GUCY2D)[73] (NCT03920007). In an open-label ascending dose study, the AAV5 expressing a healthy copy of the gene under the regulation of the human hGRK1 was delivered subretinally with a favorable safety profile. Visual function improvements in high-dose subjects, mediated by rod photoreceptors, were observed. Patients had, on average, > 2 log improvements in FST, with two having > 3 log improvements. There were also concomitant improvements on the multiluminance mobility test. These responses are ≥ improvements seen in Phase 1/2 and 3 trials of AAV-RPE65/Luxturna.[73,74] Atsena has planned a Phase 3 global clinical trial for ATSN-101 in collaboration with Nippon Shinyaku.[75]

LCA10. LCA 10 (MIM 611755) is the most common form of LCA that is caused by biallelic mutations in a cilia-centrosomal protein-encoding gene *CEP290*. The full-length CEP290 gene is ~6.8 kb, which exceeds the

packaging limit of conventional AAV vectors for gene delivery. Therefore, recent approaches have focused on antisense oligonucleotide-based (Sepofarsen; Sepul Bio) or CRISPR-Cas-based (Editas Medicine) modalities that target a frequently occurring deep intronic mutation c.2991 + 1655A>G (pCys998X) that causes a splicing defect. Sepofarsen is an antisense oligonucleotide against the mutant allele that inhibits the expression of the mutant protein and allows for skipping of the mutant region for normal protein expression. Sepul Bio is continuing Phase 3 development of this program. Editas' program was the first CRISPR-Cas-based *in vivo* gene therapy. The vector containing the SaCas9 nuclease and two guide RNAs targeting the mutant CEP290 under the regulation of the GRK1 promoter was assessed for safety in a small study (NCT03872479). Further analyses suggested that genome editing resulted in moderate efficacy (improvement in cone function) that might meet the therapeutic threshold. Questions remain about the optimal timing of intervention and the importance of targeting two alleles in patients homozygous for the variant.[76] In November 2022, the company announced that it would not proceed with this program.[77]

LHON. LHON (MIM 535000) is a rare, maternally inherited mitochondrial disease predominantly diagnosed in young Caucasian men aged 14–26 years, with a worldwide prevalence of approximately 1 in 50,000. About 10% of patients experience symptom onset after the age of 50. LHON affects RGCs by impairing their energy production capabilities. Mutations in mitochondrial DNA (mtDNA) responsible for LHON remain silent until an unknown trigger induces bilateral central visual scotoma. Following the onset of vision loss, most patients experience progressive deterioration over the subsequent months.

Three primary point mutations in mtDNA are present in 90% of LHON patients. These mutations impact different subunits of NADH dehydrogenase 4 (ND4), leading to electron transport chain (ETC) dysfunction, reduced ATP production, and excessive reactive oxidative species generation. This results in energy production failure and cell death, culminating in visual loss. Other mutations may be prevalent in specific population groups with limited genetic data.

Researchers have explored drugs aimed at restoring the mitochondrial ETC in RGCs. Currently, no treatment effectively improves the visual outcomes of LHON. However, idebenone, vitamin B_2, and vitamin C supplementation have shown some promise in improving visual recovery in one study.[78] For most patients, visual dysfunction remains permanent, although spontaneous recovery may occur in some cases, particularly those with specific mutations and younger age at symptom onset. Significant progress has been made in evaluating free radical scavengers and gene therapy as potential treatments for LHON. Despite encouraging results, clinical trials have yielded mixed outcomes in halting visual deterioration. Effective FDA-approved treatments for patients with chronic disease lasting over a year are therefore still lacking.

GenSight's gene therapy LUMEVOQ (lenadogene nolparvovec) targets LHON, in which a functional copy of the *ND4* gene is delivered using AAV2.[79] The trial showed sustained improvement in visual acuity and maintained a favorable safety profile 4 years after bilateral IVT treatment in the REFLECT Phase III (NCT03293524) trial.[80] A clinical trial conducted by Bascom Palmer Eye Institute using a unilateral IVT injection of an AAV2 (Y444,-500,730F)-P1ND4v2 vector showed a favorable safety and tolerability profile but failed to show a clear efficacy effect in the study with no randomized untreated arm[81] (NCT02161380). After a 36-month follow-up study suggested vision improvement in several treated patients[82] (NCT01267422), another gene therapy study from the Huazhong University of Science and Technology (NCT03153293) for the treatment of acute LHON has been initiated. Neurophth has started dosing patients in a Phase III clinical trial for ND4 mutations after showing promising safety and efficacy data[83] (NCT05293626 and NCT04912843). These studies highlight growing interest in LHON gene therapy with consistent safety and efficacy outcomes.

The LHON trials have reported an unexpected clinically meaningful improvement in visual acuity in the contralateral untreated eyes. Studies in nonhuman primates have demonstrated the presence of AAV in uninjected eyes, which could lead to a therapeutic effect in those eyes. Such transfer is hypothesized to be via the optic nerve. Other possible explanations include transfer of mitochondrial material and exchange of astrocyte-derived metabolites via the transorbital route via the optic chiasm.[84]

Glaucoma. Glaucoma, the leading cause of irreversible blindness, encompasses chronic optic neuropathies often linked to elevated intraocular pressure. This increase in intraocular pressure results from an imbalance between the production and outflow of aqueous humor, which drains through the trabecular meshwork located in the iridocorneal angle. The most prevalent subtype, primary open-angle glaucoma, features retinal degeneration with an open iridocorneal angle and affects around 60 million people globally, including both adult-onset (>40 years) and juvenile-onset (3–40 years) cases.

The MYOC gene (OMIM 601652), encoding myocilin, was the first identified glaucoma locus and remains the strongest genetic link to the disease. Myocilin-associated glaucoma follows an autosomal-dominant inheritance pattern with gain-of-function mutations, typically diagnosed before age 40 with intraocular pressures exceeding 25 mmHg, leading to severe progression. While the normal function of myocilin is unclear, it may play a role in

cell–matrix interactions and mitochondrial function. Mutations in MYOC are thought to impair pressure-sensitive aqueous humor outflow through the trabecular meshwork. Current treatments, including pharmacological and surgical approaches targeting elevated intraocular pressure, are insufficient to prevent glaucoma-related blindness. Therefore, new therapeutic strategies focusing on RGC neuroprotection and regeneration are anticipated to prevent or delay RGC death.

A safety, tolerability, and preliminary efficacy study using CRISPR/Cas9 Instantaneous Gene Therapy (NCT06465537) in primary open-angle glaucoma patients with intraocular hypertension and MYOC mutation was initiated in June 2024. The study will assess the potential of modified third-generation integration defective lentivirus (BD113 virus-like particle; BD113vVLP) to deliver gRNA/Cas9 ribonucleoprotein complex via intracameral injection. This CRISPR/Cas9 approach is expected to inactivate the mutated MYOC gene. The trial is still recruiting patients.

An investigator-initiated clinical study (NCT06921317) is assessing the safety and preliminary efficacy of a gene therapy (GVB-2001) for patients with primary open-angle glaucoma (MIM 137760) with high intraocular pressure. This therapy will deliver a dominant negative mutant of RhoA GTPase packaged as a self-complementary AAV (scAAV2-dnRhoA) via intracameral injection and is estimated to start by the end of October 2025.[85]

Mutation independent

Despite progress in the field, gene-specific therapies are limited due to the high genetic heterogeneity of IRDs and challenges in targeting dominant negative mutations. The development costs of individualized therapies, particularly gene therapies, are substantial relative to the prevalence of each specific IRD. Currently, RPE65-linked LCA2 is the only IRD with an approved treatment.

Advances in high-throughput sequencing have enhanced our understanding of the genetic basis of IRDs, fostering the development of gene or mutation-specific strategies for these previously untreatable conditions. Gene-agnostic therapeutic approaches, which target common pathogenic pathways driving retinal degeneration or provide functional vision rescue regardless of the genetic cause, offer potential clinical benefits to many more IRD patients. Examples of gene-agnostic approaches include retinal cell reprogramming and replacement, neurotrophic support, immune modulation, and optogenetics.

Retinitis pigmentosa. Sparing Vision is pioneering a gene-agnostic therapy (SPVN06) that has shown positive long-term favorable safety profile for low-dose (12 months) and medium-dose (6 months) intervention in patients with RP due to mutations in the genes *RHO*, *PDE6A,* or *PDE6B* (NCT05748873).[86] The enrollment for the subretinal injection at the highest dose has recently been completed. SPVN06 is expressing two isoforms of a neurotrophic factor, NXNL1 (RdCVF and RdCVFL), which stimulates glucose metabolism in cone photoreceptors while also mitigating the accumulation of reactive oxygen species, promoting cone survival, and stopping or slowing down disease progression. A challenge of such mutation mutation-independent approach is to identify patients with accelerated degeneration to guide the development and evaluation of these therapies, since they generally only slow decline rather than restore vision. The company is currently conducting a large prospective natural history study (PHENOROD2 and NTC04285398) to inform these questions and identify structural markers and functional changes in patients with a mutation in those genes.

Ocugen's OCU400 is a mutation-agnostic gene therapy expressing the Nuclear Hormone Receptor NR2E3. A new Phase III clinical trial (NCT06388200) is recruiting patients following demonstration of safety and tolerability in patients with NR2E3, RHO, and CEP290 mutations[87] (NCT05203939). The company announced positive trends in BCVA and Multi-Luminance Mobility Test, regardless of the mutations in patients with NR2E3 and RHO. For the Phase III trial, the company is enrolling patients with RHO mutations and any other RP-associated mutation and has developed a new functional assessment, the Luminance Dependent Navigation Assessment, with improved sensitivity compared with the Multi-Luminance Mobility Test.[88] An additional expanded access program for up to 75 patients with RP has also been launched (NCT-06574997).

Optogenetics. Optogenetic therapy combines optical and genetic engineering to introduce light-sensitive proteins into normally light-insensitive inner retinal neurons. By targeting surviving cells with intact neural circuitry, this approach bypasses the need to keep photoreceptors alive to restore vision in a gene-agnostic manner. This is achieved by delivering genes encoding opsins, or light-sensitive proteins from microbial or animal origins, to be expressed in retinal bipolar or ganglion cells. Following successful preclinical studies, several investigational optogenetic therapies have advanced to clinical trials.

GenSight Biologics GS030 targets the retinal ganglion of RP patients via a single IVT injection to express an optimized light-sensing channelrhodopsin protein, ChrimsonR, fused to tdTomato, under the control of the ubiquitous CAG promoter. The patients need to wear special glasses connected to a camera that amplifies the external visual stimuli to enhance ChrimsonR excitation. The PIONEER Phase I/II clinical trial suggested favorable safety and tolerability profiles at all three doses tested in patients with end-stage RP[89] (NCT03326336). Some patients from the study, after at least 1 year posttreatment, showed

improved vision.[89–91] An extension cohort at the highest dose is currently enrolling.

Bionic Sight also uses the strategy of expressing a light-sensitive protein (channelrhodopsin ChronosFP) in RGCs, a treatment that also requires patients to use goggles. However, these are transforming the images of the camera into neural impulses to the ganglion cells. All patients enrolled in the Phase I/II study treated with BS01 intravitreally showed dose-dependent vision improvement[92] (NCT04278131).

In a sham-controlled Clinical Trial (RESTORE) following a dose-escalation study (NCT04919473), Nanoscope Therapeutics recently presented positive 2-year results for patients with RP, using a Multi-Characteristic Opsin expressed from an ON Bipolar promoter mGluR6 (NCT04945772).[93,94] Optogenetic stimulation of bipolar cells might lead to higher-quality vision compared with the approaches targeting the RGCs described above.[95] Durable vision improvement in patients with severe vision loss upon IVT injection of the AAV2 MCO-010 vector provides hope that the remaining targeted bipolar cells can partially compensate for photoreceptors' sensing of light, without the need for external goggles. While long-term monitoring is ongoing (NCT06162585), the company announced preparing a Biologics License Application to the FDA.

AMD. AMD is the leading cause of visual impairment in individuals over 50 years of age in Western countries. It naturally progresses to significant vision loss, with over 60% of patients losing more than six lines of vision within 2 years. The prevalence of AMD increases with age, affecting up to one-third of those aged 75 and older, and is most common in high-income countries. In the United States, approximately 1.75 million people suffer from AMD, with an additional 7 million at risk.

AMD is a multifactorial disease characterized by the progressive deterioration of the RPE, Bruch's membrane, and the choriocapillaris–choroid complex, leading to photoreceptor cell damage. It is classified into three stages: early, intermediate, and late AMD, with late-stage AMD further divided into geographic atrophy (GA) and neovascular AMD (nAMD). Around 10–15% of late-stage AMD cases progress to nAMD, which can cause rapid vision loss and accounts for 90% of blindness in the elderly. For both late stages of AMD, current FDA-approved treatments require multiple IVT injections annually. These include anticomplement therapies for GA and anti-vascular endothelial growth factor (VEGF) treatments for nAMD. The increasing burden on clinics and inconsistent patient visits highlight a significant unmet need for long-term therapies. Consequently, there is a strong focus on developing gene therapies as a potential solution.

nAMD. *ABBV-RGX-314*—A Phase I/IIa dose-escalation study from AbbVie and Regenex Bio used an AAV8 vector coding for a soluble anti-VEGF-A protein (ABBV-RGX-314 or RGX-314) to deliver the virus subretinally to patients with nAMD (NCT03066258). The trial showed little immune response and a dose-dependent concentration of the protein in the aqueous humor, which was stable for 2 years.[96] These analyses showed that the treatment could control exudation and maintain or improve vision (mean central retinal thickness and BCVA). The study also revealed a dose-related pigmentary change in the RPE. Based on these favorable results, a pivotal program has been initiated. It is currently recruiting to compare the gene therapy with two drugs. The study is scheduled to be completed in 2026 (NCT05407636 and NCT04704921). The long-term safety and efficacy of ABBV-RGX-314 will be followed in patients for up to 5 years to evaluate the safety and efficacy of the treatment in the fellow eye for participants having bilateral disease (NCT03999801). The company is also sponsoring a Phase II randomized, dose-escalation study to evaluate the therapy via delivery of one or two suprachoroidal space injections (NCT04514653). Interim data from this suprachoroidal delivery of ABBV-RGX-314, which can be performed in the office, showed that the treatment is well tolerated and showed stable vision and retinal thickness after 6 months, with an important reduction in annualized injection rate (80%, with 50% injection-free).[97]

4D-150—4D Molecular Therapeutics is using its capsid R100, which has been engineered to deliver the virus intravitreally to photoreceptors for treating CNV. 4D-150 is a dual transgene to inhibit multiple targets of the VEGF pathway, combining a VEGF trap (Aflibercept) and an RNAi against VEGF-C. The first patient was dosed in 2021 (NCT05197270), and the latest interim data of the Phase I/IIa trial showed continued support for safety and durability of clinical activity, with a reduction in annualized anti-VEGF injections.[98] The Phase IIb interim data show that 70% of participants remained injection-free, with improved or stabilized visual acuity over 1 year.

ADVM-022—Adverum is also working on an IVT administration of vectorized Aflibercept. The long-term study of ixoberogene soroparvovec (ADVM-022) follows the initial OPTIC trial (NCT03748784) to assess safety and efficacy (NCT046452120). The 2-year, multicenter Phase I study showed a stable and durable expression of Aflibercept, improvement in retinal anatomy (CST), maintenance of vision (BCVA), and a dose-dependent reduction in anti-VEGF rescue injections.[99] Data from the LUNA Phase II (NCT05536973) at 52 weeks and 4-year OPTIC just recently showed that the treatment was able to maintain visual and anatomical outcomes.[100] The treatment burden decreased substantially (>80%), and more than 50% of patients who previously demonstrated a response to active treatment (anti-VEGF injections) were injection-free. The treatment showed no serious adverse events and was comparable to the initial trial. An

improved inflammatory profile was also observed with enhanced local corticosteroid prophylaxis. Interestingly, the vast majority of participants prefer the gene therapy over the prior anti-VEGF treatment(s) and would opt for the gene therapy in their second eye if wet AMD were to develop bilaterally.[100,101] Several additional gene therapy clinical trials for nAMD are also underway, highlighting the major unmet desire of these patients to receive a one-time anti-VEGF therapy (NCT05984927, NCT06198413, and NCT05986864).

GA. GA progresses more slowly than nAMD, with the median time from noncentral GA to central GA being approximately 2.5 years. Currently, over 40% of GA patients are classified as legally blind due to progression of the GA lesion into the fovea, leading to complete loss of central vision. The precise mechanism leading to the initial clinical signs of AMD, known as drusen (yellow lipid deposits), remains unclear due to the multifactorial nature of AMD. Excessive drusen accumulation, which contains many pro-inflammatory components, is believed to induce chronic inflammation through multiple pathways, including the complement cascade. This chronic inflammation is thought to lead to the death of photoreceptor cells, RPE cells, and choriocapillaris cells, resulting in sharply defined atrophic lesions. Consequently, complement inhibition has emerged as a promising therapeutic approach for treating GA.

JNJ-81201887—JNJ-1887 is a gene therapy developed by Janssen Pharmaceuticals (Johnson & Johnson) for the treatment of GA. It utilizes AAV2 to deliver the soluble form of CD59 (a complement pathway inhibitor) under the regulation of a CAG promoter. The therapy should prevent the formation of the membrane attack complex, thereby inhibiting complement activation, protecting RPE cells, and slowing the progression of GA. Safety of the IVT gene therapy studied at 3 different doses was established in a Phase I trial of JNJ-1887 (or HMR-1001) after 23 months of follow-up (NCT03144999). The rate of GA lesion growth was similar among cohorts, except for the highest-dose group, which showed a decline in the growth rate of GA lesions up to 23 months posttreatment.[102] While increased conversion to CNV has been observed in patients treated with complement inhibitors for GA,[103] no case of new onset CNV was reported in this study.[102] A randomized, sham-controlled Phase 2 b study will further evaluate the safety and efficacy of the treatment (NCT05811351).

OCU410—Ocugen's OCU410 is an AAV5 subretinal gene therapy that delivers the RAR-related orphan receptor A (RORα) gene to potentially target multiple pathways associated with GA (NCT06018558). The dosing of the last cohort was recently completed.[104] Preliminary safety and efficacy evaluation show no adverse events, with positive preliminary data indicating improved vision and reduced lesion growth.[105]

Diabetic retinopathy/diabetic macular edema. Like nAMD, diabetic retinopathy (DR) with diabetic macular edema (DME) is among the leading causes of visual impairment in adults in Western countries. Over the past 20 years, the rising incidence of diabetes has led to a 64% increase in DR-related visual loss and a 27% increase in blindness. Prolonged hyperglycemia is thought to cause intraretinal or subretinal fluid accumulation due to several factors: dysregulation of the blood–retinal barrier, which allows proteins and other solutes to infiltrate retinal tissue; increased hypoxia, which triggers the secretion of VEGF growth factor and leakage from damaged retinal blood vessels, as well as growth of abnormal blood vessels in the deep retina. Similar to nAMD, this fluid can accumulate diffusely in the central retina. In such cases, anti-VEGF therapy remains the only standard treatment for these exudative macular disorders. Several vectors used for the treatment of wet AMD are also assessed in DME.

4D molecular therapeutics has a Phase II study evaluating their vector in DME patients, with interim data from the Part 1 Dose confirmation cohort expected at the end of this year (NCT05930561). The vector appears to be safe and well-tolerated.[106] The dose-escalation study was completed with meaningful improvements in the reduction of treatment burden at the high dose. There was a continued lack of ocular inflammation.[107] This is in contrast to the ADVM-022 study from Adverum Biotechnologies, which stopped development of the therapy for DME due to dose-limiting toxicity[108] (NCT04418427).

The ABBV-RGX-314 described earlier also included patients with DR without center-involved DME (NCT-04567550). The 1-year data from this Phase II trial of the suprachoroidal delivery of their gene therapy showed that the treatment is well-tolerated, and there were significant clinical improvements with meaningful prevention of disease progression and reduced vision-threatening events.[109] The company is now recruiting a new cohort of patients with center-involved macular edemas with a pivotal trial expected to initiate in 2025.

CONCLUSIONS

Gene therapy trials have revealed promising outcomes, although there is considerable variation within the studies. After the success of the first human gene therapy for RPE65-LCA, there have been several programs that have reached the clinical trial stage, but we have yet to see results confirming the safety profile and/or improvements in visual acuity and function in larger studies. Most clinical studies have focused on monogenic forms of visual impairment. A major focus is on assessing the advantages and disadvantages of subretinal delivery, which is currently being used in most RP trials. New studies on

ascertaining the advantages of IVT and suprachoroidal delivery over subretinal delivery are also being conducted. With monthly or quarterly IVT injections as the current standard of care for wet AMD and GA, gene therapy offers a path to reduce the treatment burden on patients. Favorable safety profiles and efficacious outcomes are key to developing such treatments for the aged population.

The ongoing CRISPR/Cas9-mediated gene editing clinical trials, combined with the completed gene editing studies, have the potential to provide significant new knowledge on the *in vivo* potential of this approach. Although these studies are in early stages, they provide substantial hope for patients with a promise of one-time treatment for preventing or delaying vision loss.

With the rapidly evolving landscape of inherited retinal diseases, there is an urgent need for gene-agnostic approaches to overcome the challenges of the associated genetic heterogeneity and clinical diversity, and the high cost of individualized gene therapy treatments. Current advancements in gene-agnostic therapies (including optogenetics and modifier gene expression) and treatment for complex diseases such as AMD and glaucoma are showing encouraging results. These studies underscore the significant progress and future potential of gene- and mutation-agnostic approaches to transform the treatment paradigm for a spectrum of previously untreatable diseases.

Overall, although gene therapy is not yet standard of care for these diseases, continuing improvements in vector design, delivery routes and endpoint analyses hold significant potential in revolutionizing genetic medicines.

AUTHORS' CONTRIBUTIONS

N.L. and L.M.L. compiled information and wrote the early drafts. C.P. reviewed and revised the manuscript. H.K. compiled information, revised the drafts and finalized manuscript for submission.

AUTHOR DISCLOSURE STATEMENT

L.M.-L. and H.K. are employed by Astellas Pharma, Inc. N.L. was an Astellas Pharma employee at the time of writing this review article. C.P. does not have any conflict of interest to declare.

FUNDING INFORMATION

This work was supported in part by a NEI grant (R01EY032461) to C.P.

SUPPLEMENTARY MATERIAL

Supplementary Table S1

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Received for publication July 17, 2025;
accepted after revision August 29, 2025.

Published online: September 18, 2025.

IRDs	Clinical Trial ID	Trial Name	Targeted Gene	Vector serotypes	Treatment	Delivery	Phase	Follow-up studies	Sponsor	Reference	Completion date
1.1. Gene therapy for monogenic disorders											
Achromatopsia	NCT02610582	Colourbridge	CNGA3	AAV8	AAV8.CNGA3	Subretinal	I/II		STZ eyetrial	21, 22, 23, 24	2027
Achromatopsia	NCT03001310		CNGB3	AAV8	AAV2/8-hCARp.hCNGB3	Subretinal	I/II	NCT03278873	MeiraGTx UK II Ltd	25	2027
Achromatopsia	NCT03758404		CNGA3	AAV8	AAV2/8-hG1.7p.coCNGA3	Subretinal	I/II	NCT03278873	MeiraGTx UK II Ltd	25	2021
Achromatopsia	NCT02935517		CNGA3	AAV2	AGTC-402 (rAAV2tYF-PR1/7-hCNGA3)	Subretinal	I/II		Applied Genetic Technologies Corp	27	2026
Achromatopsia	NCT02599922		CNGB3	AAV2	AGTC-401 (rAAV2tYF-PR1.7-hCNGB3)	Subretinal	I/II		Applied Genetic Technologies Corp	27	2026
X-Linked Retinoschisis	NCT02416622		hRS1	AAV2	rAAV2tYF-CB-hRS1	IVT injection	I/II		Applied Genetic Technologies Corp		2023
X-Linked Retinoschisis	NCT02317887		scRS/IRBPhRS	AAV8		IVT injection	I/II		VegaVect Therapeutics	28, 29	2024
X-Linked Retinoschisis	NCT05878860	LIGHTHOUSE	hGRK1/hRS1	AAV.SPR	ATSN-201	Subretinal	I/II		Atsena Therapeutics	30, 31	2025
Choroideremia (CHM)	NCT03496012	STAR	REP1	AAV2	BIIB111	Subretinal	no data	-	NightstaRx Ltd	33	2020
Choroideremia (CHM)	NCT02341807		CHM	AAV2	AAV2-hCHM	Subretinal	I/II		Spark Therapeutics	37	2022
Retinitis Pigmentosa	NCT03116113	XIRIUS	RPGR (codon optimized)	AAV8	BIIB112 (AAV8.coRPGR)	Subretinal	II/III	NCT03584165	NightstaRx Ltd	44, 45, 46	2020
Retinitis Pigmentosa	NCT06333249	SKYLINE	RPGR	AAV2	AGTC-501 (rAAV2tYF-GRK1-RPGR)	Subretinal	II	-	Beacon Therapeutics	48	2027
Retinitis Pigmentosa	NCT03316560	HORIZON	RPGR	AAV2	AGTC-501 (rAAV2tYF-GRK1-RPGR)	Subretinal	I/II	NCT04850118 NCT06275620	Beacon Therapeutics	49, 50	2025
Retinitis Pigmentosa	NCT04517149		RPGR	R100	4D-125	IVT injection	I/II		4D Molecular Therapeutics	51, 52, 53, 54	2029
Retinitis Pigmentosa	NCT05874310		RPGR	AAV5	FT-002	Subretinal	I	NCT06492850	Frontera Therapeutics	55, 56	2027
Retinitis Pigmentosa	NCT03252847		RPGR	AAV5	MGT-009	Subretinal	I/II	NCT04671433 NCT04794101 NCT04312672	MeiraGTx UK II Ltd	57, 58	2021
Retinitis Pigmentosa	NCT03328130		hPDE6B	AAV2/5	AAV2/5-hPDE6B	Subretinal	I/II	-	eyeDNA Therapeutics	59, 60, 61	2029
Retinitis Pigmentosa	NCT04611503	PIGMENT	hPDE6A	AAV8	rAAV.hPDE6A	Subretinal	I/II		STZ eyetrial	62	2027
Retinitis Pigmentosa	NCT03374657		RLBP1	AAV8	CPK850 scAAV8-pRLBP1(short)-hRLBP1	Subretinal	I/II		Novartis Pharmaceuticals	64	2026
Stargardt	NCT01367444		ABCA4	EIAV	SAR422459	Subretinal	I/II	NCT01736592	Sanofi	65	2019
LCA2	NCT03597399		RPE65	AAV2	Voretigene Neparvovec	Subretinal	post-authorization	-	Spark Therapeutis	69, 70	2025
LCA2	NCT06088992	LIGHT	RPE65	AAV9	HG004, AAV9-hRPE65	Subretinal	I/II	NCT05906953	HuidaGene	71	2028
LCA5	NCT05616793		LCA5	AAV8	OPGx-001, AAV8.Hlca5	Subretinal	I/II	-	Opus Genetics	72	2028
LCA1	NCT03920007		GUCY2D	AAV5	ATSN-101	Subretinal	I/II	-	Atsena Therapeutics	73, 74, 75	2027
LCA10	NCT03872479	BRILLIANCE	CEP290	AAV5	Sepofarsen, EDIT-101, AAV5-GRK1-spCas9-two guides	Subretinal	I/II	-	Editas Medicine	76, 77	2025
LHON	NCT03293524	REFLECT	ND4	AAV2	lenadogene nolparvovec, GS010	IVT injection	III	-	GenSight Biologics	79, 80	2024
LHON	NCT02161380		ND4	scAAV2	scAAV2-P1ND4v2	IVT injection	I	-	Byron Lam	81	2025
LHON	NCT03153293		ND4	rAAV2	rAAV2-ND4	IVT injection	I	NCT01267422	Huazhong University of Science and Technology	82	2025
LHON	NCT05293626		ND4	rAAV2	NR082, rAAV2-ND4	IVT injection	I/II	NCT04912843	Neurophth Therapeutics	83	2029
Glaucoma	NCT06465537		MYOC	BD113vVLP	BD113vVLP-Cas9-gRNA	Intracameral injection	I	-	Shanghai Bdgene		2025
Glaucoma	NCT06921317		dn RhoA GTPase	scAAV2	GVB-2001 scAAV2-dnRhoA	Intracameral injection	I/II	-	IVIEW Therapeutics	85	2027
1.2. Mutation Independent											
Retinitis Pigmentosa	NCT05748873	PRODYGY	NXNL1 (RdCVF - RdCVFL)	AAV8	SPVN06	Subretinal	I/II	-	SparingVision	86	2029
Retinitis Pigmentosa	NCT05203939		NR2E3	AAV5	OCU400, AAV5-Hnr2e3	Subretinal	II	NCT06388200 NCT06574997	Ocugen	87, 88	2027

Retinitis Pigmentosa	NCT03326336	PIONEER	ChrimsonR-tdTomato (Optogenetic)	AAV2.7m8	GS030	IVT injection	I/II		GenSight Biologics	89, 90, 91	2027
Retinitis Pigmentosa	NCT04278131		ChronosFP (Optogenetic)	AAV2	BS01	IVT injection	I/II		Bionic Sight	92	2029
Retinitis Pigmentosa	NCT04919473	RESTORE	vMCO-I (Optogenetic)	AAV2	MCO-010	IVT injection	II	NCT04945772 NCT06162585	Nanoscope Therapeutics Inc.	93, 94	2020
nAMD	NCT03066258		anti-VEGF mAb fragment (fab)	AAV8	RGX-314	Subretinal	I/IIa	-	Regenxbio Inc.	96	2021
nAMD	NCT04832724		anti-VEGF mAb fragment (fab)	AAV8	RGX-314	Subretinal	II	NCT03999801	Regenxbio Inc.	No Information	2024
nAMD	NCT04704921	ATMOSPHERE	anti-VEGF mAb fragment (fab)	AAV8	RGX-314	Subretinal	IIb/III pivotal 1		Regenxbio Inc.	No Information	2027
nAMD	NCT05407636	ASCENT	anti-VEGF mAb fragment (fab)	AAV8	RGX-314	Subretinal	III pivotal 2		Regenxbio Inc.	No Information	2027
nAMD	NCT04514653	AAVIATE	anti-VEGF mAb fragment (fab)	AAV8	RGX-314	Suprachoroidal	II		Regenxbio Inc.	97	2026
nAMD	NCT05197270	PRISM	anti-VEGF-A and VEGF-C (RNAi)	R100	4D-150	IVT injection	I/II		4D Molecular Therapeutics	98	2031
nAMD	NCT03748784	OPTIC	Aflibercept	AAV2.7m8	ADVM-022	IVT injection	I	NCT04645212	Adverum Biotechnologies, Inc.	99	2022
nAMD	NCT05536973	LUNA	Aflibercept	AAV2.7m8	ADVM-022	IVT injection	II	-	Adverum Biotechnologies, Inc.	100	2028
GA	NCT03144999		CD59	AAV2	JNJ-1887, AAVCAGsCD59	IVT injection	I	NCT05811351	Janssen Research & Development	102	2019
GA	NCT06018558	ArMaDa	RORα	AAV5	OCU410, AAV5-hRORA	Subretinal	I/II	-	Ocugen	104	2026
Diabetic Macular Edema	NCT05930561	SPECTRA	anti-VEGF-A and VEGF-C (RNAi)	R100	4D-150	IVT injection	II	-	4D Molecular Therapeutics	106, 107	2028
Diabetic Macular Edema	NCT05930561	SPECTRA	anti-VEGF-A and VEGF-C (RNAi)	R100	4D-150	IVT injection	II	-	4D Molecular Therapeutics	106, 107	2028
Diabetic Macular Edema	NCT04418427	INFINITY	Aflibercept	AAV2.7m8	ADVM-022	IVT injection	II		Adverum Biotechnologies, Inc.	108	2023
Diabetic Macular Edema/Diabetic Retinopathy	NCT04567550	ALTITUDE	Monoclonal anti-VEGF fragment	AAV8 (NAV)	ABBV-RGX-314	Suprachoroidal	II		AbbVie/REGENEXBIO	109	2026