BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.144 Gene Therapy for Inherited Retinal Dystrophy

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Related Policies:

9.03.15 - Retinal Prosthesis

Gene Therapy for Inherited Retinal Dystrophy

Description

Description

Inherited retinal dystrophy can be caused by recessive variants in the *RPE65* gene. Patients with biallelic variants have difficulty seeing in dim light and experience progressive loss of vision. These disorders are rare and have traditionally been considered untreatable. Gene therapy with an adeno-associated virus vector expressing *RPE65* has been proposed as a treatment to improve visual function.

OBJECTIVE

The objective of this evidence review is to determine whether gene augmentation therapy improves the net health outcome for patients with vision loss due to biallelic *RPE65* variant-associated retinal dystrophy.

POLICY STATEMENT

Adeno-associated virus vector-based gene therapy via subretinal injection with voretigene neparvovec is considered **medically necessary** for individuals with vision loss due to biallelic *RPE65* variant-associated retinal dystrophy if they meet all of the following criteria:

- Are adults (age <65 years) or children (age ≥3 years)
- Documentation of the following:
    - Genetic testing confirming presence of biallelic *RPE65* pathogenic variant(s) or likely pathogenic variants (see Policy Guidelines for additional details)
        - Single *RPE65* pathogenic variant or likely pathogenic variant found in the homozygous state
        - Two *RPE65* pathogenic variants or likely pathogenic variants found in the *trans* configuration (compound heterozygous state) by segregation analysis
    - 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.
- Do not have any of the following:
    - Pregnancy in females.
    - Breastfeeding.
    - Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the *RPE65* enzyme; individuals who discontinue use of these compounds for 18 months may become eligible.
    - Prior intraocular surgery within 6 months.
    - Preexisting eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of the study. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (eg, radiotherapy of the orbit; leukemia with central nervous system/optic nerve involvement). Subjects with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (eg, macular edema, proliferative changes). Also excluded would be subjects with immunodeficiency (acquired or congenital) because they could be susceptible to opportunistic infection (eg, cytomegalovirus retinitis).

Other applications of voretigene neparvovec are considered **investigational**.

POLICY GUIDELINES

The recommended dose of voretigene neparvovec-rzyl 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 voretigene neparvovec-rzyl to each eye must be performed on separate days within a close interval, but no fewer than 6 days apart.

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

Diagnosis of Biallelic RPE65-Mediated Inherited Retinal Dystrophies

Genetic testing is required to detect the presence of pathogenic or likely pathogenic variants in the *RPE65* gene in individuals with documented vision loss. By definition, pathogenic or likely pathogenic 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 (eg, the presence of the same pathogenic or likely pathogenic variant in both copies of the *RPE65* gene) establishes a diagnosis of biallelic *RPE65*-mediated dystrophinopathy.

However, if 2 different *RPE65* pathogenic or likely pathogenic variants are detected (eg, compound heterozygous state), confirmatory testing such as segregation analysis by family studies may be required to determine the *trans* versus *cis* configuration (eg, whether the 2 different pathogenic or likely pathogenic variants are found in different copies or in the same copy of the *RPE65* gene). The presence of 2 different *RPE65* pathogenic or likely pathogenic 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 or likely 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 (eg, *trans* vs.*cis* configuration) when 2 *RPE65* pathogenic or likely pathogenic 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 or likely pathogenic variant	Yes
Heterozygous (*trans* configuration)	*RPE65* gene copy #1 (- - - - - - **X** - - - - - -) *RPE65* gene copy #2 (- - - **O** - - - - - - - - -) **X**=*RPE65* pathogenic or likely pathogenic variant #1 **O**=*RPE65* pathogenic or likely pathogenic variant #2	Yes
Heterozygous (*cis* configuration)	*RPE65* gene copy #1 (- - **O** - - **X** - - - - - -) *RPE65* gene copy #2 (- - - - - - - - - - - - -) **X**=*RPE65* pathogenic or likely pathogenic variant #1 **O**=*RPE65* pathogenic or likely pathogenic variant #2	N

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society"s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

On December 19, 2017, the AAV2 gene therapy vector voretigene neparvovec-rzyl (Luxturna™; Spark Therapeutics) was approved by the U.S. Food and Drug Administration for use in patients with vision loss due to confirmed biallelic *RPE65* variant-associated retinal dystrophy.[14,] Spark Therapeutics received breakthrough therapy designation, rare pediatric disease designation, and orphan drug designation.

RATIONALE

Summary of Evidence

For individuals who have vision loss due to biallelic retinal pigment epithelium-specific protein 65-kD (*RPE65)* variant-associated retinal dystrophy who receive gene therapy, the evidence includes systematic reviews, randomized control trials (RCTs), 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. It is recognized that there will be particular challenges in generating evidence for this condition, including recruitment for adequately powered RCTs, validation of novel outcome measures, and obtaining longer-term data on safety and durability. While gene therapy with voretigene neparvovec is approved by the U.S. Food and Drug Administration U.S. (FDA), there are no other -approved pharmacologic treatments for this condition. A recent systematic review found statistically significant improvements in full-field stimulus threshold (FST) test and Multi-Luminance Mobility Test (MLMT) from gene therapy for *RPE65*-mediated retinal dystrophies; the most common adverse events included ocular hypertension/intraocular pressure increase and ocular pain/discomfort. Another systematic review on gene therapy for *RPE65*-associated Leber congenital amaurosis (LCA) found an improvement in FST, but not in mobility, visual acuity (VA), or central retinal thickness, while a third systematic review that included the same studies found an improvement of VA and FST for up to 2 years after treatment. One RCT (N=31) comparing voretigene neparvovec with a control demonstrated greater improvements on the MLMT, 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 and the long-term efficacy and safety are unknown. Based on a small number of patients from both early and phase 3 studies, voretigene neparvovec appears to have durable effects to at least 4 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 an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Institute for Health and Care Excellence

In 2019, NICE published guidance for the use of voretigene neparvovec (Luxturna) in the treatment of inherited retinal dystrophies caused by *RPE65* gene mutations.[53,] The treatment is recommended for individuals with vision loss caused by inherited retinal dystrophy from confirmed biallelic *RPE65* mutations who have sufficient viable retinal cells. Despite uncertainty surrounding long-term durability, the committee felt this intervention is likely to provide important clinical benefits for individuals afflicted with inherited retinal dystrophies.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet. Nov 18 2006; 368(9549): 1795-809. PMID 17113430
2. O'Neal TB, Luther EE. Retinitis Pigmentosa. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 8, 2022.
3. Jin M, Li S, Moghrabi WN, et al. Rpe65 is the retinoid isomerase in bovine retinal pigment epithelium. Cell. Aug 12 2005; 122(3): 449-59. PMID 16096063
4. Naso MF, Tomkowicz B, Perry WL, et al. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. BioDrugs. Aug 2017; 31(4): 317-334. PMID 28669112
5. Stone EM. Leber congenital amaurosis - a model for efficient genetic testing of heterogeneous disorders: LXIV Edward Jackson Memorial Lecture. Am J Ophthalmol. Dec 2007; 144(6): 791-811. PMID 17964524
6. Koenekoop RK. An overview of Leber congenital amaurosis: a model to understand human retinal development. Surv Ophthalmol. 2004; 49(4): 379-98. PMID 15231395
7. den Hollander AI, Roepman R, Koenekoop RK, et al. Leber congenital amaurosis: genes, proteins and disease mechanisms. Prog Retin Eye Res. Jul 2008; 27(4): 391-419. PMID 18632300
8. Astuti GD, Bertelsen M, Preising MN, et al. Comprehensive genotyping reveals RPE65 as the most frequently mutated gene in Leber congenital amaurosis in Denmark. Eur J Hum Genet. Jul 2016; 24(7): 1071-9. PMID 26626312
9. Kumaran N, Moore AT, Weleber RG, et al. Leber congenital amaurosis/early-onset severe retinal dystrophy: clinical features, molecular genetics and therapeutic interventions. Br J Ophthalmol. Sep 2017; 101(9): 1147-1154. PMID 28689169
10. Morimura H, Fishman GA, Grover SA, et al. Mutations in the RPE65 gene in patients with autosomal recessive retinitis pigmentosa or leber congenital amaurosis. Proc Natl Acad Sci U S A. Mar 17 1998; 95(6): 3088-93. PMID 9501220
11. FDA Advisory Committee Briefing Document: Spark Therapeutics, Inc, LuxturnaTM (voretigene neparvovec). 2017; https://www.fda.gov/media/108385/download. Accessed November 11, 2022.
12. Vzquez-Domnguez I, Garanto A, Collin RWJ. Molecular Therapies for Inherited Retinal Diseases-Current Standing, Opportunities and Challenges. Genes (Basel). Aug 28 2019; 10(9). PMID 31466352
13. Campa C, Gallenga CE, Bolletta E, et al. The Role of Gene Therapy in the Treatment of Retinal Diseases: A Review. Curr Gene Ther. 2017; 17(3): 194-213. PMID 29149824
14. Food and Drug Administration (FDA). FDA News Release: FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. 2017; https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss. Accessed November 11, 2022.
15. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. Aug 26 2017; 390(10097): 849-860. PMID 28712537
16. Beck RW, Maguire MG, Bressler NM, et al. Visual acuity as an outcome measure in clinical trials of retinal diseases. Ophthalmology. Oct 2007; 114(10): 1804-9. PMID 17908590
17. Bittner AK, Gould JM, Rosenfarb A, et al. A pilot study of an acupuncture protocol to improve visual function in retinitis pigmentosa patients. Clin Exp Optom. May 2014; 97(3): 240-7. PMID 24773463
18. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. Nov 2001; 108(11): 1943-53. PMID 11713061
19. Gillespie BW, Musch DC, Niziol LM, et al. Estimating minimally important differences for two vision-specific quality of life measures. Invest Ophthalmol Vis Sci. Jun 06 2014; 55(7): 4206-12. PMID 24906863
20. Submacular Surgery Trials Research Group. Evaluation of minimum clinically meaningful changes in scores on the National Eye Institute Visual Function Questionnaire (NEI-VFQ) SST Report Number 19. Ophthalmic Epidemiol. 2007; 14(4): 205-15. PMID 17896299
21. Chung DC, McCague S, Yu ZF, et al. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. Clin Exp Ophthalmol. Apr 2018; 46(3): 247-259. PMID 28697537
22. Britten-Jones AC, Jin R, Gocuk SA, et al. The safety and efficacy of gene therapy treatment for monogenic retinal and optic nerve diseases: A systematic review. Genet Med. Mar 2022; 24(3): 521-534. PMID 34906485
23. Le Meur G, Lebranchu P, Billaud F, et al. Safety and Long-Term Efficacy of AAV4 Gene Therapy in Patients with RPE65 Leber Congenital Amaurosis. Mol Ther. Jan 03 2018; 26(1): 256-268. PMID 29033008
24. Jacobson SG, Cideciyan AV, Ratnakaram R, et al. Gene therapy for leber congenital amaurosis caused by RPE65 mutations: safety and efficacy in 15 children and adults followed up to 3 years. Arch Ophthalmol. Jan 2012; 130(1): 9-24. PMID 21911650
25. Maguire AM, High KA, Auricchio A, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. Lancet. Nov 07 2009; 374(9701): 1597-605. PMID 19854499
26. Maguire AM, Russell S, Wellman JA, et al. Efficacy, Safety, and Durability of Voretigene Neparvovec-rzyl in RPE65 Mutation-Associated Inherited Retinal Dystrophy: Results of Phase 1 and 3 Trials. Ophthalmology. Sep 2019; 126(9): 1273-1285. PMID 31443789
27. Bainbridge JW, Mehat MS, Sundaram V, et al. Long-term effect of gene therapy on Leber's congenital amaurosis. N Engl J Med. May 14 2015; 372(20): 1887-97. PMID 25938638
28. Weleber RG, Pennesi ME, Wilson DJ, et al. Results at 2 Years after Gene Therapy for RPE65-Deficient Leber Congenital Amaurosis and Severe Early-Childhood-Onset Retinal Dystrophy. Ophthalmology. Jul 2016; 123(7): 1606-20. PMID 27102010
29. Wang X, Yu C, Tzekov RT, Zhu Y, Li W. The effect of human gene therapy for RPE65-associated Lebers congenital amaurosis on visual function: a systematic review and meta-analysis. Orphanet J Rare Dis. 2020;15(1):49.
30. Tuohy GP, Megaw R. A Systematic Review and Meta-Analyses of Interventional Clinical Trial Studies for Gene Therapies for the Inherited Retinal Degenerations (IRDs). Biomolecules. May 19 2021; 11(5). PMID 34069580

31. Testa F, Maguire AM, Rossi S, et al. Three-year follow-up after unilateral subretinal delivery of adeno-associated virus in patients with Leber congenital Amaurosis type 2. Ophthalmology. Jun 2013; 120(6): 1283-91. PMID 23474247
32. Maguire AM, Russell S, Chung DC, et al. Durability of Voretigene Neparvovec for Biallelic RPE65-Mediated Inherited Retinal Disease: Phase 3 Results at 3 and 4 Years. Ophthalmology. Oct 2021; 128(10): 1460-1468. PMID 33798654
33. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. N Engl J Med. May 22 2008; 358(21): 2240-8. PMID 18441370
34. Simonelli F, Maguire AM, Testa F, et al. Gene therapy for Leber's congenital amaurosis is safe and effective through 1.5 years after vector administration. Mol Ther. Mar 2010; 18(3): 643-50. PMID 19953081
35. Ashtari M, Cyckowski LL, Monroe JF, et al. The human visual cortex responds to gene therapy-mediated recovery of retinal function. J Clin Invest. Jun 2011; 121(6): 2160-8. PMID 21606598
36. Bennett J, Ashtari M, Wellman J, et al. AAV2 gene therapy readministration in three adults with congenital blindness. Sci Transl Med. Feb 08 2012; 4(120): 120ra15. PMID 22323828
37. Ashtari M, Zhang H, Cook PA, et al. Plasticity of the human visual system after retinal gene therapy in patients with Leber's congenital amaurosis. Sci Transl Med. Jul 15 2015; 7(296): 296ra110. PMID 26180100
38. Bennett J, Wellman J, Marshall KA, et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial. Lancet. Aug 13 2016; 388(10045): 661-72. PMID 27375040
39. Ashtari M, Nikonova ES, Marshall KA, et al. The Role of the Human Visual Cortex in Assessment of the Long-Term Durability of Retinal Gene Therapy in Follow-on RPE65 Clinical Trial Patients. Ophthalmology. Jun 2017; 124(6): 873-883. PMID 28237426
40. Bainbridge JW, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med. May 22 2008; 358(21): 2231-9. PMID 18441371
41. Stieger K. tgAAG76, an adeno-associated virus delivered gene therapy for the potential treatment of vision loss caused by RPE65 gene abnormalities. Curr Opin Mol Ther. Aug 2010; 12(4): 471-7. PMID 20677098
42. Ripamonti C, Henning GB, Robbie SJ, et al. Spectral sensitivity measurements reveal partial success in restoring missing rod function with gene therapy. J Vis. 2015; 15(15): 20. PMID 26605849
43. Hauswirth WW, Aleman TS, Kaushal S, et al. Treatment of leber congenital amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: short-term results of a phase I trial. Hum Gene Ther. Oct 2008; 19(10): 979-90. PMID 18774912
44. Cideciyan AV, Aleman TS, Boye SL, et al. Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics. Proc Natl Acad Sci U S A. Sep 30 2008; 105(39): 15112-7. PMID 18809924
45. Cideciyan AV, Hauswirth WW, Aleman TS, et al. Human RPE65 gene therapy for Leber congenital amaurosis: persistence of early visual improvements and safety at 1 year. Hum Gene Ther. Sep 2009; 20(9): 999-1004. PMID 19583479
46. Cideciyan AV, Hauswirth WW, Aleman TS, et al. Vision 1 year after gene therapy for Leber's congenital amaurosis. N Engl J Med. Aug 13 2009; 361(7): 725-7. PMID 19675341
47. Cideciyan AV, Jacobson SG, Beltran WA, et al. Human retinal gene therapy for Leber congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement. Proc Natl Acad Sci U S A. Feb 05 2013; 110(6): E517-25. PMID 23341635
48. Cideciyan AV, Aguirre GK, Jacobson SG, et al. Pseudo-fovea formation after gene therapy for RPE65-LCA. Invest Ophthalmol Vis Sci. Dec 23 2014; 56(1): 526-37. PMID 25537204
49. Jacobson SG, Cideciyan AV, Roman AJ, et al. Improvement and decline in vision with gene therapy in childhood blindness. N Engl J Med. May 14 2015; 372(20): 1920-6. PMID 25936984
50. Banin E, Bandah-Rozenfeld D, Obolensky A, et al. Molecular anthropology meets genetic medicine to treat blindness in the North African Jewish population: human gene therapy initiated in Israel. Hum Gene Ther. Dec 2010; 21(12): 1749-57. PMID 20604683
51. Pennesi ME, Weleber RG, Yang P, et al. Results at 5 Years After Gene Therapy for RPE65-Deficient Retinal Dystrophy. Hum Gene Ther. Dec 2018; 29(12): 1428-1437. PMID 29869534
52. Spark Therapeutics. FDA Advisory Committee Briefing Document: Spark Therapeutics, Inc, LuxturnaTM (voretigene neparvovec). 2017; https://www.fda.gov/media/108385/download. Accessed November 11, 2022.
53. National Institute for Health and Care Excellence (NICE). Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [HST11]. October 9, 2019. http://nice.org.uk/guidance/hst11. Accessed November 11, 2022.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New policy	Policy updated with literature review through November 10, 2022; reference added. Minor editorial refinements to policy statements; intentunchanged. FEP 2024 Benefit updates. FEP new policy.