Gene Therapy for Inherited Retinal Dystrophy

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider voretigene neparvovec-rzyl adeno-associated virus vector-based gene therapy subretinal injection (Luxturna™)‡ for patients with vision loss due to biallelic human retinal pigment epithelial 65 kDa protein (RPE65) mutation-associated retinal dystrophy to be **eligible for coverage** when patient selection criteria are met**:**

Patient Selection Criteria
Coverage eligibility for the use of voretigene neparvovec-rzyl (Luxturna) will be considered when all of the following criteria are met:

- Patient is an adult aged <65 years or child aged ≥3 years; AND
  *(Note: The patient selection criterion requiring the patient to be younger than 65 years of age is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Patient has a diagnosis of a confirmed biallelic RPE65 mutation-associated retinal dystrophy (e.g. Leber congenital amaurosis, retinitis pigmentosa, or early onset severe retinal dystrophy); AND
- The requested dose for each eye is 1.5 $x10^{11}$ vector genomes administered by subretinal injection in a total volume of 0.3 mL; AND
- Patient has documentation of both of the following:
  - Genetic testing confirming presence of biallelic RPE65 variant(s):
    - Single RPE65 variant found in the homozygous state; OR
    - Two RPE65 variants found in the *trans* configuration (compound heterozygous state); AND
  - Presence of viable retinal cells as determined by treating physicians as assessed by optical coherence tomography imaging and/or ophthalmoscopy:
    - An area of retina within the posterior pole of >100 µm thickness shown on optical coherence tomography, OR
    - ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole, OR
    - Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent; AND
- The patient does not have any of the following:
  - Pregnancy in females
  - Breastfeeding

- Prior intraocular surgery within 6 months.
- Prior RPE65 gene therapy in the intended eye
- Preexisting eye conditions or complications that preclude the ability to administer and assess the efficacy of Luxturna including but not limited to:
  - Malignancies whose treatment could affect central nervous system function (e.g. radiotherapy of the orbit or leukemia with central nervous system or optic nerve involvement)
  - Retinopathy associated with diabetic macular edema or sickle cell disease
  - Immunodeficiency (acquired or congenital) making the member susceptible to opportunistic infection

*(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of voretigene neparvovec-rzyl (Luxturna) when the patient is ≥65 years old or <3 years old, is pregnant or breastfeeding, has had recent intraocular surgery, has previously received RPE65 gene therapy in the intended eye, or has a preexisting eye condition affecting the ability to administer and assess the efficacy of Luxturna to be **not medically necessary.****

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of voretigene neparvovec-rzyl (Luxturna) for any indication other than the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy who have sufficient viable retinal cells to be **investigational.***

Background/Overview

Inherited Retinal Dystrophies
Inherited retinal dystrophies are a diverse group of disorders with overlapping phenotypes characterized by progressive degeneration and dysfunction of the retina. These disorders are caused by mutations in any one of over 220 different genes. For RPE65 mutation-associated retinal dystrophy alone, approximately 125 discrete gene mutations have been identified to date. Prior to both the identification of the specific gene(s) associated with the disease and to genetic testing, precise diagnosis was challenging. Many different clinical diagnoses have been associated with inherited retinal dystrophies based on time of onset, severity, and presenting phenotype. However, distinctions in clinical diagnoses are poorly defined, and may have overlapping features, leading to inaccurate or inconsistent diagnoses. For patients with RPE65 mutation-associated retinal dystrophy, common clinical diagnoses include Leber congenital amaurosis [LCA], retinitis pigmentosa [RP], and severe early childhood onset retinal dystrophy. The hallmark symptom of these retinal dystrophies is night blindness (nyctalopia) and loss of peripheral vision. These losses lead to difficulties in performing visually dependent activities of daily living such as orientation and navigation in

dimly lit areas. Visual acuity may be maintained longer than peripheral vision, though eventually, most individuals progress to vision loss.

Diagnosis of Biallelic *RPE65*-Mediated Inherited Retinal Dystrophies
Genetic testing is required to detect the presence of pathogenic or likely pathogenic variant(s) in the *RPE65* gene. By definition, these variant(s) must be present in both copies of the *RPE65* gene to establish a diagnosis of biallelic *RPE65*-mediated inherited retinal dystrophy.

A single *RPE65* pathogenic or likely pathogenic variant found in the homozygous state (e.g., the presence of the same pathogenic variant in both copies alleles of the *RPE65* gene) establishes a diagnosis of biallelic *RPE65*-mediated dystrophinopathy.

However, if 2 different *RPE65* variants are detected (eg, compound heterogygous state), confirmatory testing such as segregation analysis by family studies may be required to determine the *trans* vs *cis* configuration (eg, whether the 2 different pathogenic variants are found in different copies or in the same copy of the *RPE65* gene). The presence of 2 different *RPE65* variants in separate copies of the *RPE65* gene (*trans* configuration) establishes a diagnosis of biallelic *RPE65*-mediated dystrophinopathy. The presence of 2 different *RPE65* pathogenic variants in only 1 copy of the *RPE65* gene (*cis* configuration) is not considered a biallelic *RPE65*-mediated dystrophinopathy.

Next-generation sequencing and Sanger sequencing typically cannot resolve the phase (e.g., *trans* vs *cis* configuration) when two *RPE65* variants are detected. In this scenario, additional documentation of the *trans* configuration is required to establish a diagnosis of biallelic *RPE65*-mediated inherited retinal dystrophy. Table PG1 provides a visual representation of the genetic status requirements to establish a diagnosis of *RPE65*-mediated inherited retinal dystrophy.

Table PG1. Genetic Diagnosis of *RPE65*-Mediated Inherited Retinal Dystrophy

Genetic Status	Diagram	Diagnosis of *RPE65*-Mediated Inherited Retinal Dystrophy?
Homozygous	*RPE65* gene copy #1 (- - - - - - **X** - - - - - -) *RPE65* gene copy #2 (- - - - - - **X** - - - - - -) **X**=single *RPE65* pathogenic variant	Yes
Heterozygous (*trans* configuration)	*RPE65* gene copy #1 (- - - - - - **X** - - - - - -) *RPE65* gene copy #2 (- - - **O** - - - - - - - - -) **X**=*RPE65* pathogenic variant #1 **O**=*RPE65* pathogenic variant #2	Yes
Heterozygous (*cis* configuration)	*RPE65* gene copy #1 (- - **O** - - **X** - - - - - -) *RPE65* gene copy #2 (- - - - - - - - - - - - - -) **X**=*RPE65* pathogenic variant #1 **O**=*RPE65* pathogenic variant #2	No

Epidemiology
RPE65-associated inherited retinal dystrophy is rare. The prevalence of LCA has been estimated to be between 1 in 33,000 and 1 in 81,000 individuals in the United States. LCA subtype 2 (*RPE65*-associated LCA) accounts for between 5% and 16% of cases of LCA. The prevalence of RP in the United States is approximately 1 in 3500 to 1 in 4000[9] with approximately 1% of patients with RP having *RPE65* variants. Assuming a U.S. population of approximately 326.4 million at the end of 2017, the prevalence of *RPE65*-associated retinal dystrophies in the United States would, therefore, be roughly 1000 to 2500 individuals. Table 1 summarizes the estimated pooled prevalence of *RPE*-associated inherited retinal dystrophy and the range of estimated cases based on the estimated 2017 U.S. population.

Table 1. Estimated Pooled Prevalence of *RPE65*-Associated Inherited Retinal Dystrophy and Estimated Number of Patients

Description	Low	High
Estimated pooled prevalence of *RPE65*-mediated inherited retinal dystrophies (eg, LCA type 2, *RPE65*-mediated RP)	1:330,000	1:130,000
Estimated number of patients	1000	2500

LCA type 2: Leber congenital amaurosis type 2; RP: retinitis pigmentosa.

GENE THERAPY
Gene therapies are treatments that change the expression of genes to treat disease, eg, by replacing or inactivating a gene that is not functioning properly or by introducing a new gene. Genes may be introduced into human cells through a vector, usually a virus. Adeno-associated viruses (AAV) are frequently used due to their unique biology and simple structure. These viruses are in the parvovirus family and are dependent on coinfection with other viruses, usually adenoviruses, to replicate. AAVs are poorly immunogenic compared with other viruses but can still trigger immune response making it a challenge to deliver an effective dose without triggering an immune response that might render the gene therapy ineffective or harm the patient. There are over 100 different AAVs, and 12 serotypes have been identified so far, labeled AAV1 to AAV12; in particular, AAV2, AAV4, and AAV5 are specific for retinal tissues. The recombinant AAV2 is the most commonly used AAV serotype in gene therapy.

The eye is a particularly appropriate target for gene therapy due to the immune privilege provided by the blood-ocular barrier and the minimal amount of vector needed, given the size of the organ. Gene therapy for *RPE65* variant-associated retinal dystrophy using various AAV vectors to transfect cells with a functioning copy of *RPE65* in the RPE cells has been investigated.

Luxturna
Voretigene neparvovec-rzyl (Luxturna) is a live, non-replicating, AAV2 which has been genetically modified to express the human RPE65 gene. Luxturna is derived from naturally occurring adeno-associated virus using recombinant DNA techniques. The recommended dose of Luxturna for each eye is 1.5×10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3 mL.

Subretinal administration of Luxturna to each eye must be performed on separate days within a close interval, but no fewer than 6 days apart. This therapy is administered at highly specialized facilities with an active ophthalmology practice treating individuals with retinal dystrophies. Access is needed to medical retina specialists, vitreoretinal surgery expertise, and specialty pharmacies. Training programs for surgeons and pharmacists will likely be necessary.

Systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/d (maximum, 40 mg/d) recommended for a total of 7 days (starting 3 days before administration of Luxturna to each eye), and followed by a tapering dose during the next 10 days.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

On December 19, 2017, the AAV2 gene therapy vector voretigene neparvovec-rzyl (Luxturna; Spark Therapeutics) was approved by the U.S. FDA for use in patients with vision loss due to confirmed biallelic *RPE65* variant-associated retinal dystrophy. Spark Therapeutics received breakthrough therapy designation, rare pediatric disease designation, and orphan drug designation.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

GENE THERAPY FOR *RPE65* VARIANT-ASSOCIATED RETINAL DYSTROPHY

Outcomes background

Because the hallmark of the disease is nyctalopia, the manufacturer developed a novel outcome measure that assesses functional vision by evaluating the effects of illumination on speed and accuracy of navigation. The measure incorporates features of visual acuity (VA), visual field (VF), and light sensitivity. The Multi-Luminance Mobility Test (MLMT) grades individuals navigating a marked path while avoiding obstacles through various courses at 7 standardized levels of illumination, ranging from 1 to 400 lux (see examples in Table 3). Graders monitoring the navigation assign each course either a “pass” or “fail” score, depending on whether the individual navigates the course within 180 seconds with 3 or fewer errors. The lowest light level passed corresponds to an MLMT lux score, which ranges from 0 (400 lux) to 6 (1 lux). The score change is the difference between the MLMT lux score at year 1 and baseline. A positive score change corresponds to passing the MLMT at a lower light level. The reliability and content validity of the MLMT were evaluated in 60 (29 normal sighted, 31 visually impaired) individuals who navigated MLMT courses 3 times over 1 year.

Randomized Controlled Trials

One gene therapy (voretigene neparvovec) for patients with biallelic *RPE65* variant-associated retinal dystrophy has RCT evidence. The pivotal RCT (NCT00999609) for voretigene neparvovec was an open-label trial of patients ages 3 or older with biallelic *RPE65* variants, VA worse than 20/60, and/or a VF less than 20^{o} in any meridian, with sufficient viable retinal cells. Those patients meeting these criteria were randomized 2:1 to intervention (n=21) or control (n=10). The trial was conducted at a children's hospital and university medical center. Patients were enrolled between 2012 and 2013. The intervention treatment group received sequential injections of 1.5E11 vg AAV2-hRPE65v2 (voretigene neparvovec) to each eye no more than 18 days apart (target, 12 days; standard deviation, 6 days). The injections were delivered in a total subretinal volume of 0.3 mL under general anesthesia. The control treatment group received voretigene neparvovec 1 year after the baseline evaluation. Patients received prednisone 1 mg/kg/d (max, 40 mg/d) for 7 days starting 3 days before injection in the first eye and tapered until 3 days before injection of the second eye at which point the steroid regimen was repeated. During the first year, follow-up visits occurred at 30, 90, 180 days, and 1 year. Extended follow-up is planned for 15 years. The efficacy outcomes were compared at 1 year. The primary outcome was the difference in mean bilateral MLMT score change. MLMT graders were masked to treatment group. The trial was powered to have greater than 90% power to detect a difference of 1 light level in the MLMT score at a 2-sided type I error rate of 5%. Secondary outcomes were hierarchically ranked: (1) difference in change in full-field light sensitivity threshold (FST) testing averaged over both eyes for white light; (2) difference in change in monocular (first eye) MLMT score change; (3) difference in change in VA averaged over both eyes. Patient-reported vision-related activities of daily living (ADLs) using a Visual Function Questionnaire (VFQ) and VF testing (Humphrey and Goldmann) were also reported. The VFQ has not been validated.

At baseline, the mean age was about 15 years old (range, 4-44 years) and approximately 42% of the participants were male. The MLMT passing level differed between the groups at baseline; about 60% passed at less than 125 lux in the intervention group vs 40% in the control group. The mean baseline VA was not reported but appears to have been between approximately 20/200 and 20/250 based on a figure in the manufacturer briefing document. One patient in each treatment group withdrew before the year 1 visit; neither received voretigene neparvovec. The remaining 20 patients in the intervention treatment and 9 patients in the control treatment groups completed the year 1 study visit. The intention-to-treat population included all randomized patients.

The efficacy outcome results at year 1 for the intention-to-treat population are shown in Table 4. In summary, the differences in change in MLMT and FST scores were statistically significant. No patients in the intervention group had worsening MLMT scores at 1 year compared with 3 patients in the control group. Almost two-thirds of the intervention arm showed maximal improvement in MLMT scores (passing at 1 lux) while no participants in the control arm were able to do so. Significant improvements were also observed in Goldmann III4e and Humphrey static perimetry macular threshold VF exams. The difference in change in VA was not statistically significant although the changes correspond to an improvement of about 8 letters in the intervention group and a loss of 1 letter in the control group. The original VA analysis used the Holladay method to assign values to off-chart results. Using, instead the Lange method for off-chart results, the

treatment effect estimate was similar, but variability estimates were reduced (difference in change, 7.4 letters; 95% confidence interval [CI], 0.1 to 14.6 letters). No control patients experienced a gain of 15 or more letters (≤0.3 logMAR) at year 1 while 6 of 20 patients in the intervention group gained 15 or more letters in the first eye and 4 patients also experienced this improvement in the second eye. Contrast sensitivity data were collected but were not reported.

Table 4. Efficacy Outcomes Results at Year 1 in the Pivotal Phase 3 Trial of Gene Therapy for *RPE65* Variant-Associated Retinal Dystrophy

Outcomes	Intervention Mean (SD)	Control Mean (SD)	Difference (95% CI)	p
Primary outcome				
Bilateral MLMT change score	1.8 (1.1)	0.2 (1.0)	1.6 (0.72 to 2.41)	0.001
Secondary outcomes				
Bilateral FST change, log10 (cd.s/m²)	-2.08 (0.29)	0.04 (0.44)	-2.11 (-3.19 to 1.04)	0.000
First eye MLMT change score	1.9 (1.2)	0.2 (0.6)	1.7 (0.89 to 2.52)	0.001
Bilateral VA change, logMAR	-0.16 (SD NR)[a]	0.01 (SD NR)[b]	-0.16 (-0.41 to 0.08)	0.17
Other supportive outcomes				
Goldmann VF III4e change (sum total degrees)	302.1 (289.6)	-76.7 (258.7)	378.7 (145.5 to 612.0)	0.006
Humphrey VF, foveal sensitivity change, dB	2.4 (9.7)	2.3 (5.3)	0.04 (-7.1 to 7.2)	0.18
Humphrey VF, macula threshold change, dB	7.7 (6.2)	-0.2 (1.7)	7.9 (3.5 to 12.2)	0.001
Visual Function Questionnaire, subject	2.6 (1.8)	0.1 (1.4)	2.4 (1.0, 3.8)	0.001

CI: confidence interval; FST: full-field light sensitivity threshold; MLMT: Multi-Luminance Mobility Test; NR: not reported; SD: standard deviation; VA: visual acuity; VF: visual field.
[a] Corresponds to mean improvement of about 8 letters (ie, ≈1.5 lines).
[b] Corresponds to mean loss of about 1 letter.

The manufacturer briefing document reports results out to 2 years of follow-up. In the intervention group, both functional vision and visual function improvements were observed for at least 2 years. At year 1, all 9 control patients received bilateral injections of voretigene neparvovec. After receiving treatment, the control group experienced improvement in MLMT (change score, 2.1; standard deviation, 1.6) and FST (change, -2.86; standard deviation, 1.49). VA in the control group improved an average of 4.5 letters between years 1 and 2. Overall, 72% (21/29) of all treated patients achieved the maximum possible MLMT improvement at 1 year following injection.

Two patients (one in each group) experienced serious adverse events; both were unrelated to study participation. The most common ocular adverse events in the 20 patients treated with voretigene neparvovec were mild to moderate: elevated intraocular pressure, 4 (20%) patients; cataract, 3 (15%) patients; retinal tear, 2 (10%) patients; and eye inflammation, 2 (10%) patients. Several ocular adverse events occurred only in 1 patient each: conjunctival cyst, conjunctivitis, eye irritation, eye pain, eye pruritus, eye swelling, foreign body sensation, iritis, macular hold, maculopathy, pseudopapilledema, and retinal hemorrhage. One patient experienced a loss of VA (2.05 logMAR) in the first eye injected with voretigene

neparvovec; the eye was profoundly impaired at 1.95 logMAR (approximately 20/1783 on a Snellen chart) at baseline.

Early Phase Trials

Based on preclinical studies performed in animals, early phase studies of gene augmentation therapy for *RPE65*-associated Leber congenital amaurosis were initiated in 2007 by several independent groups of investigators. The initial reports of the results of these studies began to be published in 2008. The studies did not have an untreated control group, but several used a patient's untreated eye as a control. Characteristics of the studies are shown in Table 5. Most cohorts included in the studies have been followed in several publications. The baseline visual function, gene constructs, vector formulations, and surgical approaches used by different investigators have varied. Voretigene neparvovec was administered to the Children's Hospital of Pennsylvania (CHOP) cohort.

Table 5. Characteristics of Phase 1/2 studies of Gene Therapy for *RPE65* Variant-Associated Retinal Dystrophy

Cohort (Registration)	Author (Year)	Country/ Institution	Participants	Treatment	Follow-Up
Voretigene neparvovec					
CHOP (NCT00516477, NCT01208389)	Maguire (2008); Maguire (2009); Simonelli (2010); Ashtari (2011); Bennett (2012); Testa (2013); Ashtari (2015); Bennett (2016); Ashtari (2017)	U.S./Children's Hospital of Pennsylvania	• N=12 • Age range, 8-44 y • *RPE65*-associated LCA	• Vector: AAV2-hRPE65v2 • Administration: subretinal space of worse seeing eye • Vector dose: 1.5E10 to1.5E11 vg • Volume delivered: 0.15 mL • Systemic steroids: Yes • Contralateral eye treated with 1.5E11 vg during follow-up study	Up to 3 y
Other gene therapies					
London (NCT00643747)	Bainbridge (2008) Stieger (2010); Bainbridge (2015); Ripamonti (2015)	U.K./Moorfield's Eye Hospital; University College London	• N=12 • Age range, 6-23 y • Early-onset, *RPE65*-associated severe retinal dystrophy	• Vector: rAAV2/2- hRPE65p-hRPE65 • Administration: subretinal space of worse seeing eye • Vector dose: 1E11 • Volume delivered: 1.0 mL • Systemic steroids: Yes	Up to 3 y
Scheie/Shands (NCT00481546)	Hauswirth (2008); Cideciyan (2008); Cideciyan (2009); Jacobson (2012) Cideciyan (2013); Cideciyan (2014); Jacobson (2015)	U.S./Scheie Eye Institute of the University of Pennsylvania; Shands Children's Hospital, University of Florida	• N=15 • Age range, 10-36 y • *RPE65*-associated LCA	• Vector: rAAV2-CBSB-hRPE65 • Administration: subretinal space of worse seeing eye • Vector dose: 5.96E10 to 18E10 • Volume delivered: 0.15-0.30 mL • Systemic steroids: No	Up to 6 y
Israel (NCT00821340)	Banin (2010)	Israel/Hadassah-Hebrew University	• N=10	• Vector: rAAV2-CB-hRPE65 • Administration: subretinal space of worse seeing eye	3 y

Cohort (Registration)	Author (Year)	Country/ Institution	Participants	Treatment	Follow-Up
		Medical Center		• Vector dose: 1.19E10 • Volume delivered: 0.3 mL • Systemic steroids: No	
Casey/UMass (NCT00749957)	Weleber (2016)	U.S./Casey Eye Institute, Oregon Health & Science University; University of Massachusetts	• N=12 • Age range, 6-39 y • *RPE65*-associated LCA or SECORD	• Vector: rAAV2-CB-hRPE65 • Administration: subretinal space of worse seeing eye • Vector dose: 1.8E11 to 6E11 • Volume delivered: 0.45 mL • Systemic steroids: No	Up to 2 y
Nantes (NCT01496040)	Le Meur (2018)	France/Nantes University Hospital	• N=9 • Age range, 9-42 y • *RPE65*-associated LCA	• Vector: rAAV2/4-hRPE65 • Administration: subretinal space of worse seeing eye • Vector dose: 1.2E10 to 4.8E10 • Volume delivered: 0.20-0.80 mL • Systemic steroids: Yes	Up to 3.5 y

AAV: adeno-associated viruses; CHOP: Children's Hospital of Pennsylvania; vg: vector genomes; LCA: Leber congenital amaurosis; SECORD: severe early-childhood onset retinal degeneration; VA: visual acuity; vg: vector genomes.

Voretigene Neparvovec

CHOP Cohort

Several publications have described various outcomes and subgroups of the cohort included in the phase 1/2 studies of voretigene neparvovec. Early results showed improvement in subjective and objective measurements of vision (ie, dark adaptometry, pupillometry, electroretinography, nystagmus, ambulatory behavior). Although the samples were too small for subgroups analyses, the investigators noted that the greatest improvement appeared to be in children. Three-year follow-up of five of the first injected eyes (in patients from Italy) was reported. There was a statistically significant improvement in VA between baseline and 3 years ($p<0.001$). All patients maintained increased VF and a reduction of the nystagmus frequency compared with baseline. Three-year follow-up is also available for both the originally injected eye and contralateral eye in 11 patients. Statistically significant improvements in mean mobility and full-field light sensitivity persisted to year 3. The changes in VA were not significant. Ocular adverse events were mostly mild (dellen formation in 3 patients and cataracts in 2 patients). One patient developed bacterial endophthalmitis.

Long-term follow-up for safety was reported in the manufacturer's FDA briefing documents. This follow-up included the 12 patients in the phase 1 study as well as the 29 patients in the phase 3 study. Two phase 2 patients had 9 years of follow-up, 8 patients had 8 years of follow-up, and all 12 patients had at least 7 years of follow-up. Four phase 3 patients had 4 years of follow-up and the remaining patients had between 2 and 3 years of follow-up. No deaths occurred. The adverse events tended to occur early and diminish and resolve over time. While all patients experienced at least 1 adverse event, 85% of the adverse events reported were of mild or moderate intensity. Fourteen serious adverse events were reported by 9 patients, but none were assessed as related to the product; one was assessed as related to the administration procedure (retinal disorder) and another as related to a periocular steroid injection (increased intraocular pressure). Ocular adverse events that were assessed as related to treatment, required clinical

management, or impacted the benefit-risk profile occurred in 81 eyes (41 patients): macular disorders (9 eyes, 7 patients), increased intraocular pressure (10 eyes, 8 patients), retinal tear (4 eyes, 4 patients), infections/inflammation (5 eyes, 3 patients), and cataracts (16 eyes, 9 patients). Nine eyes in 7 patients had a 15-letter or more loss in VA. Four of the eyes had VA loss within a month of surgery, and the other 5 eyes had VA loss at or after the first year. No deleterious immune responses were observed in any patients.

Other Gene Therapies

London Cohort

At least 4 publications following the London cohort are available. Preliminary results showed increased retinal sensitivity in 1 of 3 participants. After 3 years of follow-up in all 12 patients, 2 patients had substantial improvements (10 to 100 times as high) in rod sensitivity that peaked around 12 months after treatment and then declined. There was no consistent improvement overall in VA. A decline in VA of 15 letters or more occurred in 2 patients. Intraocular inflammation and/or immune responses occurred in 5 of the 8 patients who received the higher dose and in 1 of 4 patients who received the lower dose. The immune response was deleterious in 1 patient.

Scheie/Shands Cohort

Results for patients in the Scheie/Shands cohort have also been reported in many publications. Visual function was reported to have improved in all patients. Dark-adapted FST showed highly significant increases from baseline in the treated eye and no change in the control eye. Cone and rod sensitivities improved significantly in the treated regions of the retina at 3 months, and these improvements were sustained through 3 years. Small improvements in VA were reported, and the improvement appeared to be largest in eyes with the lowest baseline acuities. Retinal detachment and persistent choroidal effusions were reported in 1 patient each; both were related to surgery. However, at a mean follow-up of 4.6 years, the investigators noted that while improvements in vision were maintained overall, the photoreceptors showed progressive degeneration. In 3 patients followed for 5 to 6 years, improvements in vision appeared to peak between 1 and 3 years after which there was a decline in the area of improved sensitivity in all 3 patients.

Israel Cohort

Although the registration for this study indicates that 10 patients were enrolled and followed for 3 years, only the short-term results of 1 patient have been reported. In that patient, there was an increase in vision as early as 15 days after treatment.

Casey/UMass Cohort

One publication has reported results for the Casey/UMass cohort. In 9 of 12 patients, there was improvement in one or more measures of visual function. VA increased in 5 patients, 30° VF hill of vision increased in 6 patients, total VF hill of vision increased in 5 patients, and kinetic VF area increased in 3 patients. The improvements persisted to 2 years in most patients. NEI VFQ-25 scores improved in 11 of 12 patients. Subconjunctival hemorrhage occurred in 8 patients, and ocular hyperemia occurred in 5 patients.

Nantes Cohort
One publication has described results of the Nantes cohort. In 8 of 9 patients, there was an improvement in VA of more than 2.5 letters at 1 year after injection; improvements were greatest for patients with a baseline VA between 7 and 31 letters and those with nystagmus. After 2 years of follow-up, the surface area of the VF had increased in 6 patients, decreased in 2 patients, and was the same in 1 patient. For the 6 patients with 3 years of follow-up, four continued to have improvements in VF.

SUMMARY OF EVIDENCE
For individuals who have vision loss due to biallelic *RPE65* variant-associated retinal dystrophy who receive gene therapy, the evidence includes randomized controlled trials and uncontrolled trials. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Biallelic *RPE65* variant-associated retinal dystrophy is a rare condition and, as such, it is recognized that there will be particular challenges in generating evidence, including recruitment for adequately powered randomized controlled trials, validation of novel outcome measures, and obtaining long-term data on safety and durability. There are no other FDA–approved pharmacologic treatments for this condition. One randomized controlled trial (N=31) comparing voretigene neparvovec with a control demonstrated greater improvements on the Multi-Luminance Mobility Test, which measures the ability to navigate in dim lighting conditions. Most other measures of visual function were also significantly improved in the voretigene neparvovec group compared with the control group. Adverse events were mostly mild to moderate. However, there is limited follow-up available. Therefore, the long-term efficacy and safety are unknown. Based on a small number of patients from early phase studies, voretigene neparvovec appears to have durable effects to at least 3 years. Other gene therapies tested in early phase trials have shown improvements in retinal function but variable durability of effect; some patients from 2 cohorts who initially experienced improvements have subsequently experienced declines after 1 to 3 years. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

References

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Code Type	Code
CPT	67299
HCPCS	C9399, J3490, J3590 Code added eff 7/1/18: C9032
ICD-10 Diagnosis	H35.50-H35.54

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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