Gene Therapies for Inherited Retinal Diseases

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ABSTRACT

Gene therapy is an emerging therapeutic modality that has demonstrated early success in treating genetic ocular disorders. The approval of voretigene neparavovec-ryzl (tradename Luxturna®), the first single-dose *in vivo* gene therapy and only on-market treatment for Leber congenital amaurosis Type 2, marked a turning point for inherited retinal diseases. Since then, dozens of *in vivo* gene therapy products have reached clinical development for other IRDs, including retinitis pigmentosa, achromatopsia, Leber hereditary optical neuropathy, X-linked retinoschisis, and Usher syndrome type 2. This review highlights the clinical and genetic landscape of inherited retinal diseases targeted by ongoing clinical-stage gene therapy development and outcomes to date for patients treated with voretigene neparvovec. Finally, we discuss trends in gene therapy pricing and approaches in determining the cost effectiveness of single-dose gene therapies for IRDs.

Keywords: Gene therapy, retinal dystrophy, AAV.

INTRODUCTION

Nearly thirty years after the first approved successful human application of gene therapy in 1990, gene therapy has reached its coming of age. The commercialization of Luxturna® (voretigene neparvovec-rzyl) for RPE65-mediated retinal disease in 2017 marked the beginnings of a wave of gene therapies seeking to transition from experimental drug status to become mainstays of modern medicine. By 2025, the FDA anticipates approving up to 20 gene therapy products per year, with several products in the near-term pipeline targeting inherited retinal diseases.[1]

At a high level, gene therapy refers to the delivery of exogenous, healthy genetic material to rescue function of an abnormal copy of a gene. The techniques used to achieve this outcome can be further categorized based on the site of genetic modification (*in vivo* vs *ex vivo*) and molecular approach. *In vivo* gene therapies utilize a viral vector such as an adeno-associated virus or lentivirus to package genetic material, which is directly administered to the host organism for cellular uptake. By contrast, *ex vivo* gene therapy involves isolation and transduction of cells in culture, which are transplanted into the host organism.[2] Most commonly, therapeutic effect is achieved through augmentation or gene replacement therapy, as exemplified by Luxturna®, which employs an adeno-associated viral vector to deliver a normal copy of the *RPE65* gene to patients with deficient or absent levels of biologically active RPE65.[3] Other molecular approaches include gene suppression or inactivation via RNA antisense oligonucleotides or RNAi, CRISPR gene editing, and growth factor gene delivery.

Genetic Landscape and Therapeutic Approaches to IRDs

The eye has been a major site of early gene therapy development due to its immune-privileged status, accessibility for intervention, and involvement in a number of monogenic diseases that exclusively manifest in the eye.[4] Since approval of Luxturna® for Leber Congenital Amaurosis (LCA) in 2017, two additional ocular gene therapy products are publicly known to have attained FDA Regenerative Medicine Advanced Therapy (RMAT) designations: JCell for treating retinitis pigmentosa (RP) and NSR-REP1 for choroideremia.[5] In addition, there are over 30 currently ongoing clinical trials for gene therapies

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targeting ophthalmic conditions including various other forms of RP, achromatopsia, Leber hereditary optical neuropathy (LHON), X-linked retinoschisis, and Usher syndrome type 2 (Table 1). These diseases belong to a heterogeneous group of retinal disorders termed inherited retinal diseases (IRDs) that collectively affect 1 in 2000 individuals.[6] The leading cause of vision loss in individuals between the ages of 15 and 45 years, IRDs are linked to mutations in over 270 genes.[7] Disease onset, severity, and progression can vary depending on the affected gene, though early childhood onset is generally correlated with more severe forms.

Table 1. *Global, ongoing clinical trials investigating gene therapies for IRDs (clinicaltrials.gov).*

Gene Target	Disease	Vector	Surgical Procedure	Phase	Target Enrollment	Start Date	Sponsor	NCT Number
CNGB3	Achromatopsia	AAV2tYF-PR1.7	Subretinal	1|2	28	2016-02-01	Applied Genetic Technologies Corp	NCT02599922
CNGA3	Achromatopsia	AAV2tYF-PR1.7	Subretinal	1|2	24	2017-05-01	Applied Genetic Technologies Corp	NCT02935517
CNGB3	Achromatopsia	AAV2/8-hCARp	Subretinal	1|2	23	2017-06-27	MeiraGTx UK II Ltd	NCT03001310
CNGA3	Achromatopsia	AAV2/8-hG1.7p	Subretinal	1|2	18	2019-07-18	MeiraGTx UK II Ltd	NCT03758404
CHM (REP1)	Choroideremia	AAV2	IVT	1|2	15	2015-01-01	Spark Therapeutics	NCT02341807
CHM (REP1)	Choroideremia	AAV2	Subretinal	2	30	2016-08-01	University of Oxford	NCT02407678
CHM (REP1)	Choroideremia	AAV2	Subretinal	2	60	2017-11-06	Biogen	NCT03507686
CHM (REP1)	Choroideremia	AAV2	IVT	1	15	2020-06-02	4D Molecular Therapeutics	NCT04483440
RPE65	LCA2	AAV2	Subretinal	1	15	2007-07-01	University of Pennsylvania	NCT00481546
RPE65	LCA2	AAV2	Subretinal	1|2	12	2010-11-01	Spark Therapeutics	NCT01208389
CEP290	LCA 10	RNA antisense oligonucleotide	IVT	2|3	36	2019-04-04	ProQR Therapeutics	NCT03913143
CEP290	LCA 10	RNA antisense oligonucleotide	IVT	1|2	11	2019-05-13	ProQR Therapeutics	NCT03913130
RPE65	LCA2	AAV2	Subretinal	3	4	2020-11-24	Novartis Pharmaceuticals	NCT04516369
ND4	LHON	scAAV2	IVT	1	30	2014-07-14	Bascom Palmer Eye Institute	NCT02161380
ND4	LHON	AAV2	IVT	2|3	159	2017-12-27	Huazhong University of Science and Technology	NCT03153293
ND4	LHON	AAV2/2	IVT	3	61	2018-01-09	GenSight Biologics	NCT03406104
ND4	LHON	AAV2/2	IVT	3	90	2018-03-12	GenSight Biologics	NCT03293524
RS1	X-linked Retinoschisis	AAV8	IVT	1|2	24	2015-02-11	NEI (NIH)	NCT02317887
RS1	X-linked Retinoschisis	AAV2tYF	IVT	1|2	27	2015-05-01	Applied Genetic Technologies Corp	NCT02416622
MERTK	RP	AAV2	Subretinal	1	6	2011-08-01	King Khaled Eye Specialist Hospital	NCT01482195
ChR	RP	AAV2	IVT	1|2	14	2015-12-14	Allergan	NCT02556736
PDE6B	RP	AAV2/5	Subretinal	1|2	15	2017-11-06	Horama S.A	NCT03328130
PDE6A	RP	ND	Subretinal	1|2	9	2019-09-24	STZ eyetrial	NCT04611503
RLBP1	RP	AAV8	Subretinal	1|2	21	2018-08-22	Novartis Pharmaceuticals	NCT03374657
RHO	RP, autosomal dominant	RNA antisense oligonucleotide	IVT	1|2	35	2019-10-07	ProQR Therapeutics	NCT04123626
ChR	RP, non-syndromic	AAV2.7m8	IVT	1|2	18	2018-09-26	GenSight Biologics	NCT03326336
RPGR	RP, X-linked	AAV2/5	Subretinal	1|2	46	2017-07-14	MeiraGTx UK II Ltd	NCT03252847
RPGR	RP, X-linked	AAV2tYF	Subretinal	1|2	30	2018-04-16	Applied Genetic Technologies Corp	NCT03316560
RPGR	RP, X-linked	AAV variant (4D-R100)	IVT	1|2	37	2020-06-09	4D Molecular Therapeutics	NCT04517149
USH2A	Usher Type 2, RP	RNA antisense oligonucleotide	IVT	1|2	18	2019-03-06	ProQR Therapeutics	NCT03780257

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is the most common retinal dystrophy affecting roughly 1 in 3000 individuals, with about 100,000 affected individuals living in the United States.[8] RP may be inherited as a dominant, recessive, or X-linked trait or manifest as part of a syndrome. The condition is commonly characterized by nyctalopia or "night blindness" along with worsening tunnel vision caused by progressive degeneration of rod photoreceptors and retinal pigment epithelium in the midperiphery.[9] In the late stages of the disease, most RP patients lose central vision as cone photoreceptors eventually degenerate. Fundoscopic exam findings consist of a "classic triad" of bony spicule pigmentation, abnormal pallor of the optic disc, and vascular narrowing. Non syndromic RP can be traced to mutations in over 80 genes, with the RPGR gene implicated in 70-90% of X-linked RP cases.[10]

Stargardt macular dystrophy

Stargardt macular dystrophy is the most common macular dystrophy, with a prevalence of approximately 1 in 8,000 to 10,000.[11] Inheritance is typically autosomal recessive and onset often begins in childhood or early adulthood. Stargardt disease clinically manifests as early central visual loss due to accumulation of lipofuscin in the retinal pigment epithelium and subsequent retinal degeneration.[12] Other physical exam findings include central scotomas on visual field testing and macular atrophy. Stargardt is most frequently attributed to mutations in *ABCA4*, a 6.8 kb gene which encodes a membrane transporter critical for the phototransduction cascade and removal of toxic byproducts. Due to its large size, *ABCA4* cannot be packaged into AAV vectors via traditional means, hampering its development into a gene therapy.

Retinoschisis

Retinoschisis (XLRS) is an X-linked disease that begins in early childhood and results in bilateral loss of central visual acuity due to cysts that form between pathologically separated layers of the retina.[13] XLRS affects 1 in 5,000 to 20,000 individuals and commonly causes severe complications including vitreous hemorrhage and retinal detachment. Mutations in the *RS1* gene, which encodes a key protein responsible for maintenance of retinal architecture, are causative for XLRS.

Leber hereditary optic neuropathy

Leber hereditary optic neuropathy (LHON) is a mitochondrial disease characterized by an initial clouding or blurring of vision in one eye that worsens into painless bilateral central vision loss.[14] While the prevalence of LHON is unknown for most populations, it affects between 1 in 27,000 to 45,000 in North East England and the European population. Onset typically occurs between 15 and 35 years of age, with degeneration of retinal ganglion cells and development of optic atrophy after a year. The most common cause is a mitochondrial DNA point mutation within the *ND4* gene encoding NADH dehydrogenase subunit 4.[15-16]

Achromatopsia

Achromatopsia is a congenital-onset autosomal recessive disease that results in complete loss of cone photoreceptor function. The disease affects an estimated 1 in 30,000 individuals and is characterized by poor central visual acuity, partial or total color blindness, photophobia, and nystagmus.[17] To date, achromatopsia can be traced to causative mutations in 6 genes: *CNGA3, CNGB3, GNAT2, ATF6*, *PDE6H*, or *PDE6C*, with *CNGA3* and *CNGB3* accounting for 70% of achromatopsia cases.[18]

Usher Syndrome 1B

Usher syndrome 1B is an autosomal recessive ciliopathy affecting approximately 3 to 6 per 100,000 individuals and results in deafness, blindness, and vestibular dysfunction. Usher syndrome is caused by mutations in the *MYO7A* gene, which encodes an actin-based protein essential for melanosome trafficking and translocation of key phototransduction cascade proteins such as RPE65.[19]

Choroideremia

Choroideremia is an X-linked recessive chorioretinal dystrophy occurring at a prevalence of approximately 1 in 50,000 male individuals. Patients frequently present with night blindness within the first decade of life and progressive peripheral vision loss that becomes apparent by early adulthood.[20] The condition is caused by mutations in the *CHM* gene that encodes the Rab escort protein-1 (REP-1) involved in intracellular trafficking, leading to progressive degeneration of the choroid, pigment epithelium, and photoreceptors.

Leber Congenital Amaurosis

Leber congenital amaurosis (LCA) is a rare monogenic inherited retinal disease, occurring in approximately 1 in 80,000 individuals and accounting for roughly 20% of children attending schools for the blind.[21] The disease manifests within the first year of life as severe and progressive vision loss; infants are frequently blind at birth. Other symptoms and signs may include nystagmus, unusual sensitivity to light, strabismus, and cataract. LCA has an autosomal recessive inheritance pattern and can be traced to mutations in at least 6 different genes. LCA

type 2 is caused by mutations in the *RPE65* gene which encodes an isomerase crucial for normal functioning of the visual phototransduction cascade. Luxturna®, an *in vivo* replacement gene therapy of *RPE65* has achieved clinical and commercial success in treating patients with LCA type 2.

Luxturna® for *RPE65*-associated LCA2

Luxturna® is an adeno-associated viral (AAV) vector-based gene therapy indicated for biallelic *RPE65* mutation-associated retinal dystrophy. The therapy preferentially delivers a functional copy of human *RPE65* cDNA to post-mitotic retinal pigment epithelial cells for long-term expression and therefore requires presence of viable retinal cells, as determined by a treating physician. The therapy is administered through subretinal injection at a recommended dose of 1.5 x 10^{11} vector genomes (vg) in a total volume of 0.3 mL per eye, within close interval at least 6 days apart.[3] Transduction and transgenic gene expression typically occur 2 to 4 weeks post subretinal injection.

Rationale for Treatment Approach (Subretinal vs Intravitreal)

Intravitreal injections (IVT) are frequently considered an attractive route of administration for ocular gene therapies due to the ubiquitous use of the technique and well-tolerated safety profile. In early preclinical studies, intravitreal injections of AAV vectors in animal models achieved limited transduction to the foveal and peripheral retinal ganglion cells, which was attributed to the vitreous and internal limiting membrane.[22] To enhance delivery, procedures required vitrectomy prior to IVT injection, making this route of administration nearly as invasive as the subretinal approach. Additionally, the enclosed anatomic nature of the subretinal space is thought to provide greater immune privilege compared to the vitreous cavity. In the case of Luxturna®, subretinal delivery was deemed more efficacious due to the improved access and uptake by target RPE cells.

Patient Outcomes to Date

Clinical Trial Data Preceding US FDA Approval

In 2008, three independent groups published human studies investigating the use of AAV2 to deliver *RPE65* gene via subretinal injection in patients with LCA. Each of the studies followed 3 patients between 1.25-12 months after administration of doses ranging from 1.5 x 10^{10} vg to 1 x 10^{11} vg.[23-25] Preliminary data demonstrated modest improvements across a variety of visual function markers and no evidence of immune-related side effects.

Following the results of this first set of gene therapy trials, Maguire et al. reported the first dose-escalation study in 2009 involving 12 patients (age 8-44 years) which would provide further support for the therapeutic potential of voretigene neparvovec.[26] The drug was administered in the worse seeing eye at low (1.5×10^{10} vg), medium (4.8×10^{10} vg), or high dose (1.5×10^{11} vg) and patients were tracked for up to 2 years. None of the patients experienced harmful immune-related side effects. All 12 patients reported improved vision in dim lighting in the treated eye, and improved Goldmann visual fields. 3 out of 3 patients who received the low dose and 3 out of 6 patients who received the medium dose also experienced substantial and stable gains in visual acuity; the remaining patients did not experience substantial changes in visual acuity. Subjective mobility testing such as monitoring patient's ability to walk in dim illumination also showed marked improvement after treatment.

From 2010 through 2012, 11 out of the 12 patients from the dose escalation study were enrolled in a follow-on phase study, where they received subretinal injection of voretigene neparvovec (1.5×10^{11} vg) in the previously untreated contralateral eye.[27] One enrolled patient was excluded from the analysis due to a culture-positive endophthalmitis post-surgery. Among the ten remaining patients, no adverse events related to the AAV vector were evident; one patient developed a low positive cell-mediated response to AAV at week 4 follow-up. Procedure-related adverse events were mild and included early post-operative dellen formation (n=3), and cataracts (n=2) that were subsequently surgically treated. Eight out of ten patients demonstrated improved full-field light sensitivity threshold testing (FST) and collectively there was significant improvements in rod and cone function by day 30, with improvements maintained until year 3. Mobility tests also showed significant improvement in the second treated eye by day 30 that was maintained through year 3. One-year post-administration fMRI studies showed significant increased bilateral visual cortical activation compared to baseline.

During the same period, a separate study enrolled twelve patients ages 6 to 39 at the University of Massachusetts and the Casey Eye Institute.[28] Eligibility criteria included age of at least 6 years, a diagnosis of LCA or severe early-childhood-onset retinal dystrophy (SECORD), confirmed biallelic *RPE65* mutations, BCVA no better than 20/60, and visible photoreceptor layer on OCT. Patients underwent vitrectomy and subretinal injection of 450 µl containing 1.8×10^{11} or 6×10^{11} vg in their worse-seeing eye. No serious treatment-related adverse events or immune-related side effects occurred. The most common adverse events were transient, mild to moderate in intensity, and

associated with the surgical procedure. Adverse events included subconjunctival hemorrhage (n=8); ocular hyperemia in (n=5); reduced visual acuity, eye pain, eye irritation, increased intraocular pressure, headache, or back pain in (n=2 each). At 2 year follow-up, Weleber and Pennesi et al. reported 4 out of 4 pediatric patients demonstrated significant BCVA improvement, observed as a 6 to 14-letter increase in the treated eye. Of the 8 adult patients, 3 experienced a 2.5-letter increase in BCVA from a baseline of 20 to 30 ETDRS. The remaining 5 adults whose baseline BCVA was limited to counting fingers or hand movements showed no change in BCVA. Out of 12 total participants, 11 reported improved quality of life post-treatment as assessed by the National Eye Institute 25-Item Visual Function Questionnaire (NEI-VFQ-25).

In a landmark randomized and controlled phase 3 trial, Russell et al assessed the efficacy and safety of voretigene neparvovec in thirty-one patients aged 4 to 44 years with confirmed diagnoses of biallelic *RPE65* mutations.[29] Eligibility criteria also included BCVA no better than 20/60 or visual field <20 degrees in any meridian; ability to perform the standardized multi-luminance mobility test (MLMT); and viable retinal cells as assessed by clinical examination, OCT > 100 microns at the posterior pole, and fundus photography. The study was conducted by five surgeons across two US sites (Children's Hospital of Philadelphia and University of Iowa) and patients were randomized 2:1 for intervention versus control. Patients in the intervention arm underwent standard 3-port vitrectomy and received subretinal injection of the first eye, followed by subretinal injection of the second eye 6-18 days later at the now standard dose of 1.5×10^{11} vg in 0.3 mL.

The primary efficacy endpoint was MLMT performance, which integrates aspects of visual acuity, visual function, and light sensitivity into a quantitative measure for assessing functional vision changes in patients with inherited retinal diseases.[30] The MLMT consists of a 5 x 10 foot obstacle course designed to assess a participant's ability to traverse a marked path by relying on vision to recognize and avoid obstacles and potential missteps. The test is administered at 7 different luminance levels representative of real-world lighting conditions that range from an illuminance of 1 lux (a moonless summer night) to 400 lux (a well-lit office environment). Passing the MLMT requires completion of the course at the designated luminance level within three minutes with fewer than four mistakes. Secondary efficacy endpoints included FST and BCVA averaged across both eyes, as well as MLMT testing of the assigned first eye.

Two patients from the interventional arm experienced serious adverse events unrelated to the study protocol. No serious adverse events related to the AAV vector or harmful immune responses occurred. Moderate adverse events included retinal tear (n=2 out of 20 participants), eye irritation (n=1), pruritus (n=1), and macular hole (n=1). The most common adverse events were mild in nature and included elevated intraocular pressure (n=4), cataract (n=3), and transient eye inflammation (n=2).

Among twenty-nine study participants (20 intervention, 9 control), mean bilateral MLMT change score at 1 year post treatment was significantly improved at +1.8 light levels in the intervention group compared to +0.2 in the control group. 65% of intervention participants showed the maximum possible improvement in visual function by passing the MLMT at the lowest luminance level; no control participants passed at this luminance level. By day 30, participants from the intervention group attained >2 log units improvement in light sensitivity as measured by FST which was maintained over 1 year follow-up, as compared to no change in control patients. At 1 year, intervention participants saw a mean BCVA improvement of 8.1 letters versus a gain of 1.6 letters among control, though this was not statistically significant.

Post-Approval Patient Outcomes

In 2019, Maguire et al published a combined report of the 4-year and 2-year follow-up results for patients from the phase 1 follow-on and phase 3 randomized control studies.[31] Among phase 1 follow-on participants (n=8), mean MLMT score improvement was maintained at +2.4 light levels (SD 1.3) at 4 years versus +2.6 (SD 1.6) 1 year after administration. Similarly, for phase 3 intervention group participants, MLMT score improvement was maintained at +1.9 (SD 1.1) at 2 years versus +1.9 (SD 1.0) at 1 year after treatment. Mean white light FST, which improved by greater than 1.8 log units by day 30 and improved to 2.3 log units by year 1, was maintained for up to 4 years. BCVA also remained stable through year 2 across both studies, with a slight decline in performance by year 4 among participants from the phase 1 follow-on study.

Twenty-seven (68%) of the combined forty study participants experienced treatment-associated ocular adverse events, two of which were serious: one event of loss of foveal function related to the surgical procedure and one event of increased intraocular pressure in a patient receiving anti-infectives and steroid injection for endophthalmitis. Cataracts were the most common adverse event, occurring in 18% of participants (n=7), which is consistent with the risk of vitrectomy.

In January 2021, a group from the University of Tübingen, Germany published preliminary patient outcomes of

treatment with voretigene naprvovec at one and three months follow-up.[32] Seven eyes of 5 patients aged 14 to 36 years were treated with 0.3 ml of the vector suspension (dose 1.5×10^{11} vg) in each eye. Stingl et al. reported marked clinical improvement in rod function post-treatment that suggested a correlation between age, retinal volume, and FST improvement, with the youngest patient attaining the largest FST improvement of approximately 30 dB at 3 months. Measurable FST improvement was observed in all patients except the oldest, while visual acuity remained relatively stable across all eyes.

Evaluating Cost Effectiveness of Gene Therapies for Inherited Retinal Disease

Gene Therapy Pricing Trends

Gene therapies are entering the market with list prices ranging from hundreds of thousands to multi-millions of dollars. In 2017, Luxturna® entered the US market as a first-in-class gene therapy at a price point of $425,000 USD per eye, or $850,000 for the typical patient, making it the most expensive on-market drug in the US at the time. ZolgenSMA, a SMA gene replacement therapy approved for children under the age of 2 with spinal muscular atrophy, overtook Luxturna® as the single most expensive drug at its price point of $2.125 million USD for a potentially curative dose. Similarly, BioMarin Pharmaceutical is considering pricing its phase 3 gene therapy product (Valrox) for hemophilia A anywhere between $2 to 3 million USD.

Unfortunately, these unprecedented, high prices are not outliers but likely part of the growing trend (Table 2) for a class of drugs characterized by moderate to long-term therapeutic durability that targets rare, clinically severe, and otherwise incurable conditions. The current price points of gene therapies are largely driven by the tremendous R&D costs which pharmaceutical companies struggle to recoup from small populations due the rarity of the conditions that these products serve. The single-dose nature of many gene therapies further compounds this, depleting the available pool of untreated patients for low-incidence diseases.

The average cost of developing a typical originator biologic has been estimated to be between $1.3 and $2.6 billion, taking into account expenditures for failed drugs in the pipeline for a successfully marketed product.[33-34] The cost of developing gene therapies is projected to be even higher due to increased risk of clinical failure associated with a nascent technology, cost of novel manufacturing approaches, cost of goods, and cost of building commercial infrastructure for patient access.

Approaches to Evaluating Cost-Effectiveness for IRDs

The quality-adjusted life year (QALY) metric has commonly been utilized in evaluating cost efficacy.[35-37] According to standards set by the Institute for Clinical and Economic Review (ICER), one QALY afforded by a given treatment should cost no more than $150,000, with the caveat that in cases of ultra-rare diseases, decision-makers may give special weighting to "other benefits and contextual considerations" that may be used to justify higher cost-effectiveness ratios.[38]

In a final evidence report analyzing the cost efficacy of Luxturna®, ICER modeled a population reflective of the clinical trial demographics (mean age of 15 years, 43% male) with categories of visual impairment defined by visual acuity and visual field, where persons with a VA worse than <0.63 decimals but better than 0.015 decimals or VF < 1200 degrees (Goldmann III4e) were defined as visually impaired, and VA worse than 0.015 decimals or VF <48 degrees were considered blind.[39]

The study considered cost-efficacy from a health system perspective which takes into account direct medical costs (drug wholesale acquisition cost, medical procedure, adverse-events, other ophthalmic medical costs), as well as a modified societal perspective which additionally includes direct non-medical costs (caregiver, transport, and nursing home costs) and indirect costs (costs related to losses in productivity and education) in the calculation. Total costs were divided by total QALYs, as well as blindness-free years, producing two different measures for evaluating cost-efficacy. The long-term durability and health risks of Luxturna® is uncertain with current outcomes data limited to 4 years; the model assumed a benefit of roughly 10 additional blindness-free years. The report concluded that at its current wholesale acquisition cost of $850,000, for the average patient treated at age 15, Luxturna® costs

Table 2. *List prices and disease prevalence for on-market single-dose gene therapies.*

Launch Year	Cell/Gene Therapy	Disease Target	Est. US Prevalence	List Price
2017	Kymriah	Relapsed/refractory B-cell ALL	16,300	$476,000
2017	Yescarta	Relapsed/refractory Large B-cell lymphoma	39,000	$373,000
2017	Luxturna	Inherited Retinal Disease (biallelic RPE-65 mutations)	2,000	$850,000
2019	ZolgenSMA	Spinal Muscular Atrophy (biallelic SMN1 mutations)	900	$2,125,000

$643,813 per additional QALY or $77,937 per additional blindness-free year (health care system perspective). The study concluded that Luxturna® does not meet the threshold of $150,000 per QALY from a US healthcare perspective nor a modified societal perspective which takes into account indirect non-medical benefits. ICER further modeled the cost-efficacy for individuals treated at age 3, which was significantly more cost-effective at $287,914/QALY.

CONCLUSION

Inherited retinal diseases have been the focus of substantial pharmaceutical development of single-dose gene therapies. Given the heterogeneity of IRDs, therapeutic development has been piecemeal, with ongoing gene therapy clinical trials to date targeting 16 out of over 270 genes implicated in IRDs. Over three years since the FDA approval, longitudinal follow-up data indicates continued clinical efficacy and durability of Luxturna for biallelic RPE65 mutations. Real-world outcomes data of patients treated post-approval though still preliminary, is suggestive of clinical benefit in line with the clinical trial outcomes that informed approval. As more gene therapies attain regulatory approval, how these therapies will be valued, accessed, and paid for, is still taking shape.

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