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Opinion

Toward low-cost gene therapy: mRNA-based therapeutics for treatment of inherited retinal diseases

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Inherited retinal diseases (IRDs) stem from genetic mutations that result in vision impairment. Gene therapy shows promising therapeutic potential, exemplified by the encouraging initial results with voretigene neparvovec. Nevertheless, the associated costs impede widespread access, particularly in low-to-middle income countries. The primary challenge remains: how can we make these therapies globally affordable? Leveraging advancements in mRNA therapies might offer a more economically viable alternative. Furthermore, transitioning to nonviral delivery systems could provide a dual benefit of reduced costs and increased scalability. Relevant stakeholders must collaboratively devise and implement a research agenda to realize the potential of mRNA strategies in equitable access to treatments to prevent vision loss.

Retinal gene therapy: a promising treatment accessible to a selective few

IRDs are a diverse group of hereditary disorders that cause progressive retinal degeneration, leading to severe visual impairment or complete vision loss. Most of these blinding conditions stem from monogenic variations in genes primarily expressed in the retinal pigment epithelium (RPE) and/or photoreceptors, which are crucial for supporting the retina and converting light into electrical signals. Significant advances have been made in decoding the genetic origins of IRDs, with ~300 causative genes identified to date[i]. The genetic diversity of IRDs results in a broad spectrum of clinical manifestations, encompassing different symptoms, inheritance patterns, age of onset, rate of progression, and disease severity. Notable examples of IRDs include Leber congenital amaurosis, X-linked retinitis pigmentosa, and **choroideremia** (see Glossary).

IRDs are not merely a health concern. They are a life-altering predicament that affects millions globally. The importance of addressing these conditions cannot be overstated, especially when gene therapy offers a beacon of hope. However, the cost of such treatments presents a significant barrier for vulnerable populations in low-to-middle income countries. In this opinion, we explore how access to gene therapy could be realized through innovative approaches, such as mRNA technology and nonviral delivery systems. These strategies could be the key to unlocking global access, but this necessitates a concerted effort from all stakeholders. Our discussion delves into the challenges and possible solutions to making gene therapies an accessible reality for all.

Clinical progress in gene therapy for IRDs

Over recent years, the single gene basis of most IRDs, coupled with the unique properties of the eye, has positioned gene therapy as a prominent research focus in the field. First, the anatomical

Highlights

Numerous clinical trials have explored adeno-associated virus (AAV)-mediated gene therapy for inherited retinal diseases (IRDs). Yet, recent findings indicate serious adverse effects, and some trials have failed to meet endpoints.

The advent of *in vitro*-transcribed (IVT) mRNA has broadened the possibility of new ocular gene therapies. Synthetic mRNA achieves higher translation efficiency without nuclear translocation, poses no genomic integration risks, is transiently expressed, and its production is cost-effective, making therapies more accessible globally.

Ocular gene therapy relies heavily on viral vectors, such as AAVs; however, AAVs face challenges, including limited gene-carrying capacity, restricting treatment for certain IRDs, while the use of large transgenes, such as CRISPR tools, requires further refinement to enable their packaging into AAVs. Recently, nonviral nanoparticles emerged as promising alternatives, offering increased packaging, stability, and cost-effectiveness.

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accessibility of the eye and its compartmentalized architecture simplify delivery and reduce the dose of therapeutic agents required. Second, the blood–retinal barrier offers a relatively immune-privileged status [1], preventing systemic immune responses to therapy and restricting safety concerns to the eye. Furthermore, there are many reliable non-invasive imaging techniques for monitoring disease progression and measuring treatment safety and efficacy, such as scanning laser ophthalmoscopy and electroretinography. Lastly, the development of ocular gene therapy benefits from a plethora of pertinent animal models suitable for preclinical studies and the possibility of using the contralateral eye as a control [2].

The field of ocular gene therapy has witnessed substantial advancements, with the Gene Therapy Clinical Trials Worldwide database listing more than 30 active clinical trials for IRDs (Table 1). Gene supplementation is the leading method and is increasingly adopted in clinical settings. **Voretigene neparvovec (commercial name 'Luxturna')**, the only ocular gene therapy approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency, is specifically designed for treating IRDs caused by biallelic *RPE65* mutations, namely **Leber congenital amaurosis type 2 (LCA type 2)** and rare forms of retinitis pigmentosa. It uses an **adeno-associated virus (AAV)** to deliver a functional *RPE65* cDNA to affected RPE cells, restoring the active RPE65 protein levels via a single subretinal injection (for a detailed review, see [3]). Results from a Phase 3 trial reported significant improvements in navigational ability and light sensitivity, with clinically meaningful effects maintained for at least 1 year and without serious adverse events or deleterious immune responses [4]. AAV-mediated gene therapy is under clinical investigation for a broad range of retinal pathologies extending beyond LCA, including choroideremia, and Leber hereditary optic neuropathy. The first Phase 1/2 gene therapy clinical trial for choroideremia (Box 1) successfully met its primary endpoint of enhanced visual acuity in the treated eyes, with these improvements persisting for up to 5 years [5]. As the field of delivery systems and genome-editing tools advances, gene therapy is ushering in a new era of treatment options. With the growing number of clinical trials, the potential to restore vision through genetic intervention is becoming an attainable reality.

Economic implications of IRDs and the adequacy of costing methodologies

While most IRDs are considered rare diseases, they collectively emerge as the leading cause of blindness in the Western working-age population [6], affecting over 2 million individuals worldwide [7]. This represents an immense social and economic burden. The estimated annual costs attributable to IRDs are as high as US$31.7 billion in the USA alone, 63% of which are related to well-being costs [8]. Even more distressing is the profound and lifelong impact an IRD diagnosis carries. For those living with an IRD, it often means grappling with chronic progressive morbidity that severely impairs visual function, drastically limiting daily activities and overall quality of life. This is a poignant reflection of the disparity between scientific understanding and actionable treatment solutions, emphasizing the pressing need for further research and therapeutic advancements within this field. Additionally, several countries have moved to support higher prices in return for health gains in rare diseases, as well as to legislate in favor of orphan drug research and development [9].

Despite the identification of ~300 genes linked to IRDs, the realm of therapeutic interventions remains disproportionately narrow. The development of gene therapy products for IRDs presents a unique set of challenges. The limited patient number, the costly research, development, and manufacturing processes, the fact that each individual product must navigate stringent quality checks and regulatory assessments, along with multiple distribution challenges, often drive a steep price tag, making it difficult to achieve sustainable access to these treatments from conventional commercial standpoints. To contextualize, a 2016 study conducted by Tufts Center for the Study of Drug Development estimated the average capitalized out-of-pocket preapproval cost of

Glossary

Adeno-associated viruses (AAVs): small, nonpathogenic viruses that are commonly used as vectors in gene therapy to deliver therapeutic genes into cells. Due to their ability to infect a range of cell types and induce long-lasting gene expression without integrating into the host genome, AAVs have emerged as a preferred choice for many gene therapy applications, especially for targeting tissues, such as the retina.
Choroideremia: rare inherited retinal degenerative disorder characterized by the progressive loss of the choroid, RPE, and photoreceptors, leading to vision impairment and eventual blindness. The condition primarily affects males, because it is inherited in an X-linked recessive manner. Choroideremia is caused by mutations in *CHM*, which encodes the REP1 protein essential for intracellular trafficking processes. Initial symptoms, which often emerge in childhood, include night blindness and a narrowing field of vision, and these symptoms gradually progress to complete blindness over time.
Leber congenital amaurosis type 2 (LCA type 2): a subtype of LCA, a rare inherited retinal dystrophy characterized by severe vision loss or blindness at birth or within the first months of life. LCA type 2 is specifically caused by mutations in *RPE65*, which encodes an enzyme essential for the visual cycle in the retina. It is one of the most common forms of LCA and is a prime target for gene therapy interventions, such as Luxturna.
Nanoparticles (NPs): particles that have at least one dimension measuring between 1 and 100 nm. Due to their nanoscale size, NPs often exhibit unique physical, chemical, and biological properties. These distinct characteristics have led to their widespread application in areas such as medicine, electronics, energy storage, and environmental remediation. NPs can comprise various materials, including metals, polymers, lipids, and ceramics, and can be engineered for specific functionalities and purposes.
Voretigene neparvovec (commercial name 'Luxturna'): a gene therapy drug developed to treat inherited retinal dystrophy caused by biallelic *RPE65* mutations. Introduced by Spark Therapeutics, it works by delivering a healthy copy of *RPE65* directly to retinal cells, restoring their ability to produce the missing enzyme

bringing a new drug to market to be US$2.6 billion [10]. For example, consider the following currently FDA-approved gene therapies: tisagenlecleucel and axicabtagene ciloleucel, both chimeric antigen receptor (CAR) T cell therapies, are priced at US$373 000 and US$475 000 per eye, respectively [11]; onasemnogene abeparvovec, a treatment for spinal muscular atrophy in patients under 2 years of age, carries a staggering price tag of US$1.9 million per patient [12]; meanwhile, voretigene neparvovec bears a cost of US$425,000 per eye [13].

necessary for vision. It was the first gene therapy for a genetic disease approved by the FDA, in December 2017. Additionally, the European Commission granted voretigene neparvovec a conditional marketing authorization in November 2018 following a recommendation from the European Medicines Agency.

While these therapies can, in theory, mitigate or even eradicate conditions necessitating lifelong and expensive medical care, their out-of-pocket and upfront costs remain prohibitive for many, even in countries where a significant portion of healthcare expenditures is covered by public health systems. Given the FDA's projection of 10–20 new cell and gene therapy approvals annually by 2025, and the current evaluation of 900 potential gene therapy drugs, the economic conundrums poised by these therapies become even more pertinent.

Paving the path for universal access to retinal gene therapy

To transform the potential of retinal gene therapy into a global tool, a parallel strategy is needed. From a scientific perspective, the incorporation of new advancements, notably mRNA technology and **nanoparticle (NP)**-mediated vectors, serves as a conduit to improve the precision and efficacy of therapeutic interventions while minimizing the associated costs. Moreover, such technological advances promise to engender therapies that are potentially less invasive. Simultaneously, within the economic and political sphere, there is a pressing need to recalibrate regulatory frameworks, facilitating more streamlined approval pathways, and fostering economic models that prioritize the production of cost-effective retinal gene therapies. By judiciously navigating both these scientific and regulatory terrains, we can endeavor to ensure that the benefits of gene therapy are disseminated universally. In striving for global access to gene therapy, harnessing innovative, cost-effective technologies and enacting strategic, patient-centered regulatory reforms will be pivotal in shaping a future where these transformative treatment options are accessible to everyone.

Embarking on an evolution: from DNA to mRNA in gene therapy

The remarkable advances in mRNA engineering have opened doors to the first real-world therapies using nonviral mRNA-based therapeutics, most notably the mass-produced coronavirus disease 2019 (COVID-19) vaccines. Extensive preclinical and clinical investigations are underway for a range of potential applications, including protein replacement therapies [14–17], immunotherapies [18,19], cancer and infectious disease vaccines [20–23], cellular reprogramming [24–26], and genome editing [27]. The use of synthetic mRNA holds several benefits over traditional DNA-based methods (Figure 1). First, because mRNA is fully functional in the cytoplasm, it does not require nuclear translocation and, therefore, achieves higher translation efficiency and rapid protein synthesis, even in post-mitotic cells [28]. Second, it entails no risk of genomic integration and associated mutagenesis, offering a superior safety profile for clinical applications. Third, mRNA is only transiently expressed and is eventually completely degraded, which prevents long-term toxicity and makes it uniquely suitable for retinal reprogramming and genome-editing applications, where gene expression is only required for a limited time window. Finally, the production of *in vitro*-transcribed mRNA is relatively simple, reproducible, and reasonably priced, potentially extending access to gene therapy treatments to low- and middle-income countries. Nevertheless, the relatively short half-life and immunogenicity of conventional mRNA have delayed research and ruled out its clinical application for a long time. However, a new wave of interest has recently emerged with the discovery that chemical modifications of the mRNA molecular structure could reduce its inherent instability and immunogenicity while improving translation efficiency [29–34]. The mRNA sequence can now be optimized by tailoring the poly(A) tail length, incorporating 5′ cap analogs or chemically modified nucleosides, among others.

Table 1. Ongoing gene therapy clinical trials for inherited retinal diseases[a]

Condition	Sponsor	Gene therapy product	Injection	Phase/type	Completion	Trial ID
X-linked retinitis pigmentosa	MeiraGTx UK II Ltd	AAV5-RPGR	SR	3	2024	NCT04671433[i]
	NightstaRx Ltd, a Biogen Company	AAV8-RPGR (BIIB112)	SR	3	2026	NCT03584165[ii]
	Applied Genetic Technologies Corp	rAAV2tYF-GRK1-RPGR	SR	1/2	2026	NCT03316560[iii]
		rAAV2tYF-GRK1-hRPGRco	SR	2/3	2029	NCT04850118[iv]
	4D Molecular Therapeutics	AAV.R100-hcoRGPR (AAV-4D-125)	IVT	1/2	2029	NCT04517149[v]
	MeiraGTx UK II Ltd	AAV5-RPGR	SR	3	2029	NCT04794101[vi]
Retinitis pigmentosa	Nanoscope Therapeutics Inc	vMCO-010 (AAV2)	IVT	2	2024	NCT04945772[vii]
	AbbVie	RST-001 (AAV2-ChR2)	IVT	1/2	2024	NCT02556736[viii]
	Ocugen	OCU400 (AAV5)	SR	1/2	2024	NCT05203939[ix]
	GenSight Biologics	GS030 (rAAV2.7m8-CAG-CHrimsonR-tdTomato)	IVT	1/2	2025	NCT03326336[x]
	Peking University Third Hospital	ZVS203e (rAAV-mediated CRISPR/Cas9 silencing)	SR	1	2026	NCT05805007[xi]
	STZ eyetrial	rAAV.hPDE6A	SR	1/2	2027	NCT04611503[xii]
	Bionic Sight LLC	AAV2-CAG-ChronosFP	IVT	1/2	2029	NCT04278131[xiii]
	Coave Therapeutics	AAV2/5-hPDE6B	SR	1/2	2029	NCT03328130[xiv]
Choroideremia	NightstaRx Ltd, a Biogen Company	AAV2-REP1 (BIIB111)	SR	3	2026	NCT03584165[xv]
	4D Molecular Therapeutics	4D-110	IVT	1	2027	NCT04483440[xvi]
LCA	ProQR Therapeutics	Sepofarsen (splice-modulating oligonucleotide)	IVT	2/3	2023	NCT04855045[xvii]
	Editas Medicine, Inc	EDIT-101 (AGN-151587, CRISPR-Based)	SR	1/2	2025	NCT03872479[xviii]
	Spark Therapeutics	AAV2-hRPE65v2 (voretigene neparvovec)	SR	Observational	2025	NCT03597399[xix]
	HuidaGene Therapeutics Co, Ltd	HG004 (rAAV9-RPE65)	SR	1/2	2025	NCT05906953[xx]
	University of Pennsylvania	rAAV2-CBSB-hRPE65	SR	1	2026	NCT00481546[xxi]
	Atsena Therapeutics Inc	SAR439483 (AAV5)	SR	1/2	2027	NCT03920007[xxii]
	Spark Therapeutics	AAV2-hRPE65v2 (voretigene neparvovec)	SR	3	2029	NCT00999609[xxiii]
		AAV2-hRPE65v2-102 (voretigene neparvovec)	SR	1/2	2030	NCT01208389[xxiv]
		AAV2-hRPE65v2 (voretigene neparvovec)	SR	Observational	2030	NCT03602820[xxv]
Leber hereditary optic neuropathy	Byron Lam	scAAV2-P1ND4v2	IVT	3	2024	NCT02161380[xxvi]
	GenSight Biologics	GS010 (rAAV2/2-ND4)	IVT	3	2024	NCT03293524[xxvii]
	Applied Genetic Technologies Corp	rAAV2tYF-PR1.7-hCNGB3	SR	1/2	2026	NCT02599922[xxviii]
		AGTC-402 (rAAV2tYFPR1.7-hCNGA3)	IVT	1/2	2026	NCT02935517[xxix]
X-linked juvenile retinoschisis	National Eye Institute	AAV8-scRS/IRBPhRS	IVT	1/2	2025	NCT02317887[xxx]
CNGA3 achromatopsia	STZ eyetrial	rAAV.hCNGA3	SR	1/2	2027	NCT02610582[xxxi]

[a]Abbreviations: IVT, intravitreal; SR, subretinal.

Box 1. AAV-mediated gene therapy for IRDs

Gene supplementation is the leading gene therapy method adopted in clinical settings. Voretigene neparvovec is an ocular gene therapy specifically designed for treating IRDs caused by biallelic *RPE65* mutations, namely LCA type 2. It uses an AAV to deliver a functional *RPE65* cDNA, restoring the active RPE65 protein levels via a single subretinal injection. An open-label, randomized, controlled Phase 3 trial (NCT00999609[xxxii]) reported significant improvements in navigational ability and light sensitivity, without serious adverse events or deleterious immune responses [4]. As well as for LCA, AAV-mediated gene therapy is under clinical investigation for other retinal pathologies, such as choroideremia, and Leber hereditary optic neuropathy. The inaugural Phase 1/2 multicenter, open-label, dose escalation, and randomized trial of retinal gene therapy for choroideremia (NCT01461213[xxxiii], University of Oxford [5,76]) involved 14 participants who were administered AAVs carrying the human CHM transgene to supplement the faulty REP1 protein. The trial met its primary endpoint of enhanced visual acuity in the treated eyes, while these improvements persisted for up to 5 years in 12 patients, who did not encounter adverse events [5]. Two patients experienced significant complications, one resulting from surgical-induced retinal stretching and the other from intraocular inflammation, which was most likely vector related.

Three subsequent clinical trials assessed the safety and efficacy of the same vector at the higher dose in cohorts of six patients with choroideremia: (i) Phase 1/2, open-label clinical trial (NCT02077361[xxxiv], University of Alberta [77]); (ii) monocentric Phase 2, open-label clinical trial (NCT02553135[xxxv], Bascom Palmer Eye Institute, University of Miami [78]); and (iii) monocentric Phase 2, open-label trial (NCT02671539[xxxvi], University Hospital Tübingen [79]). Consistent with the first report, treatment resulted in sustained improvement or maintenance of visual acuity in all three trials and no serious adverse events were recorded in either the Miami or Tübingen trials. However, in the Alberta trial, one patient experienced severe intraretinal inflammation, which resulted in permanent structural and functional sequalae. More recently, the results of a randomized, masked, Phase 3 clinical trial using the AAV2 vector-based construct were published (NCT03496012[xxxvii]). This trial evaluated the safety and efficacy over 12 months of follow-up in adult males with choroideremia, randomized to receive a high dose (69 patients) or low dose (34 patients) by subretinal injection [80]. However, the study failed to meet the primary endpoints.

The utilization of mRNA technology in the treatment of IRDs is still in its infancy, offering both challenges and promising avenues for future research. A study compared the performance of unmodified and modified mRNA to traditional plasmid DNA (pDNA)-based transfection on human embryonic stem cell (hESC)-derived RPE cells [30]. Synthetic mRNA was modified by substitution of uridine (UTP) and cytidine (CTP) triphosphate for pseudo-UTP and 5-methyl-CTP. The results showed the superiority of both unmodified and modified mRNA over pDNA in terms of transfection efficiency and translation capacity in RPE cells. Importantly, administration of modified mRNA avoided the strong innate immune response elicited by its unmodified counterpart and promoted efficient and functional expression of delivered mRNA. More recently, another study further explored the potential of nonviral delivery of chemically modified mRNA for ocular applications via subretinal and intravitreal administration [29] by synthesizing 16 differently modified mRNAs harboring partial (25%) or full (100%) substitution with modified nucleotides, ARCA capping, and extended poly(A) tails. Consistent with previous research, the authors demonstrated that mRNA outperformed pDNA in different retinal cell types. Notably, chemical modification of mRNA further enhanced its translation capacity and intracellular stability, with gene expression persisting for at least 20 days after a single *in vitro* administration. When delivered to the subretinal space, mRNA expression was detected *ex vivo* and *in vivo* in photoreceptors and RPE cells. By contrast, intravitreal administration resulted in limited expression *in vivo*, which was found to be mainly attributable to the inner limiting membrane (ILM) preventing NP transfer to the outer retina. A more recent study demonstrated robust mRNA expression in RPE cells, photoreceptors, and Müller glial cells within a nonhuman primate model following subretinal administration of optimized peptide-conjugated lipid NPs. However, challenges remain in crossing the ILM via intravitreal injection using this NP formulation [35]. For conditions featuring compromised cellular barriers, the ILM may not pose a significant obstacle. Nevertheless, enhancing NP penetration capabilities and exploring alternative administration routes may offer feasible solutions to address this challenge.

Transforming gene delivery from viruses to nanoparticles

Until recently, research on ocular gene therapy mainly focused on viral vectors, such as lentiviruses, adenoviruses, and AAVs, owing to their unparalleled transduction efficiency in a variety

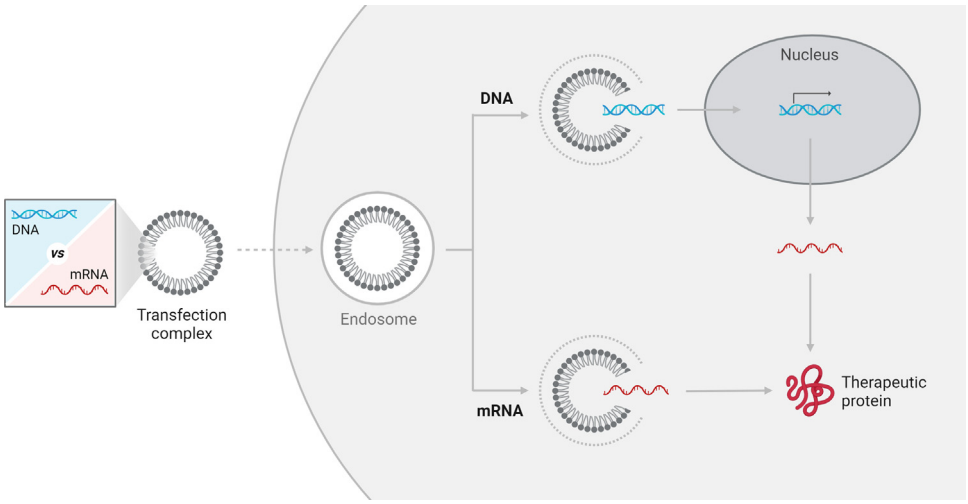

Figure 1. Contrasting mechanisms of mRNA and DNA-based gene therapy. This schematic illustrates the fundamental distinctions between mRNA and DNA-based gene therapy approaches. In mRNA gene therapy, exogenous mRNA molecules, carrying genetic instructions, are delivered directly into the cytoplasm. Ribosomes then proceed to translate the mRNA, enabling transient gene expression without necessitating nuclear entry. By contrast, DNA gene therapy requires the transportation of foreign DNA sequences into the nucleus before translation initiation. Notably, synthetic mRNA markedly enhances translation efficiency and expedites protein synthesis, demonstrating efficacy even in nondividing cells. Figure generated using BioRender (biorender.com/).

of cell types. Among these, AAVs emerged as the vector of choice for retinal gene transfer following the early clinical success of voretigene neparvovec in patients with LCA type 2 [4]. Compared with other widely investigated viral platforms, AAVs stand out as being nonpathogenic, genetically stable, and non-integrating [36]. Furthermore, they exhibit tropism for retinal tissue [37–39] and provide long-lasting transgene expression in nondividing cells, circumventing the need for frequent intraocular injections, which often induce serious adverse events, including cataract development, endophthalmitis, and retinal detachment [40]. However, despite encouraging therapeutic effects, alarming safety concerns are arising from the detection of treatment-related serious adverse events in 35% of clinical trials assessing subretinal AAV gene therapies [41]. For instance, follow-up studies of patients receiving voretigene neparvovec reported intraocular inflammation in the form of vitritis, outer retinal infiltrates, and uveitis [4,42–44]; progressive retinal atrophy within and outside the subretinal bleb [45,46]; and generation of neutralizing antibodies and cytotoxic T cells against the vector [44,47]. Similarly, clinical trials investigating AAV-based gene supplementation for choroideremia have also documented detrimental outcomes in some patients (Box 1). While the etiology of the deleterious reactions remains elusive in most cases, there are several potential factors that could be involved, either independently or in combination, such as direct toxicity of the vector or transgene, immune response to the vector or transgene, and subretinal delivery-induced trauma [45,46].

Another long-standing challenge facing the use of AAVs is their limited packaging capacity. AAVs have a limited gene-carrying capacity of ~4.7 kb of DNA [48], preventing the accommodation of large transgenes and CRISPR-based genome-editing tools. This leaves recessive IRDs involving larger genes as well as dominant IRDs beyond reach. To address this limitation, the splitting of transgenes into separate AAV vectors has been explored. However *in vivo* reconstitution has proven inefficient due to the need for co-transduction in the same cell by two independent vectors, recombination in the correct orientation, and the expression of a large transgene cassette [49].

Within the realm of genome editing, recent studies have focused on enhancing CRISPR technology to surmount these challenges. For instance, a dual AAV system utilizing a fast-splicing split-intein base editor demonstrated the capability to attain therapeutically relevant editing efficiencies in the mouse retina, using viral dosages that fall within the human tolerability range [50]. Additionally, prime editor delivery via dual AAV systems has been improved by engineering a truncated reverse transcriptase and optimizing both the slip site and inteins [51]. In recent years, nonviral NPs have garnered considerable interest as a potential alternative to obviate some of the unique shortcomings of viral gene delivery. Today, a wide range of nanocarriers are being developed for this purpose, with lipid-based and polymeric NPs being the most widely explored [52]. Notably, these systems offer superior packaging capacity, low immunogenicity, high biocompatibility, long-term stability, and cost-effective manufacturing on a large scale [52]. Furthermore, owing to the vast versatility and tunability of their physicochemical properties, such as size, shape, surface chemistry, charge, and hydrophobicity, they can be specifically designed to overcome biological barriers and improve biodistribution in target tissues and cell types [53–59]. Their surface can also be easily functionalized with targeting ligands or moieties to promote tissue/cell-specific tropism and enhance transfection efficiency [35,60–62]. Another remarkable feature of most nanomaterials is their innate biodegradability, which can be optimized to promote controlled cargo release and minimize cytotoxicity [63–65]. Although nonviral NPs may tackle the main limitations of their viral counterparts, they have thus far failed to compete with the transduction efficiency achieved by viral vectors in the retina. This low performance in the eye has been attributed not only to challenges in crossing physiological barriers and escaping endosomes, but mostly to difficulties in entering the nucleus of nondividing retinal cells to deliver DNA molecules [29,53]. Moreover, while nonviral vectors are generally regarded to be safer compared with AAVs, there have been reports suggesting they still induce immune responses in the eye [66]. Upcoming long-term follow-up clinical trials will be instrumental in establishing the safety profile of NPs in ocular applications and addressing any potential risks.

In the meantime, pending the development of safe and efficient nonviral strategies, AAV vectors are likely to remain the benchmark in retinal gene therapy, particularly in the context of gene supplementation therapies necessitating enduring transgene expression. To propel the clinical advancement of nonviral formulations, it becomes imperative to explore multifaceted optimization strategies and adhere to standardized reporting protocols within nanomedicine research, thereby enabling comprehensive characterization and reliable comparative analysis of various nanomaterials and enhancement methods [52]. In cases where prolonged expression is required, repeated administration of mRNA NPs via less invasive administration routes, such as intravitreal and suprachoroidal, holds promise [67]. However, further NP optimization is needed to surmount ocular barriers within the posterior segment. Furthermore, improving NP-targeting capabilities remains a crucial ongoing effort. While AAV tropism can be tailored through directed evolution, NPs demand innovative approaches, such as surface modification and ligand conjugation, to enhance their specificity and precision. These research endeavors, combined with robust preclinical studies using larger, more clinically relevant animal models, will collectively drive forward the clinical translation of nonviral retinal gene therapy and broaden the scope of therapeutic options for patients with IRD.

Reducing costs and improving risk management

Addressing the economic constraints of gene therapy requires a comprehensive review of the production pipeline, starting with viral vector manufacturing, which is currently both cost-intensive and complex [68]. A recent McKinsey analysis stresses the challenges to scaling up viral vector production, affecting both cost and speed to market for emerging therapies [69]. From a broader development standpoint, the limitations in scaling up current production methods

Clinician's corner

Ocular gene therapy research primarily uses viral vectors. AAVs in particular became the preferred vector for retinal gene transfer after the clinical success of voretigene neparvovec in patients with LCA type 2, given their nonpathogenicity, stability, and retinal tissue specificity. However, adverse events in clinical trials raised safety concerns, with issues, such as inflammation and retinal atrophy, linked to treatments.

Current AAVs struggle with retinal penetration, necessitating invasive subretinal delivery, and face challenges including packaging limitations and high production costs. By contrast, nonviral NPs, especially lipid-based and polymeric NPs, are being investigated for their larger packaging capacity, biocompatibility, and cost-effectiveness, although their retinal transduction efficiency currently lags behind that of viral vectors.

The transition of gene therapy from DNA to mRNA mitigates impediments encountered in retinal cells, wherein DNA transgenes encounter difficulties in passing the nuclear membrane, particularly in postmitotic cells, resulting in diminished efficacy. Recent advances, highlighted by COVID-19 vaccines, show the potential of mRNA, yet its application in vision diseases remains nascent.

impede progress into later-Phase (2/3) clinical trials. Most existing trials are small, typically involving fewer than 100 patients and utilizing low-yield adherent cell transduction processes. This limited scalability raises serious concerns about meeting the demand for large quantities of viral vectors, even for orphan diseases, which have small patient populations but require high doses. Furthermore, irrespective of the scale or method of vector production, achieving a robust downstream purification process is crucial for generating clinical-grade material with high titer, potency, and purity. Currently, most downstream approaches are adapted from traditional laboratory methods, which are neither scalable nor suitable for clinical-grade manufacturing. These approaches create several bottlenecks, further complicating the path toward more cost-effective gene therapies.

The cost of goods and manufacturing alone for one gene therapy can range from US$500 000 to US$1 million, excluding the significant expenses associated with research and development, clinical trials, and creating commercial platforms for patient access [70]. Given the nature of these treatments, often a one-time administration to limited patient populations, sometimes numbering just a few hundred globally, it is vital for companies to recover their investments to continue addressing these significant unmet medical needs. Despite the initial higher costs, several studies suggest that, when advancing to later stages in clinical validation, the risk of investment is much reduced for orphan drugs [71–73]. Currently, the industry is exploring reimbursement models, such as payment-over-time and pay-for-performance. However, these models may not be compatible with healthcare systems in low-to-middle income nations.

We advocate here nonviral mRNA delivery as a more cost-efficient alternative to AAV gene therapies. Nonviral vectors offer simplified and scalable manufacturing, significantly reducing production costs and resource allocation, while streamlining purification processes. Moreover, mRNA synthesis is straightforward and highly reproducible, in contrast to the intricate design and production demands of plasmid DNA required for viral vectors [74]. Nonetheless, the costs of licensing patented chemical modifications into mRNA structure must be carefully considered, because they could impact affordability and widespread accessibility to innovative mRNA gene therapies. Hence, we believe that it is crucial to consider cooperative/collaborative approaches, such as the Access to Gene Therapies for Rare Diseases (AGORA) initiative for rare diseases [75].

While significant strides have been made in the field of gene therapy, the challenges are multifaceted and demand a concerted effort. Taking inspiration from AGORA, we must contemplate the establishment of a similar initiative tailored for IRDs. As a preliminary step, the initiative would serve as a hub to foster streamlined approval, delivery, and accessibility to gene therapies and create more global, adaptable financial solutions. Stakeholders from industry, public and private payers, clinical academics, scientists, patient organizations, regulators, and policymakers must convene to ensure global access to these innovative therapies without prohibitive costs. Theoretical frameworks are being explored that combine models of social enterprise and impact investment, while considering industry-standard and benchmarked financial returns. As a second step, the initiative would stimulate entrepreneurship, incentivize early-stage investment, and pool together financial resources to support collaborative efforts in research, proof of concept, and validation.

Concluding remarks

The advent of ocular gene therapy marks a transformative period in medicine, offering solutions for previously untreatable eye diseases. Exploration of mRNA technology and nanoparticle-mediated vectors represents a significant innovation in the field (see Clinician's corner). However, these emerging technologies require rigorous validation for both safety and efficacy, particularly compared with the well-established effectiveness of viral vectors (see Outstanding questions).

Outstanding questions

How can we develop gene therapies for the hundreds of IRDs caused by different genetic variations?

How long will the benefits of a one-time gene therapy last? Will patients require repeated treatments?

While some gene therapies aim to introduce a functional copy of a gene, technologies such as CRISPR offer the potential to directly edit or repair faulty genes *in situ*. What are the challenges and prospects in applying these technologies for IRDs?

Some genes implicated in IRDs are too large for common vectors, such as AAV. How can we effectively deliver these larger genes?

How can ongoing research better address the safety concerns and adverse events associated with viral vectors, such as AAVs, to improve the overall risk–benefit profile of these therapies?

How can nonviral mRNA-based therapeutics be optimized for efficient and safe use in ocular gene therapy to overcome some of the limitations faced by viral vectors?

What are the best strategies for achieving more effective retinal penetration of nonviral NPs, particularly for intravitreal delivery?

What regulatory and economic frameworks can be established to ensure that gene therapies for IRDs become universally accessible, especially in low-to-middle income countries?

Furthermore, the economic complexities associated with ocular gene therapy and the introduction of such advanced treatments necessitate collaborative frameworks akin to the AGORA initiative. By fostering collaboration, we can address scientific challenges, streamline regulatory pathways, develop innovative reimbursement models, and ensure that therapies reach those in need without causing financial strain.

Gene therapy for IRDs offers both incredible promise and substantial challenges. While advancements in understanding IRD genetics provide hope to many with these conditions, developing accessible and affordable treatments remains complex. Despite these obstacles, the significant societal and economic impacts of IRDs necessitate greater attention in medical research. The global community, including researchers, policymakers, and industry stakeholders, must unite to leverage our growing genetic knowledge for real-world therapeutic solutions. Although the road ahead is complex, the potential rewards, such as restored vision for millions, are invaluable.

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Authors' contributions

All authors have significantly contributed to the intellectual aspects of the work, and they unanimously endorse the publication of the manuscript.

Declaration of interests

The authors declare no conflicts of interest.

Resources

[i]https://sph.uth.edu/retnet/
[ii]https://clinicaltrials.gov/study/NCT04671433
[iii]https://clinicaltrials.gov/study/NCT03584165
[iv]https://clinicaltrials.gov/study/NCT03316560
[v]https://clinicaltrials.gov/study/NCT04850118
[vi]https://clinicaltrials.gov/study/NCT04517149
[vii]https://clinicaltrials.gov/study/NCT04794101
[viii]https://clinicaltrials.gov/study/NCT04945772
[ix]https://clinicaltrials.gov/study/NCT02556736
[x]https://clinicaltrials.gov/study/NCT05203939
[xi]https://clinicaltrials.gov/study/NCT03326336
[xii]https://clinicaltrials.gov/study/NCT05805007
[xiii]https://clinicaltrials.gov/study/NCT04611503
[xiv]https://clinicaltrials.gov/study/NCT04278131
[xv]https://clinicaltrials.gov/study/NCT03328130
[xvi]https://clinicaltrials.gov/study/NCT03584165
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