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REVIEW ARTICLE

Can Gene Therapy Transform the Treatment Landscape of Posterior Segment Eye Diseases? A Comprehensive Review of Recent Advancements

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Abstract

Posterior segment eye diseases (PSEDs) encompass a diverse group of conditions affecting the retina, choroid, optic nerve, and vitreous humor, often leading to progressive and irreversible vision loss. Age-related macular degeneration (AMD), diabetic retinopathy (DR), retinitis pigmentosa (RP), and inherited retinal diseases (IRDs) are among the most clinically significant PSEDs with a substantial global burden and economic impact. Conventional treatments for PSEDs have limitations that necessitate the development of novel therapies that address the underlying molecular drivers of the disease. Gene therapy has emerged as a promising approach, offering the potential for durable and curative outcomes through precise genetic manipulation. Advancements in gene therapy strategies, including gene augmentation, gene editing, RNA-based therapies, and optogenetics, have led to significant progress in preclinical studies and clinical trials across various PSED subtypes. US Food and Drug Administration (FDA) approval of voretigene neparvovec (Luxturna®) for *RPE65*-associated IRDs validated the clinical viability of ocular gene therapy, while ongoing trials for AMD, DR, and other IRDs continue to expand the therapeutic landscape. Innovations in viral and non-viral delivery systems, such as dual AAV vectors, lipid nanoparticles, and novel biomaterials, have enhanced the efficiency and specificity of gene delivery to the retina. However, challenges persist, including immune responses to viral vectors, limited transduction efficiency in certain cell types, and anatomical barriers posed by the blood–retinal barrier. Future directions in ocular gene therapy include the development of precision genome editing techniques, such as prime editing, miRNA-based regulation, and combinatorial approaches integrating gene therapy with stem cell transplantation or neuroprotective agents. As the field continues to evolve, addressing these challenges and optimizing gene therapy strategies will be crucial in translating the transformative potential of ocular gene therapy into clinical reality for patients with PSEDs.

Key Points

Gene therapy is transforming the treatment of blinding eye diseases by targeting the root genetic causes, offering hope for long-lasting vision improvement.

Recent clinical trials show that one-time gene therapies can reduce or eliminate the need for frequent eye injections in conditions such as age-related macular degeneration.

Ongoing research is expanding gene therapy options for inherited retinal diseases, with new delivery methods and gene editing tools under development.

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1 Introduction

Posterior segment eye disease (PSED) represents a heterogeneous group of conditions affecting the retina, choroid, optic nerve, and vitreous humor and often culminates in progressive and irreversible vision loss. Clinically significant PSEDs include age-related macular degeneration (AMD), diabetic retinopathy (DR), retinitis pigmentosa (RP), and inherited retinal diseases (IRDs), each characterized by distinct pathophysiological mechanisms but unified by their anatomical localization and potential for devastating functional consequences [1, 2]. The global burden of PSEDs is substantial, with AMD alone affecting approximately 196 million individuals worldwide as of 2020, a figure projected to escalate to 288 million by 2040 as populations age [2]. Similarly, DR, a microvascular complication of diabetes mellitus, impacts more than 103 million adults globally, with prevalence rates mirroring the rising incidence of diabetes itself [3]. RP, though less common, affects roughly 1 in 4000 individuals, often leading to legal blindness by mid-adulthood due to progressive photoreceptor degeneration [4]. Beyond their clinical impact, PSEDs impose significant economic burdens, with direct healthcare costs for AMD management in the USA exceeding $30 billion annually, alongside immeasurable losses in quality of life and productivity [5]. These statistics underscore the urgent need for therapies that not only mitigate symptoms, but also address the underlying molecular drivers of disease.

Conventional treatments for PSEDs, such as intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections for neovascular AMD or laser photocoagulation for DR, are fraught with limitations. While anti-VEGF agents such as ranibizumab and aflibercept have revolutionized care by stabilizing vision in many patients, their transient efficacy necessitates frequent and often long-term administration, invasive administrations at 4- to 12-week intervals, leading to high treatment burden, cumulative risks of endophthalmitis, and suboptimal real-world adherence [6]. Similarly, corticosteroid implants for diabetic macular edema offer only temporary relief, often accompanied by complications such as cataract formation and intraocular pressure elevation [7]. For inherited conditions such as RP or IRDs, no curative therapies exist, leaving patients reliant on palliative low vision aids or genetic counseling. These challenges have catalyzed a paradigm shift toward gene therapy, a modality capable of delivering durable, even curative, outcomes through precise genetic manipulation.

Gene therapy's promise in PSEDs lies in its ability to target disease mechanisms at their source. For monogenic IRDs caused by mutations in genes such as *RPE65* or *CEP290*, adeno-associated virus (AAV)-mediated gene replacement strategies aim to restore functional protein expression in photoreceptors or retinal pigment epithelium (RPE) cells [8]. In complex, multifactorial diseases such as AMD, approaches such as CRISPR-Cas9 gene editing, RNA interference (RNAi), or anti-angiogenic gene delivery (e.g., *sFLT1*) seek to silence pathological pathways or confer sustained neuroprotection [7, 9]. Recent milestones, including the 2017 Food and Drug Administration (FDA) approval of voretigene neparvovec (Luxturna®) for *RPE65*-associated IRDs, validate the clinical viability of ocular gene therapy, while emerging non-viral delivery systems (e.g., lipid nanoparticles) and optogenetic techniques further expand the therapeutic arsenal [10]. Nevertheless, significant hurdles persist, including immune responses to viral vectors, limited transduction efficiency in certain cell types, and the anatomical barriers posed by the blood–retinal barrier (BRB).

Gene therapy offers several advantages over conventional treatments for posterior segment eye diseases. For example, Luxturna (voretigene neparvovec) provides long-term restoration of visual function in patients with *RPE65*-associated Leber congenital amaurosis (LCA) after a single subretinal injection, whereas traditional management is limited to supportive care and does not halt disease progression. Clinical studies and real-world data show significant improvements in visual function, including full-field stimulus threshold testing, visual fields, and visual acuity, with benefits persisting for at least 1 year and often longer [11, 12].

In age-related macular degeneration (AMD), gene therapies such as RGX-314 and ADVM-022 have demonstrated a substantial reduction in the frequency of anti-VEGF injections required to maintain vision. Patients treated with RGX-314 experienced up to a 67% reduction in annualized injection rates, with stable or improved visual acuity over several years, compared with the ongoing burden and risks of repeated intravitreal injections in standard care [13, 14]. Similarly, ADVM-022 has shown that a single intravitreal injection can maintain therapeutic aflibercept levels and visual outcomes for over a year, with many patients remaining injection-free and reporting a favorable safety profile [14].

This review aims to critically evaluate the transformative advancements in gene therapy for PSEDs, with three overarching objectives. First, it synthesizes innovations in delivery platforms, including viral and non-viral vectors, intravitreal versus subretinal injection routes, and novel biomaterials engineered to enhance retinal targeting. Second, it analyzes outcomes from landmark preclinical studies and clinical trials, emphasizing efficacy, safety, and translational challenges across diverse PSED subtypes. Third, it identifies persisting obstacles—such as immune reactivity, vector genome size constraints, and scalability—while proposing future directions, including CRISPR prime editing, miRNA-based regulation, and combinatorial approaches integrating

gene therapy with stem cell transplantation or neuroprotective agents. By contextualizing these developments within the broader landscape of precision medicine, this review aims to inform researchers, clinicians, and policymakers about the evolving potential of gene therapy to redefine standards of care for PSEDs.

2 Overview of Posterior Segment Eye Diseases (PSEDs)

PSEDs encompasses a diverse group of conditions affecting the retina, choroid, vitreous, and optic nerve, representing the leading causes of irreversible vision loss worldwide. The complexity of these diseases stems from their varied etiologies—ranging from age-related degenerative processes to inherited genetic mutations and vascular pathologies—as well as the intricate anatomy and physiology of the posterior eye segment. Table 1 gives a summary of all the PSEDs discussed in this review.

2.1 Age-Related Macular Degeneration (AMD)

AMD is the predominant cause of central vision impairment in individuals over 50 years in developed countries, with prevalence rising markedly with age. In the United States, approximately 20 million people are affected (18.34 million with early AMD and 1.49 million with late AMD). Medicare data indicate an annual prevalence of 2.6% for early AMD and 1.6–1.7% for advanced disease. Globally, the number of cases is projected to reach 288 million by 2040. Age-specific estimates show that about 10% of Americans aged ≥50 years have early AMD and ~1% have late AMD, increasing to ~30% and ~10%, respectively, among those aged ≥80 years [5, 15, 16]. AMD manifests in two principal forms: dry (non-neovascular) and wet (neovascular) AMD, each with distinct pathological features and clinical courses.

Table 1: Overview of posterior segment eye diseases (PSEDs)

Disease	Pathophysiology	Clinical features	Current treatments	Gene therapy advancements
Age-related macular degeneration (AMD)	Drusen accumulation (dry) Choroidal neovascularization (wet) Complement/oxidative stress	Central vision loss Geographic atrophy (dry) Hemorrhages (wet)	Anti-VEGF injections Complement inhibitors (pegcetacoplan)	RGX-314 (AAV8 anti-VEGF) ADVM-022 (AAV.7m8 aflibercept) GT005 (CFI gene therapy)
Posterior vitreous detachment (PVD)	Vitreous liquefaction Vitreoretinal traction	Floaters Photopsia Risk of retinal tears	Observation Vitrectomy (if complications)	Pharmacologic vitreolysis (ocriplasmin) Investigational enzymatic agents
Retinal detachment and tears	Rhegmatogenous (retinal break) Tractional (fibrovascular proliferation)	Sudden vision loss "Curtain-like" field defect Photopsia	Pneumatic retinopexy Scleral buckling/vitrectomy	Gene therapy targeting PVR (e.g., TGF-β inhibitors) mRNA-based antifibrotics
Epiretinal membrane and macular hole	ILM defects → glial cell proliferation Vitreofoveal traction	Metamorphopsia Central scotoma (hole)	Vitrectomy + membrane peeling ILM flap technique	Anti-fibrotic gene therapies (preclinical)
Vitreous hemorrhage	Diabetic neovascularization Retinal vein occlusion Trauma	Sudden floaters Vision obscuration	Observation (mild) Vitrectomy (severe)	Anti-VEGF gene therapy (e.g., for diabetic hemorrhage prevention)
Diabetic retinopathy (DR) and vascular diseases	VEGF-driven angiogenesis Blood–retinal barrier breakdown	Microaneurysms Macular edema Neovascularization	Anti-VEGF injections Laser photocoagulation	RGX-314 (suprachoroidal AAV8) ADVM-022 (intravitreal AAV.7m8)
Diseases of the optic nerve	Glaucoma: RGC apoptosis LHON: mitochondrial (MT-ND4) mutations	Cupped optic disc Visual field loss Acute bilateral vision loss (LHON)	IOP-lowering drugs Neuroprotection trials	GS010 (AAV2-ND4 for LHON) BDNF/CNTF gene therapy (glaucoma)
Inherited retinal diseases (IRDs)	*RPE65*, RPGR, *ABCA4* mutations Photoreceptor/RPE dysfunction	Night blindness (RP) Childhood blindness (LCA) Macular atrophy (Stargardt)	Luxturna® (*RPE65*) Vitamin A (RP)	CRISPR editing (*CEP290*) Dual-AAV for large genes (e.g., MYO7A)

Dry AMD, accounting for approximately 90% of cases, is characterized by the accumulation of drusen—extracellular deposits between the retinal pigment epithelium (RPE) and Bruch's membrane—along with progressive geographic atrophy (GA) of the RPE and photoreceptors [17]. The more visually devastating wet AMD, though less common, is marked by the growth of abnormal blood vessels from the choroid or retina into the subretinal or sub-RPE spaces, encompassing all types of macular neovascularization, leading to hemorrhage, exudation, and rapid central vision loss if untreated. The pathogenesis of AMD involves a complex interplay of genetic predisposition, environmental factors, and age-related changes. Genome-wide association studies have identified more than 30 genetic loci associated with AMD risk, with polymorphisms in complement pathway genes (*CFH*, *C3*, *CFB*) being particularly significant [18]. Environmental risk factors include smoking, which doubles AMD risk, and nutritional deficiencies in lutein, zeaxanthin, and omega-3 fatty acids [19]. At the cellular level, AMD involves chronic oxidative stress, mitochondrial dysfunction, and impaired protein degradation pathways in the RPE, culminating in lipofuscin accumulation and drusen formation [20].

Recent breakthroughs in gene therapy have transformed treatment prospects for neovascular (wet) AMD, a leading cause of blindness among older adults characterized by the proliferation of abnormal subretinal blood vessels and fluid accumulation resulting in rapid, severe loss of central vision. Traditional anti-VEGF injections, while effective, require frequent administration (often monthly or bi-monthly), presenting a major burden for elderly patients, and are associated with risks of endophthalmitis and undertreatment in real-world settings. RGX-314 (Regenxbio/AbbVie) is a gene therapy candidate designed for patients with active or recurrent wet AMD who have demonstrated prior response to anti-VEGF agents but require ongoing injections to maintain vision. It utilizes an adeno-associated virus 8 (AAV8) vector to deliver a gene encoding a ranibizumab-like anti-VEGF antibody fragment directly to retinal cells. The transduced cells then act as "biofactories," providing continuous intraocular VEGF suppression after a single surgical administration by subretinal or—more recently—suprachoroidal injection. In clinical studies, RGX-314 performed strongly: in the pivotal bilateral "fellow eye" trial, 97% of treated eyes required no or only one supplemental anti-VEGF injection in the 9 months post-treatment, with 78% remaining fully injection free. Most importantly, visual acuity (VA) and central subfield thickness were maintained or improved, and the safety profile was favorable, with only mild intraocular inflammation responding well to a short steroid course [14, 21, 22].

ADVM-022 (Adverum Biotechnologies), now in phase II trials, offers another leap for wet AMD by using the engineered AAV.7m8 capsid for nonsurgical, office-based intravitreal delivery of the aflibercept gene. ADVM-022 is intended for patients with chronic, previously injection-dependent wet AMD. In the OPTIC trial, more than 80% of eyes remained free of supplementary aflibercept injections for up to 2.5 years, with durable control of exudation and median visual stability. Most adverse events were mild–moderate inflammatory reactions, all resolving with topical steroids and no permanent vision loss [21, 23]. Together, these gene therapies provide the promise of a one-time, long-lasting therapy for patients with AMD, with the potential to greatly reduce treatment burden and improve both vision outcomes and quality of life for those with sight-threatening disease. Ongoing phase III trials (ATMOSPHERE, ASCENT, LUNA) will determine comparative durability, optimal delivery route, and long-term safety, addressing the needs of a rapidly growing, aging population at risk for visual disability.

2.2 Posterior Vitreous Detachment (PVD), Retinal Detachment (RD), Epiretinal Membrane (ERM), Macular Holes, and Vitreous Hemorrhage (VH)

PVD, retinal detachment (RD), epiretinal membrane (ERM), macular holes, and vitreous hemorrhage (VH) are common posterior segment conditions. While these disorders can cause significant visual morbidity, current gene therapy research is primarily focused on diseases with a clear genetic basis or major unmet therapeutic needs. For most of these conditions, conventional surgical and pharmacological treatments remain standard, and gene therapy approaches are still in early preclinical stages or not yet applicable. Therefore, detailed clinical and surgical descriptions are omitted here to maintain focus on gene therapy-relevant diseases [24–27].

2.3 Diabetic Retinopathy (DR)

DR is the most common microvascular complication of diabetes mellitus and a leading cause of preventable blindness in working-age adults. The global prevalence of DR is estimated at 27% among diabetics, with 6% affected by vision-threatening stages such as proliferative diabetic retinopathy (PDR) or diabetic macular edema (DME) [3]. The pathogenesis of DR involves chronic hyperglycemia-induced damage to retinal capillaries, leading to pericyte loss, breakdown of the blood–retinal barrier, and progressive retinal ischemia. The resulting hypoxia triggers upregulation of vascular endothelial growth factor (VEGF), promoting pathological angiogenesis in PDR and vascular permeability in DME [28]. In 2021, an estimated 9.6 million people in the USA (26.4% of those with diabetes) had diabetic retinopathy (DR), and 1.84 million (5.1%) had vision-threatening DR [29]. The global prevalence of DR among diabetics is

estimated at 27% [29, 30]. DR prevalence is higher among patients with type 1 diabetes (up to 68.8%) compared with type 2 (35.2%) [30]. Prevalence rates are higher for Black (8.7%) and Hispanic (7.1%) individuals than for white individuals (3.6%) [29].

DR is classified into non-proliferative (NPDR) and proliferative (PDR) stages on the basis of the presence of retinal neovascularization. NPDR is further subdivided into mild, moderate, and severe on the basis of the extent of microaneurysms, intraretinal hemorrhages, venous beading, and intraretinal microvascular abnormalities (IRMA) [31]. DME, characterized by retinal thickening due to fluid accumulation, can occur at any stage of DR and is a major cause of vision loss. Treatment strategies for DR have evolved significantly with the advent of anti-VEGF therapy. Intravitreal injections of aflibercept, ranibizumab, and bevacizumab are first-line treatments for center-involving DME, with studies demonstrating superior visual outcomes compared with laser photocoagulation [32]. However, challenges such as treatment burden, variable patient response, and risk of fibrosis in chronic DME persist. For PDR, panretinal photocoagulation (PRP) remains standard, though anti-VEGF agents are increasingly used as adjuncts or alternatives, particularly in cases with vitreous hemorrhage or high-risk characteristics. Emerging gene therapies aim to provide sustained VEGF suppression (Sect. 6.2).

2.4 Diseases of the Optic Nerve

Diagnosis relies on structural [optic nerve head assessment (OCT), retinal nerve fiber layer analysis] and functional (visual field testing) assessments. Recent advances in OCT angiography allow for early detection of microvascular changes in the optic nerve head, preceding detectable visual field loss. Treatment focuses on intraocular pressure (IOP) reduction via topical medications (prostaglandin analogs, beta-blockers), laser trabeculoplasty, or surgical interventions such as trabeculectomy and minimally invasive glaucoma surgeries (MIGS) [33]. Non-glaucomatous optic neuropathies include ischemic optic neuropathy (e.g., NAION), inflammatory (optic neuritis), and hereditary forms [Leber hereditary optic neuropathy (LHON)]. LHON, caused by mitochondrial DNA mutations (e.g., m.11778G>A in MT-*ND4*), leads to acute bilateral vision loss in young adults. Gene therapy (GS010, lenadogene nolparvovec) has shown promise in clinical trials, with some patients achieving partial visual recovery [34].

2.5 Inherited Retinal Diseases (IRDs)

Inherited retinal diseases (IRDs) encompass a genetically heterogeneous group of disorders caused by mutations in more than 300 genes critical for retinal function. RP, the most common IRD (prevalence ~1:4000), presents with night blindness and progressive peripheral vision loss due to rod photoreceptor degeneration [4]. Late-stage RP often involves cone dysfunction, leading to tunnel vision and eventual blindness. Choroideremia, an X-linked disorder caused by *CHM* mutations, leads to progressive RPE and choroidal atrophy, while Leber congenital amaurosis (LCA), the most severe childhood IRD, results in profound vision loss from birth due to mutations in *RPE65*, *CEP290*, or other phototransduction genes [8]. Therapeutic breakthroughs include FDA-approved voretigene neparvovec (Luxturna®), an AAV2-based gene therapy for *RPE65*-associated IRDs, which improves light sensitivity and mobility in treated patients [35]. CRISPR-based gene editing (e.g., *EDIT-101* for *CEP290*) and optogenetic therapies are under investigation for previously untreatable forms of IRD. For large genes exceeding AAV capacity, such as *ABCA4* in Stargardt disease, dual AAV vectors and nanoparticle delivery systems are in development, showing promise in preclinical models and early phase trials. Additionally, trials in choroideremia employing *CHM* gene replacement have reported significant gains in visual acuity and maintenance of retinal structure. Collectively, IRD gene therapy exemplifies a leading paradigm in ocular therapeutics, addressing otherwise untreatable conditions with high unmet need. However, challenges related to vector size limitations, host immunity, and optimal delivery remain active areas of innovation.

2.6 Emerging Biomarkers in PSEDs

Recent advances have identified novel biomarkers for posterior segment eye diseases. In AMD, genetic variants in the *CFH* and *ARMS2* loci, as well as plasma complement factor I, are now used to stratify risk and predict disease progression [29]. Imaging biomarkers identified by OCT, such as ellipsoid zone and external limiting membrane abnormalities, provide strong prognostic value for progression to late AMD. In diabetic retinopathy, circulating microRNAs and retinol binding protein 3 (RBP3) are emerging as sensitive biomarkers for early detection and monitoring [36]. Quantitative imaging of peripheral nonperfusion and neovascularization using ultra-widefield imaging, along with artificial intelligence (AI)-based screening algorithms, are transforming the landscape of DR diagnosis and management.

3 Molecular Basis And Pathophysiology of PSEDs

3.1 Genetic Determinants of PSEDs

The genetic architecture of PSEDs span monogenic IRDs to complex, multifactorial disorders with polygenic risk factors. Monogenic IRDs demonstrate striking genetic

heterogeneity, with more than 300 identified causative genes accounting for varied phenotypes. For instance, mutations in *RPGR* (retinitis pigmentosa GTPase regulator) account for 70–80% of X-linked retinitis pigmentosa cases, disrupting ciliary transport in photoreceptors through impaired protein trafficking across the connecting cilium [37]. The *RPGR ORF15* isoform, containing a purine-rich repetitive region, is particularly susceptible to frameshift mutations that abolish interaction with structural proteins such as *RPGRIP*1, leading to progressive photoreceptor degeneration [38]. Stargardt disease, the most common inherited macular dystrophy, primarily results from mutations in *ABCA4*, which encodes an ATP-binding cassette transporter critical for clearing all-trans-retinaldehyde from photoreceptor discs. More than 900 pathogenic *ABCA4* variants have been identified, with null alleles causing severe early onset disease through toxic bisretinoid (A2E) accumulation in RPE cells [39]. The molecular pathology involves defective N-retinylidene-PE clearance, leading to fluorescent lipofuscin deposits that promote oxidative stress and RPE apoptosis, as demonstrated by fundus autofluorescence imaging patterns [40].

For complex PSEDs such as AMD, genome-wide association studies (GWAS) have identified 52 risk loci accounting for ~60% of disease heritability. The 1q31.3 locus containing *CFH* (complement factor H) and five complement genes shows the strongest association, with the Y402H polymorphism (rs1061170) increasing AMD risk 3–7-fold by reducing *CFH*'s ability to inhibit alternative pathway activation on RPE cells [41]. Epistatic interactions between *CFH* and *ARMS2*/*HTRA1* variants on chromosome 10q26 further modulate risk, potentially through mitochondrial dysfunction and extracellular matrix remodeling [42].

Genome-wide association studies identify common genetic variants, typically single nucleotide polymorphisms (SNPs), which confer increased risk for complex diseases such as AMD, often with modest effect sizes. These common variants are widespread in the population and contribute to disease susceptibility but are not usually sufficient to cause disease on their own. In contrast, rare mutations in specific genes, such as those causing inherited retinal diseases, directly disrupt gene function and are typically sufficient to cause disease. For example, GWAS has linked common variants in the *CFH* and *ARMS2* genes to AMD susceptibility, while rare mutations in *RPE65* or *ABCA4* result in monogenic retinal dystrophies [43–46].

3.2 Pathophysiological Mechanisms in PSEDs

3.2.1 Photoreceptor and RPE Dysfunction

The RPE-photoreceptor metabolic ecosystem is vulnerable to multiple insults. In AMD, oxidative modification of drusen components (e.g., carboxyethylpyrrole adducts from oxidized docosahexaenoic acid) generates damage-associated molecular patterns (DAMPs) that activate NLRP3 inflammasomes in RPE cells via Toll-like receptor 2/4 signaling. This triggers caspase-1-mediated IL-1β/IL-18 secretion and pyroptotic cell death, while complement activation (*C3*a, C5a) promotes choroidal macrophage infiltration, creating a proinflammatory feedback loop [47]. In retinitis pigmentosa, mutant rhodopsin proteins (RHO mutations) misfold in the endoplasmic reticulum (ER), activating the unfolded protein response (UPR) through PERK, IRE1α, and ATF6 pathways. Persistent ER stress leads to CHOP-mediated apoptosis, while defective outer segment phagocytosis by RPE cells exacerbates photoreceptor degeneration. Autosomal dominant RHO mutations (e.g., P23H) additionally cause gain-of-function toxicity through aberrant G-protein signaling, making them prime targets for allele-specific CRISPR editing [48].

3.2.2 Vascular Pathobiology

DR pathogenesis involves hyperglycemia-induced metabolic memory through epigenetic modifications. Sustained PKC-β activation increases histone deacetylase (HDAC) activity at VEGF promoter regions, while advanced glycation end-products (AGEs) bind RAGE receptors on Müller cells, inducing NF-κB-mediated cytokine production. The resulting breakdown of the blood–retinal barrier involves claudin-5/ZO-1 tight junction disassembly and increased vesicular transport via caveolin-1 upregulation. Retinal vein occlusions (RVOs) demonstrate thrombotic and inflammatory components. Turbulent flow at arteriovenous crossings promotes endothelial dysfunction with increased von Willebrand factor (vWF) multimer secretion and platelet adhesion. Local tissue hypoxia upregulates HIF-1α, which stimulates VEGF, angiopoietin-2, and platelet-derived growth factor (PDGF) expression, exacerbating vascular leakage and macular edema [49].

3.2.3 Neurodegenerative Processes

Glaucomatous optic neuropathy involves both mechanical and metabolic insults. Elevated IOP distorts laminar cribrosa pores, impairing axonal transport of neurotrophins such as BDNF. Mitochondrial dysfunction in retinal ganglion cells (RGCs) increases ROS production, activating BAX/BAK-mediated apoptosis [50]. Notably, the superior and inferior optic nerve regions show selective vulnerability due to reduced astrocyte coverage and higher metabolic demands. LHON exemplifies mitochondrial dysfunction, with m.11778G>A (*MT-ND4*), m.3460G>A (*MT-ND1*), and m.14484T>C (*MT-ND6*) mutations impairing complex I function. This reduces ATP production while increasing

superoxide leakage, causing preferential degeneration of small-caliber papillomacular bundle axons [34].

4 Gene Therapy Strategies for PSEDs

Gene therapy has emerged as a transformative approach for treating PSED, particularly IRDs. These therapies aim to address the underlying genetic causes of retinal degeneration, offering the potential to restore or modify gene function and improve visual outcomes. The unique characteristics of the eye—immune privilege, small tissue size, and accessibility—make it an ideal target for gene therapy interventions [51–53]. Various strategies, including gene augmentation, gene editing, RNA-based therapies, and optogenetics, have been developed to tackle these diseases (Fig. 1). Below is a detailed exploration of these strategies.

4.1 Gene Augmentation Therapy

Gene augmentation therapy is one of the most established approaches in retinal gene therapy. It involves delivering functional copies of defective genes to target cells to restore normal protein production and cellular function. This strategy has shown significant success in treating inherited retinal diseases such as LCA caused by *RPE65* mutations. The mechanism of gene augmentation therapy relies on the use of viral vectors, predominantly AAV, which transduce retinal cells efficiently while minimizing immune responses (Fig. 2). AAV vectors are particularly suited for ocular applications due to their ability to target both dividing and non-dividing cells such as photoreceptors and RPE cells [8, 51, 54].

A prime example of gene augmentation therapy is Luxturna (voretigene neparvovec-rzyl), which was the first FDA-approved gene therapy for IRDs in 2017. Luxturna targets *RPE65* mutations associated with LCA by introducing functional *RPE65* genes into RPE cells via subretinal injection. Clinical trials demonstrated substantial improvements in visual function, including enhanced light sensitivity and navigational ability under low-light conditions [10, 55, 56]. Post-marketing studies confirmed long-term therapeutic benefits lasting up to 5 years, highlighting the potential for sustained visual improvement [8].

Beyond LCA, gene augmentation therapy is being explored for other inherited retinal diseases such as choroideremia and Stargardt disease. Clinical trials targeting choroideremia have utilized AAV vectors to deliver *CHM* genes to restore protein production in RPE cells [51, 57]. Similarly, ongoing research is investigating AAV-mediated delivery of *ABCA4* genes for Stargardt disease despite challenges posed by the large size of the *ABCA4* gene exceeding AAV's carrying capacity [53, 58].

Fig. 1 Gene therapy strategies for posterior segment eye diseases. An overview of key therapeutic approaches, including gene augmentation, gene editing, RNA-based therapies, and optogenetics, aimed at treating retinal and other posterior segment disorders

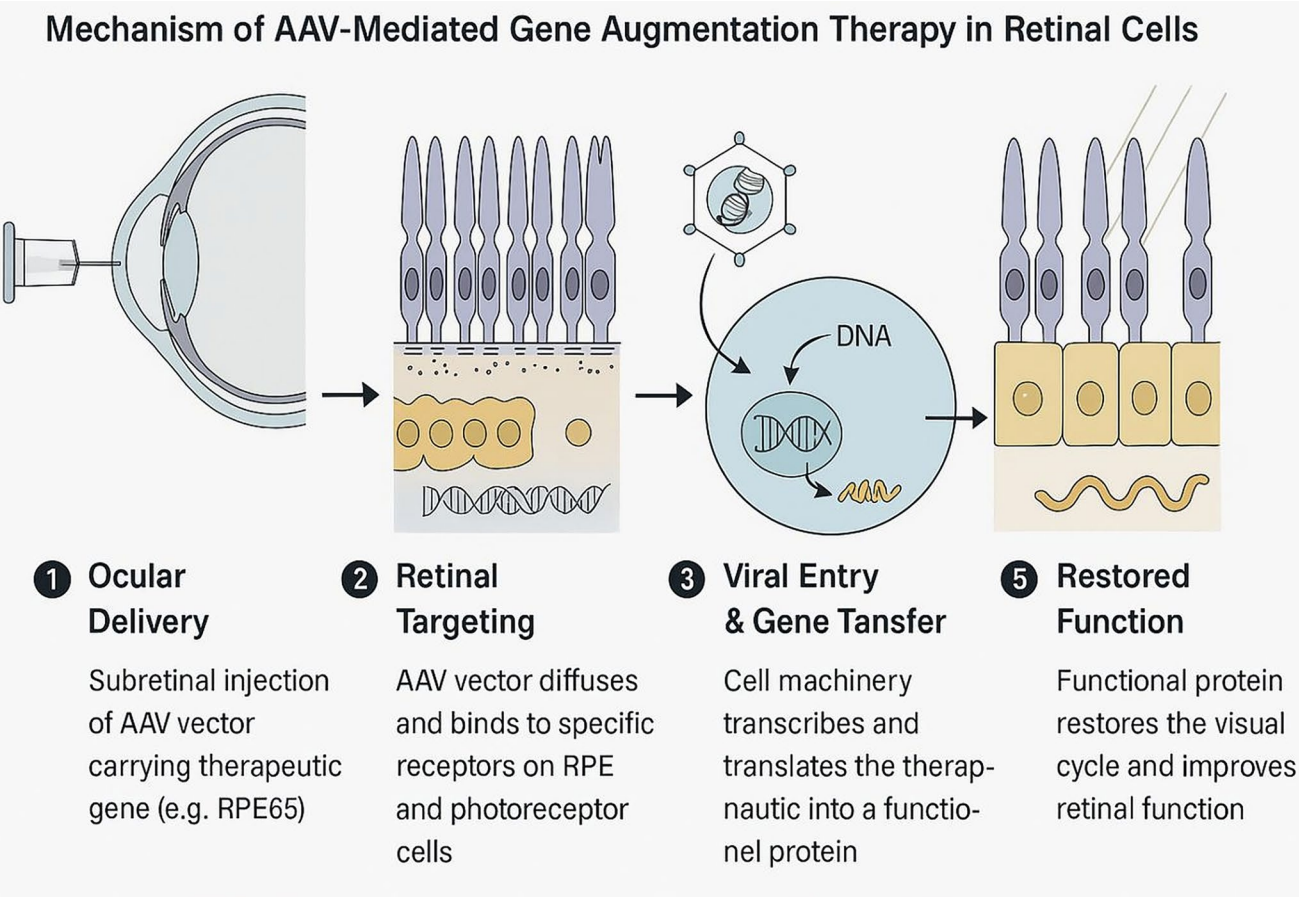

Fig. 2 Mechanism of AAV-mediated gene augmentation therapy in the retina. Illustrates how adeno-associated virus (AAV) vectors deliver functional copies of genes to retinal cells to restore protein expression in inherited retinal diseases. *RPE* retinal pigment epithelium

However, gene augmentation therapy faces several challenges. The limited carrying capacity of AAV vectors (~4.7 kb) restricts their use for larger genes such as *ABCA4*. Additionally, potential immune responses and inflammation due to viral delivery systems can complicate treatment outcomes. Accelerated retinal degeneration has been reported in up to 50% of treated eyes post-Luxturna, necessitating careful patient selection and monitoring [51, 58].

Emerging solutions include the development of hybrid vectors and non-viral delivery systems capable of accommodating larger genes while minimizing immunogenicity. These advancements aim to overcome the limitations of current viral vectors, providing a broader range of therapeutic options for IRDs [51, 53].

4.2 Gene Editing Approaches

Gene editing technologies enable precise modifications to the genome, offering promising solutions for inherited retinal diseases caused by dominant-negative mutations or large genes that exceed the carrying capacity of conventional viral vectors. CRISPR-Cas9 is a revolutionary tool for targeted genome editing that uses guide RNA (gRNA) to direct Cas9 nuclease to specific DNA sequences for correction or deletion (Fig. 3). Preclinical studies have demonstrated its potential in correcting *RPGR* mutations associated with X-linked retinitis pigmentosa (XLRP), restoring photoreceptor function and improving visual outcomes [54, 59].

Advanced techniques such as base editing and prime editing allow single-nucleotide changes without introducing double-strand breaks. Prime editing offers higher precision and reduced off-target effects compared with CRISPR-Cas9 [60]. Base editing has been applied successfully in animal models of *RPE65* mutations, demonstrating restored visual function with minimal off-target effects [61]. These approaches are particularly advantageous for dominant-negative mutations that cannot be addressed by gene augmentation, offering potentially long-lasting effects through permanent correction of genetic defects.

Despite these advancements, gene editing faces significant challenges. Delivery efficiency remains a major hurdle, especially for deep retinal layers where photoreceptors

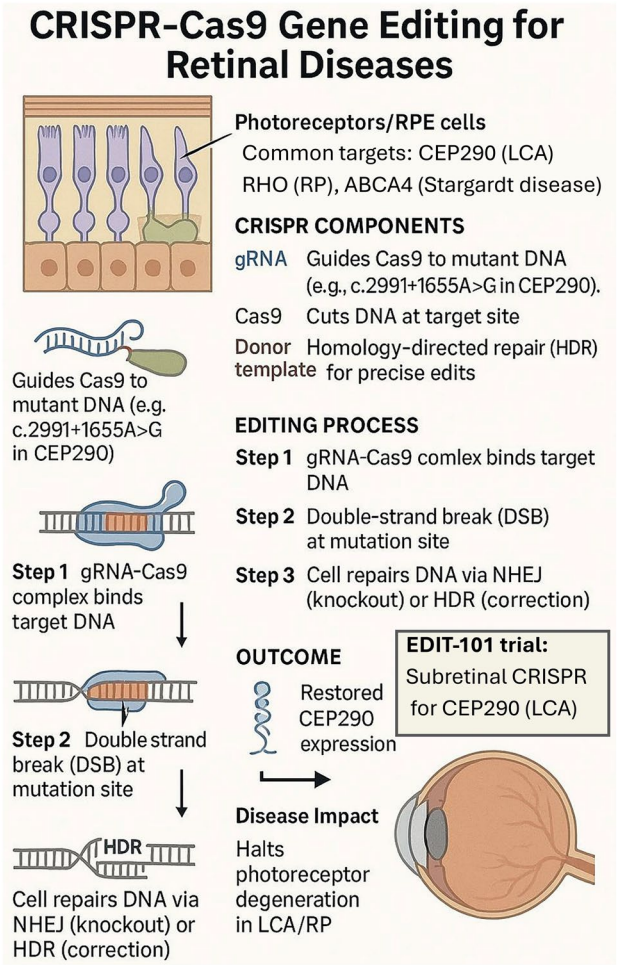

Fig. 3 CRISPR-Cas9 gene editing for retinal diseases. Depicts the use of CRISPR-Cas9 technology for targeted genome editing in retinal cells to correct disease-causing mutations

reside. Safety concerns regarding off-target effects and unintended genomic alterations are also critical, as these could lead to unforeseen complications. Recent advancements include the development of lipid nanoparticles and polymer-based carriers for delivering CRISPR components into retinal cells with higher efficiency and reduced toxicity [62, 63].

4.3 RNA-Based Gene Therapy

RNA-based therapies offer transient but highly specific modulation of protein production by targeting messenger RNA (mRNA). These approaches are particularly useful for conditions where permanent genomic modification is unnecessary or undesirable. Antisense oligonucleotides (ASOs) are short RNA sequences that bind complementary mRNA strands to modulate splicing or prevent translation into harmful proteins [64, 65]. RNAi uses small interfering RNA (siRNA) molecules to form RNA-induced silencing complexes (RISCs) that degrade target mRNA sequences [65, 66]. MicroRNAs (miRNAs) regulate multiple genes simultaneously, offering potential for complex diseases such as AMD (Fig. 4) [66].

RNA-based therapies have shown promise in treating AMD, DR, and IRDs such as autosomal dominant RP caused by rhodopsin mutations [64, 66]. siRNA-based therapies targeting VEGF have been investigated as alternatives to anti-VEGF injections in patients with AMD, potentially reducing the frequency of injections and improving patient compliance [65].

However, RNA-based therapies face several challenges. The instability and degradation of RNA molecules necessitate repeated administration, which can be burdensome for patients. Efficient delivery into retinal cells remains challenging due to the BRB, which limits the penetration of therapeutic agents into the retina [67]. Despite these

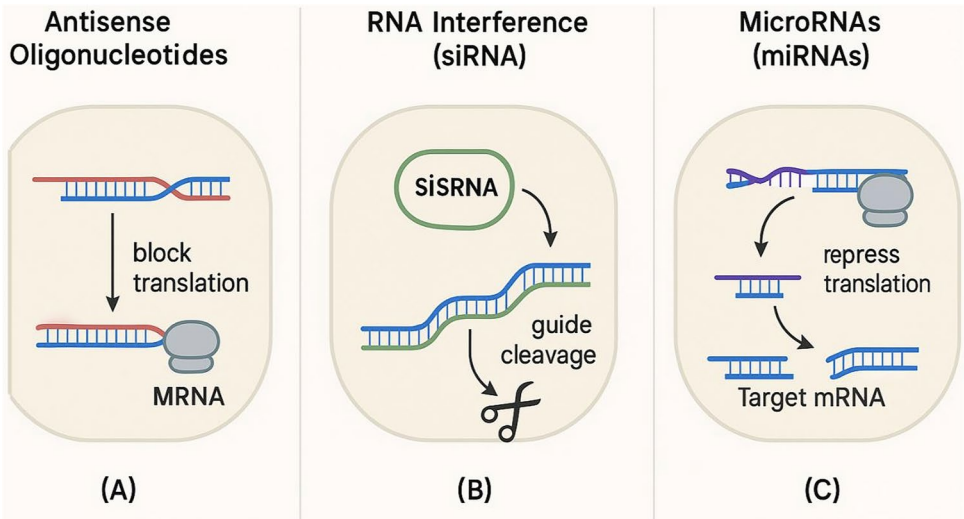

Fig. 4 Mechanisms of RNA-based gene therapy. **A** Antisense oligonucleotides (ASOs) bind to complementary messenger RNA (mRNA) sequences to block translation or modulate splicing. **B** Small interfering RNAs (siRNAs) incorporate into RNA-induced silencing complexes (RISCs) to guide the cleavage of target mRNAs. **C** MicroRNAs (miRNAs), processed from endogenous precursors, regulate gene expression by binding to multiple mRNA targets, leading to translational repression or destabilization

limitations, RNA-based therapies continue to advance, with ongoing research focusing on improving delivery methods and stability to enhance their therapeutic potential.

Although early clinical investigations of siRNA-based therapies for AMD and DME showed initial promise, this strategy has not advanced to clinical use due to limited efficacy in later trials. Current gene therapy research in these diseases is focused on other modalities [68, 69].

4.4 Optogenetics and Cell-Based Gene Therapy

Optogenetic therapy represents a novel approach to restoring vision in patients with advanced retinal degeneration by introducing light-sensitive proteins into surviving retinal cells. The mechanism involves delivering microbial opsins such as channelrhodopsins via viral vectors to convert inner retinal neurons into artificial photoreceptors capable of responding to light stimuli [70, 71].

Clinical trials have validated the potential of optogenetic therapy as a therapeutic option for patients with severe vision loss due to advanced RP. ChrimsonR opsin therapy, for example, has shown promise in restoring light perception in patients with late-stage retinal degeneration [72, 73]. Optogenetic approaches offer several advantages, including the ability to provide visual restoration even when photoreceptors are completely lost. However, they also face significant challenges. High-intensity light activation is required, which may damage residual retinal tissue. Immune responses against microbial opsins remain a concern, potentially limiting the long-term efficacy of the therapy [72, 73].

Recent advancements in optogenetics include mutation-independent strategies such as multi-characteristic opsins (MCOs), which aim to overcome some of these limitations by providing broader light sensitivity and reducing the need for high-intensity light. These developments, along with ongoing clinical trials, offer hope for patients with severe vision loss, expanding the therapeutic landscape for PSED.

5 Delivery Methods of Gene Therapy in Posterior Segment Eye Diseases (PSEDs)

Gene therapy delivery methods for PSED have evolved significantly, incorporating both viral and non-viral vectors, as well as various administration routes.

5.1 Viral Vectors

Viral vectors are the most commonly used for ocular gene therapy due to their high efficiency in transducing retinal cells:

- Adeno-Associated Virus (AAV): AAV is the preferred vector for retinal gene delivery due to its ability to provide long-term transgene expression, safety profile, and capacity to transduce non-dividing cells such as photoreceptors and RPE [74, 75]. However, its cargo capacity is limited to approximately 4.7 kb, which restricts its use for larger genes [76]. AAV vectors have been successfully used in clinical trials for inherited retinal dystrophies, including the FDA-approved Luxturna therapy for *RPE65*-associated LCA [77, 78]. The vector's ability to transduce both inner and outer retinal cells makes it particularly advantageous for treating a wide range of retinal diseases [79].
- Lentiviral vectors: These vectors can accommodate larger genes and provide sustained expression, but they carry risks of insertional mutagenesis, which can lead to oncogenesis [76]. They are particularly useful for conditions requiring long-term gene expression, such as choroideremia, where the *CHM* gene needs to be delivered to RPE cells [57]. Lentiviral vectors have shown promise in preclinical studies, demonstrating efficient transduction of RPE cells and sustained gene expression [79].
- Adenoviral vectors: Offering high transgene capacity, adenoviral vectors elicit stronger immune responses compared with AAVs, which can limit their use in ocular applications. They are more suited for transient gene expression, making them less ideal for long-term treatments but potentially useful for short-term interventions or in cases where immune responses are not a significant concern [79].

A comparative study highlighted that AAV vectors showed the most efficient and long-lasting transduction in both inner and outer retinal cells, while lentivirus primarily transduced RPE cells and adenovirus demonstrated transient expression mainly in the anterior chamber [79]. This study underscores the importance of selecting the appropriate vector on the basis of the specific requirements of the disease being treated.

5.2 Non-viral Delivery Systems

Non-viral gene therapy systems offer several advantages over viral vectors:

- Lipid nanoparticles (LNPs) and liposomes: These synthetic carriers can efficiently transfect retinal cells, providing long-term gene expression. Recent advancements have shown LNPs can penetrate the neural retina and deliver mRNA to photoreceptor cells, potentially treating blindness associated with genetic conditions [80, 81]. For example, *ECO/pRHO-ABCA4* nanoparticles demonstrated sustained *ABCA4* expression and delayed disease progression in a mouse model of Stargardt disease [82].

- Polymer-based vectors: Polymers such as polyethyleneimine (PEI) have been modified to enhance biocompatibility and reduce toxicity, making them suitable for gene delivery in the eye. These vectors can encapsulate and deliver genetic material to target cells, offering a versatile and scalable option [80, 82]. Polymer-based vectors have shown promise in preclinical studies, with some demonstrating long-term expression of therapeutic genes in the retina [81].
- Electroporation: This physical method uses electrical pulses to create temporary pores in cell membranes, allowing genetic material to enter. It is particularly useful for in vitro and in vivo gene delivery to various tissues, including the retina. Electroporation has been used to deliver plasmids encoding therapeutic genes, showing efficient gene transfer in animal models [83].

Non-viral vectors face challenges such as lower transduction efficiency compared with viral vectors, but ongoing research aims to optimize these systems for clinical use [84]. Efforts are being made to enhance the stability of the vectors, improve their targeting capabilities, and reduce potential toxicity to ensure their safe and effective use in gene therapy for PSED. Comparison of viral and non-viral vectors for PSED gene therapy is summarized in Table 2.

5.3 Routes of Administration

- Subretinal injection: This method involves delivering vectors directly between the RPE and photoreceptor layers. It has been used successfully in clinical trials for inherited retinal dystrophies, including the FDA-approved Luxturna therapy for *RPE65*-associated LCA [77, 78]. The procedure requires a pars plana vitrectomy and is invasive, with potential risks such as retinal detachment. However, subretinal injection offers more direct targeting of affected cells compared with intravitreal injection, making it the preferred method for many retinal gene therapies [85].
- Intravitreal injection: Less invasive than subretinal injection, intravitreal delivery faces challenges in achieving effective retinal transduction due to vector dilution, immune responses, and barriers such as the inner limiting membrane [86]. Pararetinal intravitreal delivery, where the vector is placed deep in the vitreous near the retina, has shown improved retinal transduction compared with mid-vitreous injection. However, subretinal delivery still demonstrates superior retinal gene transfer and a more favorable biodistribution profile compared with intravitreal injection in nonhuman primates [87]. Ongoing research focuses on developing strategies to overcome the limitations of intravitreal delivery, including viral capsid modifications and non-viral vectors, to achieve panretinal transduction comparable to subretinal delivery [86].
- Suprachoroidal injection: An emerging method, suprachoroidal injection involves delivering vectors into the space between the choroid and sclera. It offers advantages such as less invasiveness, potential for outpatient administration, and higher drug concentrations in the posterior segment [88, 89]. This technique has shown promise in preclinical studies, demonstrating short-term effectiveness and ocular tolerability. However, challenges include ensuring vectors reach target retinal tissues and managing immune responses. While suprachoroidal delivery has the potential to provide widespread transgene expression in the retina and RPE, further research is needed to address long-term safety, durability of gene expression, and effective delivery to the macula before clinical

Table 2 Comparison of viral and non-viral vectors for posterior segment eye disease (PSED) gene therapy

Vector type	Advantages	Disadvantages	Current applications in PSED
AAV vectors	Long-term transgene expression Low immunogenicity Retinal cell tropism	Limited cargo capacity (~4.7 kb) Preexisting immunity in some patients	Luxturna® (AAV2-*RPE65*) RGX-314 (AAV8) ADVM-022 (AAV.7m8)
Lentiviral vectors	Larger cargo capacity (~8–10 kb) Sustained expression	Risk of insertional mutagenesis Complex manufacturing	Choroideremia (AAV2-CHM) trials
Adenoviral vectors	High cargo capacity (~30 kb)	Strong immune response Transient expression	Limited use in ocular therapy due to inflammation
Lipid nanoparticles (LNPs)	No viral components Larger cargo capacity Scalable production	Lower transfection efficiency Transient expression Potential toxicity	Stargardt disease (preclinical) mRNA delivery for PVR
Polymer-based vectors	Customizable Reduced immunogenicity	Variable efficiency Unclear long-term safety	Experimental retinal delivery
Electroporation	Physical delivery method Avoids viral risks	Invasive Limited to accessible tissues	Preclinical retinal gene editing

Table 3 Gene therapy delivery routes for posterior segment eye diseases

Delivery method	Advantages	Disadvantages	Best for	Examples
Subretinal injection	Direct access to photoreceptors/RPE High transduction efficiency Lower immune response	Invasive (requires vitrectomy) Risk of retinal detachment Limited diffusion to wider retina	Monogenic IRDs (e.g., Luxturna® for *RPE65)* AMD with localized targets	Voretigene neparvovec (AAV2) RGX-314 (AAV8) for AMD
Intravitreal injection	Minimally invasive Outpatient procedure Panretinal potential	Inner limiting membrane barrier Higher immune response Dilution in vitreous	Diseases targeting ganglion cells (e.g., LHON) Anti-VEGF therapies	ADVM-022 (AAV.7m8 aflibercept) GS010 (AAV2-ND4 for LHON)
Suprachoroidal injection	Less invasive than subretinal Targets choroid/RPE Reduced inflammation	Variable transduction efficiency Limited clinical data Macular reach uncertain	Diffuse retinal diseases Sustained drug delivery	RGX-314 (phase II ALTITUDE trial for DR) 4D-150 (AAV anti-VEGF)

AAV adeno-associated virus, *AMD* age-related macular degeneration, *IRD* inherited retinal disease, *LHON* Leber hereditary optic neuropathy, *RPE* retinal pigment epithelium, *VEGF* vascular endothelial growth factor

implementation [90]. Table 3 presents a summary of gene therapy delivery routes for PSED.

6 Gene Therapy Applications in Specific Posterior Segment Eye Diseases (PSEDs)

Gene therapy for PSEDs typically involves delivering genetic material to retinal cells via viral vectors (most commonly AAV) injected into or under the retina [91–93]. Depending on the target cells, vectors can be administered intravitreally, subretinally, or suprachoroidally, each route having advantages and limitations. The overarching goal is to introduce therapeutic genes or molecules to either replace a defective gene, silence a harmful gene, or provide a sustained source of a therapeutic protein in the eye, thereby addressing chronic retinal conditions with a one-time treatment.

6.1 Age-Related Macular Degeneration (AMD)

The standard treatment for AMD involves anti-VEGF injections, which need to be administered frequently. Recent gene therapy trials for neovascular AMD, such as RGX-314 and ADVM-022, are designed to provide sustained intraocular anti-VEGF expression, reducing the need for frequent injections. RGX-314 uses an AAV8 vector for subretinal or suprachoroidal delivery, aiming for long-term expression in retinal cells. The subretinal route targets the retinal pigment epithelium and photoreceptors directly, while the suprachoroidal approach offers a less invasive alternative with the potential for widespread retinal transduction. ADVM-022 employs an engineered AAV2.7m8 capsid for intravitreal delivery, which is designed to enhance retinal penetration and minimize invasiveness compared to subretinal injection. The rationale behind these designs is to transform the retina into a "biofactory" for anti-VEGF proteins, thereby addressing the burden of repeated treatments and improving patient adherence. Clinical trials have demonstrated that these approaches can significantly reduce the frequency of anti-VEGF injections while maintaining or improving visual outcomes [14, 21]. Neovascular AMD typically presents with metamorphopsia and central vision loss driven by macular neovascularization. Anti-VEGF gene therapy aims to convert the eye into a biofactory for sustained intraocular anti-VEGF expression, lowering injection burden while maintaining retinal anatomy and vision. Ongoing trials of RGX-314, ADVM-022 (ixo-vec), and 4D-150 assess reduction in rescue injections, Best-Corrected Visual Acuity(BCVA), and OCT fluid as key endpoints [14, 91, 94–98]. Early phase and mid-stage studies of RGX-314 (subretinal; suprachoroidal in phase 2) show fewer rescue injections with stable vision and a generally favorable ocular safety profile at subretinal doses. ADVM-022 (ixo-vec) has demonstrated marked reductions in injection burden with steroid-manageable inflammation, with dose optimization following DME experience. 4D-150 advanced to phase 3 (4FRONT-1/-2) on the basis of phase 2 data supporting strong treatment-burden reduction with maintained vision [99–101]. Notable gene therapy options for AMD are RGX-314, ADVM-022, and 4D-150:

- RGX-314 (REGENXBIO/AbbVie): This treatment employs an AAV8 vector to introduce a gene that encodes a monoclonal antibody fragment akin to ranibizumab, an anti-VEGF agent [21, 102]. Delivered through a single subretinal injection in clinical trials or a suprachoroidal injection in more recent studies, the transduced retinal cells continuously release the anti-VEGF Fab,

which treats active, established macular Neovascularization (MNV) in patients with neovascular AMD [14, 103]. In an early phase study involving 42 patients with wet AMD, RGX-314 was well tolerated, with no unusual immune reactions or significant inflammation detected in the treated eyes [14, 104]. Importantly, patients showed a decreased need for standard anti-VEGF injections; in one group, the yearly injection rate fell by approximately 67%, with vision remaining stable or improving over several years. These promising outcomes have led to ongoing pivotal trials, such as ATMOSPHERE [105], which administer RGX-314 subretinally, and phase II trials, AAVIATE and ALTITUDE, which are assessing less invasive suprachoroidal delivery methods for wet AMD and diabetic retinopathy, respectively [94, 95].

- ADVM-022 (Adverum Biotechnologies, now called ixoberogene soroparvovec): ADVM-022 is a gene therapy administered via intravitreal injection, using an AAV2.7m8 capsid to enhance retinal transduction and carrying a gene for a protein similar to aflibercept, a strong anti-VEGF agent [96]. In the phase 1 OPTIC trial for wet AMD, a single intravitreal dose significantly reduced treatment burden: high-dose patients experienced a 96% decrease in additional anti-VEGF injections during the first year, while low-dose patients saw about an 85% reduction [97]. Therapeutic levels of aflibercept protein were maintained in ocular fluids for up to 2 years after dosing [98]. The primary adverse event was intraocular inflammation, especially in high-dose groups, but it was controlled with steroid eye drops, with no severe vasculitis or endophthalmitis reported [23]. These findings support intravitreal AAV gene delivery for sustained anti-VEGF therapy. However, in the INFINITY trial for diabetic macular edema, one patient experienced prolonged hypotony following high-dose injection, leading to early termination [14]. This incident highlights the need for dose optimization and safety monitoring in intraocular gene therapy. ADVM-022 continues to be investigated at safer doses for AMD. Other AMD gene therapies are being developed, such as 4D-150 (4D Molecular Therapeutics), which uses a proprietary AAV capsid (R100) to deliver dual anti-VEGF factors via intravitreal injection and has shown promising interim results with minimal inflammation.
- 4D-150 (4D Molecular Therapeutics): 4D-150 is a dual-mechanism gene therapy delivered by intravitreal injection, currently in phase 3 trials for wet AMD. In phase 2b, 4D-150 reduced the need for anti-VEGF rescue injections by 89% at 24 weeks, with 77% of patients remaining injection free and with improved visual acuity. The therapy uses a proprietary AAV vector to deliver genes encoding inhibitors of multiple VEGF isoforms, aiming for durable, one-time treatment. Phase 3 trials (4FRONT-1 and 4FRONT-2) are underway as of 2025 [100, 101, 106].

Beyond neovascular AMD, gene therapy is also being investigated in dry AMD (geographic atrophy). Approaches here target complement cascade dysregulation—e.g., *GT005* delivers a gene for complement factor I to the RPE to reduce complement-mediated damage, *HMR59* delivers a soluble CD59 to inhibit complement activation, and OCU410 (Ocugen), all in early phase clinical trials [107–109]. These therapies target complement regulation, inflammation, and multiple disease pathways, with early results showing safety and potential efficacy in slowing geographic atrophy progression. Multiple companies are pursuing these approaches, and ongoing trials are evaluating subretinal and intravitreal delivery of complement factor genes and other targets. While not yet as advanced as the wet AMD programs, they broaden the scope of gene therapy's applicability in AMD.

6.2 Diabetic Retinopathy and Retinal Vascular Diseases

The RGX-314 trial, known as ALTITUDE, exemplifies this effort by investigating the use of suprachoroidal AAV8-RGX314 injections in diabetic retinopathy patients to provide ongoing anti-VEGF treatment [110]. This method could help sustain retinal health and avert the advancement to proliferative DR or diabetic macular edema without the need for monthly injections. In a similar vein, ADVM-022 (AAV.7m8-aflibercept) has been tested for diabetic macular edema; while high doses resulted in complications, lower doses may still offer potential benefits.

Beyond anti-VEGF treatments, gene therapies have the potential to address other pathways involved in DR. For example, diabetic retinal damage is associated with inflammation and factors induced by ischemia. Current research is exploring the gene delivery of antiinflammatory cytokines or inhibitors of angiogenesis, such as endostatin or angiopoietin regulators, to manage retinal vascular diseases [111]. Although no gene therapy for DR has been approved yet, these trials demonstrate the application of the "one-and-done" treatment approach to retinal vascular disorders. The goal is to achieve long-term stabilization of diabetic retinopathy and macular edema, thereby minimizing vision loss in the increasing diabetic population.

6.3 Inherited Retinal Diseases (IRDs)

IRDs are excellent candidates for gene replacement or correction therapies, as they often result from mutations in a single gene. The eye's unique immune privilege and its compartmentalized structure make it particularly suitable for these types of treatments [91, 92].

Prominent examples include RP, LCA, choroideremia, Usher syndrome, and Stargardt disease, each caused by distinct genetic mutations [8]. Gene therapy for IRDs mainly involves gene replacement or editing to restore normal gene function. The first successful gene replacement is voretigene neparvovec (Luxturna), approved by the FDA and the European Medicines Agency (EMA) for biallelic mutations in the *RPE65* gene causing LCA [8, 112]. Luxturna uses an AAV2 vector to deliver a functional *RPE65* gene into retinal pigment epithelium cells, significantly improving visual function, especially under low-light conditions [112, 113]. Clinical trials showed durable improvements in vision, including navigation abilities, maintained for more than 3 years, illustrating the potential long-term benefit of retinal gene therapy [112, 113].

Gene therapy trials targeting *RPGR* gene mutations for XLRP have shown promising early results. Botaretigene sparoparvovec (*AAV5-RPGR*), delivered via subretinal injection, improved or stabilized visual function in patients, with increased retinal sensitivity and visual fields measured by microperimetry [114, 115]. Higher vector doses caused inflammatory responses, but dosage optimization and immunomodulation strategies are being employed to manage these issues [114]. Choroideremia, another X-linked IRD caused by *CHM* gene mutations, has been addressed using gene replacement therapy (timrepigene emparvovec). A recent phase 3 trial did not meet its primary efficacy endpoint for visual acuity improvement in the overall population, but some treated patients showed significant vision preservation compared with untreated counterparts, indicating therapeutic potential if administered early [115, 116].

Addressing IRDs from large gene mutations, such as Usher syndrome (*MYO7A* gene) and Stargardt disease (*ABCA4* gene), is challenging due to AAV vectors' limited capacity. Dual-AAV systems, splitting large sequences across two vectors, are under clinical evaluation. Recent advancements have enabled *MYO7A* gene delivery in patients with Usher syndrome type 1B, potentially overcoming gene size constraints [117]. Genome-editing techniques such as base editing and prime editing show promise preclinically for correcting point mutations in large genes linked to IRDs. Base editing corrected *ABCA4* mutations in Stargardt disease mouse models, reducing retinal toxic byproducts and partially restoring visual function, showing potential for clinical translation [59]. Precision editing techniques offer hope for developing treatments for IRDs previously beyond therapeutic reach due to genetic complexity. In conclusion, gene therapy has significantly progressed in addressing various inherited retinal diseases, highlighted by the success of Luxturna for *RPE65*-related LCA and ongoing clinical trials in *RPGR*-associated XLRP and choroideremia. Innovations such as dual-AAV vectors and genome editing approaches continue to expand the therapeutic landscape, demonstrating great promise for treating large-gene IRDs such as Usher syndrome and Stargardt disease [8, 117].

6.4 Glaucoma and Optic Neuropathies

Glaucoma is a leading cause of irreversible blindness globally, characterized by progressive degeneration of RGCs and their axons within the optic nerve. Traditional therapies for glaucoma primarily focus on reducing IOP but often fail to halt the underlying neurodegeneration completely [118]. Gene therapy has emerged as a promising approach to provide sustained neuroprotection by delivering genes encoding neurotrophic factors such as brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), and neurotrophin-3 (NT-3) to retinal cells. Preclinical studies have shown that intravitreal AAV-mediated delivery of BDNF or CNTF significantly enhances RGC survival and preserves visual function in animal glaucoma models, highlighting the potential clinical utility of neuroprotective gene therapies [119, 120]. However, clinical translation faces challenges, including potential intraocular inflammation or aberrant nerve growth induced by continuous neurotrophic factor expression.

Optic neuropathies such as LHON, caused by mitochondrial *ND4* gene mutations, benefit from gene therapy. Recent trials used intravitreal AAV vectors to deliver a functional *ND4* gene to affected retinal ganglion cells. Clinical studies with patients with LHON showed that gene therapy improved visual acuity in treated eyes compared with untreated controls, marking one of the first successful gene therapy interventions for optic neuropathy [121–123]. These successes support the feasibility and safety of targeting optic nerve pathologies via intravitreal delivery. Future gene therapies for glaucoma and optic neuropathies may combine neuroprotective strategies with IOP-lowering treatments for comprehensive disease management. Continued trials and research are essential to optimize vector delivery, control transgene expression, and mitigate inflammatory risks, translating promising laboratory successes into clinical therapies for glaucoma and other optic neuropathies [122, 123].

6.5 Retinal Detachment and Vitreoretinal Interface Disorders

Retinal detachment and vitreoretinal interface disorders, such as proliferative vitreoretinopathy (PVR), constitute significant complications in ophthalmology, often resulting in severe visual impairment despite surgical interventions. PVR, the leading cause of retinal detachment repair failure, involves the pathological proliferation and migration of RPE cells, glial cells, and fibroblasts, resulting in fibrotic scar formation and retinal traction [124]. Current

therapeutic approaches involve surgical membrane removal combined with pharmacological agents, yet recurrence remains common. Gene therapy presents a novel strategy to prevent fibrosis and scarring by modulating the expression of key fibrogenic molecules. For instance, experimental AAV-mediated gene delivery of soluble TGF-β inhibitors or platelet-derived growth factor (PDGF) receptor sequestrants significantly reduces fibrosis and membrane contraction in animal models, highlighting potential therapeutic efficacy in mitigating PVR progression post-surgery [125, 126].

Recent innovations have explored mRNA-based gene therapy to address retinal scarring. A preclinical study showed that intraocular injection of modified mRNA encoding dominant-negative RUNX1 suppressed fibrotic membrane formation in animal models of PVR, highlighting the potential of transient genetic modulation [127]. A total of 38 gene therapies using apoptosis-inducing genes targeting proliferative retinal cells involved in fibrotic membrane formation have shown promise in reducing tractional retinal detachment in experimental models [124, 125]. While these approaches have not advanced to human trials, their preclinical successes underline the potential of gene-based interventions to prevent or minimize fibrovascular complications in retinal detachments. Optimizing vector design, transgene selection, and controlled expression will be crucial to translating these promising laboratory outcomes into safe, effective treatments for patients with complex vitreoretinal interface disorders.

7 Clinical Trials and Approved Gene Therapies

Significant progress in ocular gene therapy has translated from preclinical success into clinical applications, marked notably by the approval of voretigene neparvovec (Luxturna) for treating LCA and other retinal dystrophies associated with *RPE65* mutations. Luxturna, developed by Spark Therapeutics, was approved by the FDA and EMA as the first retinal gene therapy based on robust clinical data demonstrating sustained visual improvements in treated patients. Clinical outcomes highlighted significant functional gains in low-light mobility, visual acuity, and visual field sensitivity maintained for over 3 years post-treatment [8, 112]. Despite high treatment costs, its approval set a regulatory and therapeutic precedent for future gene therapies targeting other inherited retinal conditions.

Several other promising gene therapies targeting PSED have entered advanced clinical trials. These include RGX-314 and ADVM-022, which utilize AAV vectors to deliver genes encoding anti-VEGF molecules to treat neovascular AMD. Both therapies showed significant reductions in anti-VEGF injection frequency in treated patients, demonstrating prolonged therapeutic efficacy and supporting continued development in larger trials [96, 128]. Similarly, gene therapies for inherited conditions such as XLRP, choroideremia, Usher syndrome, and Stargardt disease have shown early indications of efficacy and manageable safety profiles, with ongoing trials expected to confirm clinical benefits and optimize therapeutic strategies [114–117].

Table 4 presents a curated selection of prominent gene therapy candidates for major PSED indications, emphasizing FDA-approved therapies, late-phase clinical trials, and notable early clinical candidates with published data. This table is not an exhaustive listing of all ongoing gene therapy studies but serves to illustrate important advances and representative modalities in the field.

In conclusion, ocular gene therapies have shown substantial clinical progress, demonstrating both therapeutic promise and the potential to fundamentally alter treatment paradigms for inherited and acquired retinal diseases. Luxturna's success paved the way for numerous trials targeting various posterior segment eye diseases. While challenges persist in vector optimization, dose-related inflammation, and cost management, ongoing and upcoming clinical trials continue to refine these therapies, offering hope for significant advancements in preventing and potentially reversing vision loss associated with retinal pathologies [8, 112, 115].

8 Challenges and Limitations of Gene Therapy in Posterior Segment Eye Diseases (PSEDs)

Despite the exciting progress, significant challenges remain before gene therapy is widely adopted for posterior eye diseases. An overview of challenges and limitations are shown in Fig. 5. Key limitations include biological hurdles, safety concerns, and practical/economic issues:

- Immune responses and inflammation: The eye is often termed "immune privileged," indicating its ability to handle antigens without triggering a full immune response. However, gene therapy in the eye can still provoke immune reactions, impacting safety and effectiveness [91]. AAV vectors may face preexisting neutralizing antibodies, potentially hindering transduction or causing inflammation. Intravitreal delivery is generally more immunogenic than subretinal delivery: in trials with intravitreal AAV, inflammation in the anterior chamber was a common adverse effect varying with dosage [23]. In one instance, severe inflammation after injection led to hypotony and vision loss, suspending a trial [129]. Intravitreal AAV encounters the inner limiting membrane and resident immune cells, potentially provoking inflamma-

Table 4 Summary of key gene therapies for posterior segment eye diseases, including approved and investigational treatments with details on vectors, delivery routes, clinical phases, sponsors, and references

Disease	Therapy	Vector	Delivery route	Clinical phase/status	Key efficacy outcome	Safety profile	Sponsor	Key references
LCA (*RPE65* mutation)	Voretigene neparvovec (Luxturna)	AAV2	Subretinal	Approved (III, EMA/FDA)	> 2 luminance level gain in mobility/FST/fields, sustained for ≥ 9 years; 93% of eyes improved in phase III, effect in both children and adults	3 late chorioretinal atrophy, no systemic vector events	Spark Therapeutics	Russell et al. [8]; Maguire et al. [110]
AMD (wet)	RGX-314	AAV8	Subretinal/suprachoroidal	Phase III (ongoing)	97% reduction in injection frequency at 9 months (fellow eye trial), 78% eyes injection free, maintained/improved BCVA, dose effect seen	No serious drug-related events; mild, steroid-responsive inflammation	Regenxbio	Heier et al. [126]
AMD (wet)	ADVM-022	AAV7m8	Intravitreal	Phase II (ongoing)	> 80% of patients injection free at 2.5 years (OPTIC); maintained therapeutic aflibercept; improved/maintained vision	39% mild–moderate inflammation, all responsive to topical steroids	Adverum Biotechnologies	Khanani et al. [98]
X-linked RP (RPGR)	Botaretigene sparoparvovec	AAV5	Subretinal	Phase III (ongoing)	At 24 weeks: ~50% of eyes gained ≥ 7 letters, improved visual function; BCVA gain reported; statistical significance varies; trial ongoing	Ocular inflammation, retinal tears/detachment (all managed)	MeiraGTx/Janssen	Cehajic-Kapetanovic et al. [112], Fischer et al. [113]
Choroideremia (CHM)	Timrepigene emparvovec	AAV2	Subretinal	Phase III completed (mixed results)	14% (high dose), 18% (low dose) gained ≥ 10 letters versus 2% controls (STAR); majority maintained ≥ 1 line improvement	No new AAV safety signals; inflammation resolves with steroids	Biogen	MacLaren et al. [114]

Table 4 (continued)

Disease	Therapy	Vector	Delivery route	Clinical phase/status	Key efficacy outcome	Safety profile	Sponsor	Key references
Usher syndrome (MYO7A)	Dual-AAV MYO7A therapy	Dual AAV8	Subretinal	Phase I (ongoing)	Preclinical: persistent MYO7A expression/photoreceptor rescue; clinical efficacy pending	No dose-limiting toxicities reported to date	Nanoscope/AAVantgarde	Trapani et al. [115]
Stargardt disease (*ABCA4*)	Dual-AAV and base editing	Dual AAV or nanoparticles	Subretinal (preclinical/early clinical)	Preclinical stage	First-in-human dual-AAV (ASTRA) ongoing; preclinical: robust ABCA4 expression and function restored in vivo; human efficacy pending	No significant gene-therapy-related toxicity in early trials	Various academic and biotech groups	Zernant et al. [127]; Yan et al. [128]
Diabetic retinopathy	RGX-314 (ALTITUDE trial)	AAV8	Suprachoroidal	Phase II (ongoing)	CST stabilization, reduced supplemental injection need; supportive efficacy trend; primary endpoint results expected in 2025	Mild inflammation, resolved with topical steroids	Regenxbio	Heier et al. [126]

AAV adenoassociated virus, *AMD* age-related macular degeneration, *CST* contrast sensitivity test, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *FST* full-field stimulus threshold test, *LCA* Leber congenital amaurosis

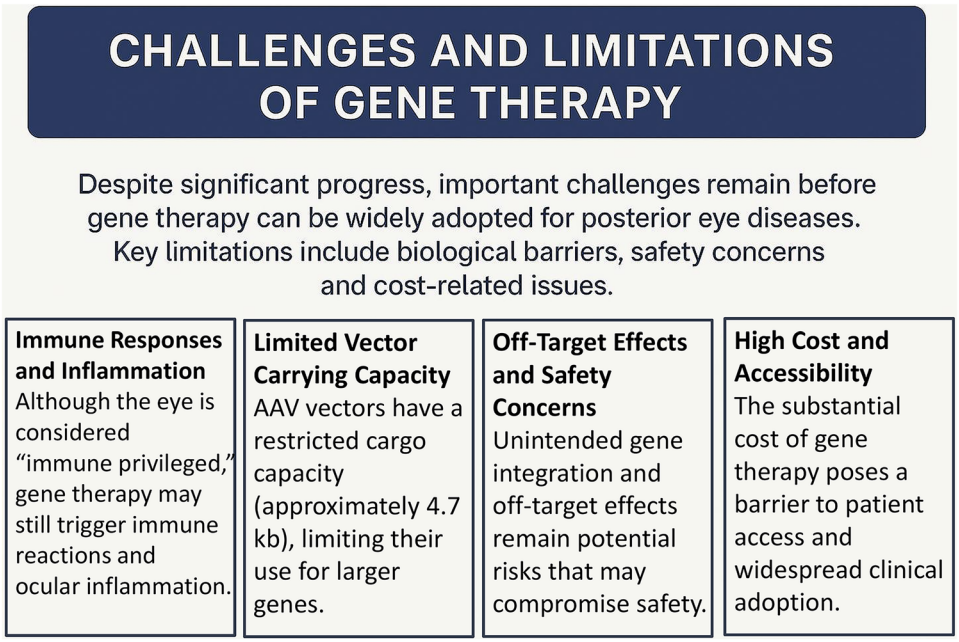

Fig. 5 Overview of challenges and limitations in ocular gene therapy. Summarizes the key barriers to effective gene therapy for posterior segment eye diseases, including vector delivery, immune responses, anatomical constraints, and long-term safety considerations

tion, especially at high vector doses. Subretinal delivery typically results in less vector dispersion and reduced immune exposure. Nonetheless, subretinal gene therapy can still cause vitritis or chorioretinitis if the patient develops a T-cell response to the AAV capsid or newly expressed protein. This risk increases if the transgene is a novel protein perceived as foreign. Strategies to reduce immunogenicity include using the lowest effective vector dose, short-term immunosuppression, and designing new AAV capsids to avoid preexisting antibodies. Second-generation vectors often show reduced immune recognition and can achieve transduction at lower doses. Immune responses can cause short-term inflammation, damaging the eye and potentially eliminating transduced cells, reducing long-term treatment benefits [99, 130]. Research focuses on identifying biomarkers to predict individuals at risk for inflammation and adjusting immunosuppression accordingly. While most ocular gene therapy trials have not encountered severe systemic immune events, managing ocular inflammation remains a primary concern for safe gene therapy.

- Limited vector carrying capacity: The most commonly used vectors in retinal gene therapy are AAVs, with a cargo limit of around 4.7 kb of DNA [99]. This suffices for many genes, but several important retinal disease genes are larger (*ABCA4*, *MYO7A*, *USH2A*, *CEP290*, etc., exceeding 5 kb) [99]. Delivering such large genes requires splitting across two vectors or using alternatives. Lentiviral vectors can carry ~8–10 kb and adenoviral vectors up to ~30 kb, but these have issues: lentiviruses integrate into the genome, raising concerns about insertional mutagenesis and oncogenic risk, while first-generation adenoviruses can cause immune reactions and transient expression. AAV remains preferred for safety, but its small capacity is a bottleneck. Dual AAV systems address this limit, showing success in animal models and entering clinical trials [131]. However, dual AAV approaches have lower efficiency and recombination may not be fully accurate. Non-viral vectors or RNA approaches offer alternatives [131]. Nanoparticles carrying mRNA could bypass the DNA size issue, but expression is transient, requiring repeated dosing. Non-viral delivery methods such as electroporation, liposomes, or polymer nanoparticles have been tested in retina with some success, but struggle with low efficiency and duration of expression [132]. The field is actively working to stretch AAV's capacity or find alternatives, as the inability to package large genes limits treating many IRDs.
- Off-target effects and safety concerns: Gene therapy raises concerns about unintended effects. For AAV gene replacement, ectopic expression is a worry—the gene might express in unintended cells, causing toxicity [133]. Cell-specific promoters can help (e.g., RPE-specific promoter for *RPE65*). AAV rarely integrates into the genome, which is safer, but low-frequency integration can disrupt host genes [99]. In systemic AAV studies, some liver cell integration events raised theoretical cancer risks, but this is minimal in post-mitotic retinal cells [134–138]. More relevant to the retina is off-target transduction of the optic nerve if vectors diffuse—careful injection and improved vectors have managed this. For CRISPR gene editing, off-target DNA cuts are a concern; however, the eye's confined nature allows for local delivery, reducing systemic exposure. In the ongoing EDIT-

101 CRISPR trial, no significant off-target issues have been reported, but deep sequencing analyses are underway. Long-term safety is another unknown: how long will therapy last? AAV-transduced non-dividing cells could express the gene for years (Luxturna's 3–5-year data suggest persistent benefit). Could protein overexpression stress cells or trigger immune clearance? Could a patient's immune system attack the eye upon later exposure? These questions require prolonged follow-up of trial participants. No serious late-onset adverse effects have emerged in ocular gene therapy trials up to 5–7 years. Another issue is vector shedding—does any vector escape the eye after injection? Studies have found minimal AAV in blood or saliva after intraocular injection, indicating low risk of unwanted gene transfer beyond the eye. When treating inherited diseases, secondary effects must be considered: saving photoreceptors could stress downstream neurons. Restoring input to a long-deprived visual cortex might cause neuroplasticity issues (though no evidence yet; fMRI in Luxturna patients showed visual cortex re-activation) [139]. Ensuring gene therapy safety involves robust preclinical testing for off-target effects, cautious dose escalation, and long-term vigilance in clinical studies. Regulatory agencies require up to 15 years of follow-up on gene therapy trial subjects. Responsible development means monitoring and reporting potential rare risks (such as insertional mutagenesis, off-target editing, and immune-mediated delayed toxicity).

- High cost and accessibility: Gene therapies are costly to develop and purchase, highlighted by Luxturna's $850,000 per treatment price [140]. It is justified as a potential lifetime cure for a blinding disease, and possibly cost-effective compared with long-term low-vision care. However, such prices burden healthcare systems and insurers, limiting access for patients, especially in low- and middle-income countries. Manufacturing viral vectors is complex and expensive—AAV is produced in cell cultures, purified, and tested extensively. Unlike mass-produced pills, each gene therapy lot requires significant biotechnology infrastructure. Innovative payment models are proposed to address costs [141]. Luxturna's maker offered rebates to insurers if efficacy benchmarks were not met and some payment-over-time options. Surgical delivery is another factor—therapies such as Luxturna or RGX-314 require a vitreoretinal surgeon for subretinal injection, adding procedural cost and limiting therapy to specialized centers. General anesthesia adds further cost and complexity. Access issues also involve infrastructure: many regions lack retinal specialists trained in gene therapy delivery or diagnostic facilities for identifying genetic mutations. A genetic diagnosis of retinal disease is needed, which can be costly or unavailable. Efforts to improve accessibility include companies sponsoring genetic testing programs or distributing surgical training simulators. Without substantial cost reductions, gene therapies risk widening healthcare disparities, being available only to wealthier systems. Some patients might not meet treatment criteria (e.g., too advanced disease—Luxturna requires sufficient viable retina). Those who qualify might face insurance hurdles. In Europe, some national health services negotiated lower prices or declined coverage, delaying availability. As more gene therapies enter the market, manufacturing efficiencies could improve, and competition may reduce costs. The one-time nature means upfront but not recurring cost. Health economists are analyzing these tradeoffs. Developers and regulators are pressured to ensure pricing does not make treatments inaccessible. Logistical challenges (travel to specialized centers, follow-up) also limit accessibility. A child from a rural area with LCA may travel to a city gene therapy center and stay for monitoring—burdensome for families. Overcoming these challenges requires health system preparedness, including training more surgeons, setting up centers of excellence, and developing less invasive delivery methods for outpatient clinics.

In summary, while ocular gene therapy has clear potential, it faces significant challenges: immune/inflammatory issues that must be controlled, vector design limitations for large genes, ensuring precision and safety of gene delivery, and making treatments affordable and accessible. Each of these areas is an active focus of researchers. For instance, newer immune-suppression regimens and capsids are reducing inflammation; dual vectors and base editors are addressing gene size; careful trial design is assuaging safety concerns; and health policy innovations are starting to tackle cost. Recognizing and surmounting these limitations is crucial for gene therapy to fulfill its promise for PSEDs.

9 Future Perspectives and Emerging Technologies

Gene therapy targeting diseases of the eye's posterior segment is advancing swiftly, propelled by significant breakthroughs in gene editing, enhanced vectors, and personalized medicine. Cutting-edge editing methods such as base editing, prime editing, and epigenetic editing offer remarkable precision by directly correcting harmful mutations in retinal cells without causing damaging double-stranded DNA breaks. Base editing has already shown success in preclinical models for conditions such as Stargardt disease and Leber congenital amaurosis, providing an effective means to fix single-nucleotide mutations, potentially

leading to long-lasting and safe one-time treatments. Prime editing further extends these capabilities, enabling precise insertion, deletion, or replacement of short DNA sequences, and holds significant promise for addressing genetic disorders once deemed untreatable. Additionally, epigenetic editing techniques such as CRISPR interference (CRISPRi) or activation (CRISPRa) can adjust gene expression without permanently changing DNA sequences, offering reversible and finely adjustable therapies for complex retinal diseases such as AMD or glaucoma.

One significant advancement in ocular gene therapy is the improvement of delivery systems. Although AAV vectors are commonly used due to their safety and effectiveness, their limited capacity poses challenges for delivering large genes associated with conditions such as Usher syndrome or Stargardt disease. To address this issue, innovative methods such as dual-AAV vectors, nanoparticle-based delivery systems, and lipid nanoparticles (LNPs) are being actively investigated. These alternatives facilitate the safe and effective delivery of larger therapeutic genes or complex gene-editing tools directly into retinal cells. Moreover, personalized medicine is becoming increasingly important, allowing for customized treatments on the basis of the unique genetic profiles and disease characteristics of patients. This precision approach, enhanced by advanced artificial intelligence algorithms for genetic and phenotypic analysis, ensures optimal therapeutic results by providing the right treatment at the right time to the most appropriate candidates. Additionally, combining gene therapies with other modalities such as stem cell transplantation, pharmacotherapy, or visual prosthetics may improve therapeutic effectiveness, enabling clinicians to comprehensively address retinal diseases. Together, these innovations hold the promise of significantly broadening the therapeutic landscape, transforming previously untreatable conditions into manageable, and potentially curable, visual disorders within the next decade.

10 Conclusions

Gene therapy for posterior segment eye diseases has made remarkable strides, offering hope for patients with previously untreatable conditions. The FDA approval of Luxturna and promising clinical trial results for various retinal disorders demonstrate the potential of this approach. Advancements in viral and non-viral delivery systems, gene editing technologies, and optogenetic approaches have expanded the toolkit for addressing diverse eye diseases. However, significant challenges remain, including immune responses, vector limitations, long-term safety concerns, and accessibility issues. As research progresses, focus areas include refining gene editing techniques, exploring combinatorial therapies, and developing personalized treatment strategies. These efforts aim to overcome current limitations and broaden the scope of treatable posterior segment eye diseases, potentially revolutionizing ophthalmology and improving the lives of millions affected by vision loss.

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Declarations

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Consent for publication and to participate Not applicable. This study does not involve individual data.

Conflict of interest The authors (Kai-Yang Chen, Hoi-Chun Chan, and Chi-Ming Chan) declare that they have no competing interests.

Author contributions K.-Y. C. contributed to conceptualization, methodology, software, investigation, validation, writing the original draft, visualization, and formal analysis. H.-C. C. was responsible for conceptualization, methodology, and software. C.-M. C. handled methodology, investigation, validation, supervision, and project administration. All authors reviewed the manuscript.

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