Editorial

Gene therapy for inherited retinal diseases – one train left the station, but others are still being built

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Introduction

Advances in gene therapy have transformed inherited retinal disorders (IRDs) from largely untreatable conditions into a field where durable visual gains are now realistic, but the gap between scientific promises and what we can offer in clinics remains uncertainly wide. As eye care providers, we may be tasked with translating complex, high-cost, high-expectation therapies into possible conversations with families who have lived through generations of vision loss.[1-4]

From proof of concept to clinical care

The approval of voretigene neparvovec-rzyl (Luxturna) for biallelic *RPE65* mutation-associated retinal dystrophy in 2017 marked the first gene therapy for any inherited retinal disease. This single treatment can turn an IRD from purely diagnostic entity into a treatable condition, with Luxturna now available in North America and Europe and incorporated into public reimbursement pathways in several regions.[5-7]

Long-term data have validated the original phase 3 results: full-field light sensitivity and mobility performance improvements persist for at least several years in treated patients, with previous preclinical canine models lasting up to a decade of durability. These outcomes confirm a central premise of gene augmentation, that once non-dividing retinal cells can make sufficient functional proteins, the retina can operate effectively for years.[1,3,5,6,8]

Yet the Luxturna experience has also revealed the limits of early optimisms. Post-marketing experiences describe accelerated chorioretinal atrophy in roughly 13–50% of treated eyes, sometimes encroaching on the central macula and undermining visual gains. Even in pediatric series showing significant improvements in best-corrected visual acuity at 12 months, atrophy at the injection site is the most common structural complication and a reminder that subretinal administration has its iatrogenic adverse effects and limits.[5,8,9]

Beyond gene augmentation: editing and RNA strategies

Most current IRD programs still rely on adeno-associated virus (AAV)–mediated gene augmentation by delivering a functional cDNA under a suitable promoter, typically via subretinal injection. This approach works well for smaller genes such as retinal pigment epithelium 65 kDa protein (*RPE65)*, but size constraints and the complexity of dominant-negative mechanisms have forced the field toward more innovative platforms.[1–3]

Clustered regularly interpaced palindromic repeats (CRISPR)-based in vivo gene editing has now moved from theory to first-in-human data. In the Phase 1/2 BRILLIANCE trial of EDIT-101 for centrosomal protein 290 (*CEP290)*-associated leber congenital amaurosis (LCA10), a single subretinal injection of a CRISPR/Cas9 construct targeting the intronic c.2991+1655A>G variant produced measurable improvements in vision in the majority of participants, with safety as the primary endpoint and efficacy as secondary. Reports from this cohort indicate that 11 of 14 treated individuals including children and adults experienced quantifiable visual benefit, establishing proof of concept that in vivo editing can modify disease course in a severe early-onset IRD.[1,2, 10–12]

In parallel, RNA-based therapies are advancing for the same *CEP290* mutation using antisense oligonucleotides to modulate splicing. Sepofarsen and related agents have progressed to late-phase clinical evaluation, including a Phase 3 program targeting LCA10 due to the canonical intronic *CEP290* variant. These strategies avoid permanent genomic change and can be delivered intravitreally, but at the cost of repeated dosing and ongoing treatment burden as another option to the one-and-done promise of AAV or CRISPR approaches.[2,3,13]

The widening genetic and clinical foundation

The pace of therapeutic innovation has been enabled by equally rapid advances in IRD genetics. More than 300 genes have now been implicated in inherited retinal degenerations, and comprehensive molecular testing can identify a causative variant in roughly 70% of patients, making genotyping essential for contemporary IRD care. This diagnostic yield is the gateway to both approved therapy and clinical trial enrollment, and it should be central to how we structure teaching and counseling clinics for future clinicians.[2,4]

At the same time, large natural-history cohorts and disease-specific outcome measures have reshaped how we judge success. Functional metrics such as full-field light sensitivity testing, multi-luminance mobility tests, and microperimetry, together with high-resolution OCT and wide-field imaging, have become standard tools in IRD gene therapy trials and post-market surveillance. The recognition of chorioretinal atrophy as a relatively frequent structural change after *RPE65* gene augmentation emerged only because these patients were followed longitudinally with detailed imaging that was not available previously.[1,2,5,6,8,9]

The uncomfortable reality: a rich pipeline, one approval

Despite the proliferation of early-phase trials targeting *CEP290*, *CHM (choroideremia)*, *RPGR (retinitis pigmentosa GTPase regulator)*, *RS1(retinoschisin 1)*, and other genes, current clinical

reality is curbed. In 2026, we still have only one FDA-approved gene therapy for inherited retinal disease. Commentators have noted that, despite intense interest and investment, "we don't have another FDA-approved retinal gene therapy for inherited retinal disease yet," underscoring how hard it is to convert promising phase 1/2 signals into definitive, registrational data.[2,5,7]

This disconnect matters at the eye clinics. Families read headlines about CRISPR curing blindness and reasonably expect a menu of gene-specific treatments; what we can actually offer now is Luxturna for a small subset of *RPE65*-IRD patients, plus access to a limited number of clinical trials with uncertain benefit–risk profiles. As eye care providers, we must learn to celebrate the genuine scientific breakthroughs without overselling their immediate clinical impact.[3,5,7,10,11]

Safety, inflammation, and the "price" of vision

The safety profile of ocular gene therapy remains under active scrutiny. Intraocular inflammation—often mild to moderate and steroid-responsive features prominently in AAV-based protocols and directly influences dose selection and re-dosing strategies. Long-term concerns include vector-related toxicity, surgical complications of subretinal delivery, and the unknown consequences of permanent genome editing in the case of CRISPR-based therapies.[1–3,13]

Even when biological and surgical risks are acceptable, economic and logistical barriers loom large. Voretigene neparvovec is a high-cost, highly centralized therapy, delivered only in select centers with specialized surgical and perioperative expertise, and post-marketing reviews emphasize the need to identify patients most likely to benefit, those with sufficient viable outer retina, given the expense and irreversibility of treatment. For many IRD families worldwide, the practical availability of gene therapy remains theoretical and limited.[2,5–8]

What this means for young clinicians in 2026

For residents rotating through retina or inherited disease clinics, these advances should change day-to-day practice in several concrete ways. First, we must treat genetic testing as standard of care for suspected IRDs, explaining to patients that a molecular diagnosis not only clarifies prognosis but is often the ticket into both current and future therapies. Second, we should be fluent in the basic distinctions between gene augmentation, gene editing, and RNA-based approaches so that we can explain, in plain language, what it means when a patient is eligible for a trial.[1-4] Third, expectation management is now a core clinical skill. Luxturna patients may experience substantial functional gains, but visual acuity may not dramatically improve in advanced disease, and emerging data about chorioretinal atrophy must be part of an honest consent discussion. For CRISPR and RNA programs still in early-phase testing, we need to emphasize that initial results are encouraging but not definitive, with ongoing follow-up required to understand durability and rare adverse events.[2,3,5–9,11,12]

Finally, we should see ourselves not just as consumers of this science but as future contributors. Many of the key questions including optimal timing of intervention, combination approaches, re-treatment strategies, and how to equitably deliver gene therapy at scale, would be answered over the next decade. Our responsibility is to approach each new data set with the same rigor we bring to a fluorescein angiogram or visual field: What is the real effect size? How durable is it? Who is left out?[1–3,7]

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