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MEDICAL POLICY – 2.04.144

Gene Therapy for Inherited Retinal Dystrophy

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Select a hyperlink below to be directed to that section.

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RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

The retina is found at the back of the eye. It is made up of several layers. One of these layers contains cells called rods and cones. The rods and cones are stimulated when light enters our eyes. They convert the light energy into chemicals, which then create an electrical signal. The optic nerve sends the electrical signal to the brain. Many steps are required for this process to work correctly. One of these steps involves a protein called RPE65. This protein helps make some of the chemical changes that happen in the retina. A specific gene tells the body how to make this protein. If that gene is not normal, the protein cannot be made. The person without this protein will have visual problems called retinal dystrophy and can become blind, even at an early age. Changes in the RPE65 gene are rare. A new treatment uses an engineered virus to insert a healthy copy of the gene into the retinal cells. This treatment requires a genetic test to confirm the specific type of retinal dystrophy. Treatment also requires a specific amount of healthy retina to be available. This policy describes when this treatment may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Therapy	Medical Necessity
Luxturna (voretigene neparvovec-rzyl)	**Luxturna (voretigene neparvovec-rzyl), an adeno-associated virus vector-based gene therapy given via subretinal injection, is considered medically necessary for individuals with vision loss due to biallelic RPE65 variant-associated retinal dystrophy when ALL the following criteria are met:** • Adults aged less than 65 years or children aged 3 years or older) **AND** • Documentation of the following: ○ Genetic testing confirms presence of biallelic RPE65 pathogenic variant(s) or likely pathogenic variants (see **Related Information** below 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 **AND** ○ Viable retinal cells as determined by treating physicians as assessed by optical coherence tomography imaging and/or ophthalmoscopy are present: ▪ An area of retina within the posterior pole of >100 µm thickness shown on optical coherence tomography OR ▪ 3 or more 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** • None of the following are present: ○ Pregnancy in females ○ Breastfeeding

Therapy	Medical Necessity
	○ 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 study. Complicating systemic diseases 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 (e.g., radiotherapy of the orbit; leukemia with central nervous system/optic nerve involvement). Subjects with diabetes or sickle cell disease are excluded if they have any manifestation of advanced retinopathy (e.g., macular edema, proliferative changes). Subjects with immunodeficiency (acquired or congenital) because they could be susceptible to opportunistic infection (e.g., cytomegalovirus retinitis) are also excluded.

Drug	Investigational
As listed	**Other applications of Luxturna (voretigene neparvovec-rzyl), including re-treatment of previously treated individuals, are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for Luxturna (voretigene neparvovec-rzyl) may be approved up to 12 months.**

Length of Approval	
Approval	**Criteria**
	All other reviews for Luxturna (voretigene neparvovec-rzyl) may be approved as a one-time per eye treatment.
Re-authorization criteria	**Repeat treatment of Luxturna (voretigene neparvovec-rzyl) is considered investigational.**

Recommended Dosage and Quantity Limits

- 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

Documentation Requirements

The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

Clinical documentation of ALL the following for adults (age <65 years) or children (age ≥3 years):

- Genetic testing result confirms presence of pathogenic variant(s) or likely pathogenic variants in both copies of the RPE65 gene:
  - 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
- Optical coherence tomography imaging and/or ophthalmoscopy demonstrates the individual has viable retinal cells as determined by the following:
  - An area of retina within the posterior pole of >100 µm thickness shown on optical coherence tomography

  OR
  - Three or more-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

Documentation Requirements

- Absence of 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 include the following:
    - When the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (e.g., radiotherapy of the orbit; leukemia with central nervous system/optic nerve involvement)
    - Individuals with diabetes or sickle cell disease are excluded if they have any manifestation of advanced retinopathy (e.g., macular edema, proliferative changes)
    - Individuals with immunodeficiency (acquired or congenital) because they could be susceptible to opportunistic infection (e.g., cytomegalovirus retinitis) are also excluded.

Coding

Code	Description
CPT	
67036	Vitrectomy, mechanical, pars plana approach;
67299	Unlisted procedure, posterior segment (used to report Luxturna injection)
Code	**Description**
HCPCS	
J3398	Injection, voretigene neparvovec-rzyl (Luxturna), 1 billion vector genomes

Related Information

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

However, if 2 different RPE65 pathogenic or likely pathogenic variants are detected (e.g., compound heterozygous state), confirmatory testing such as segregation analysis by family studies may be required to determine the trans versus cis configuration (e.g., whether the two different pathogenic or likely pathogenic variants are found in different copies or in the same copy of the RPE65 gene). The presence of two 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 two different RPE65 pathogenic or likely pathogenic variants in only one 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 versus cis configuration) when two 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 1** provides a visual representation of the genetic status requirements to establish a diagnosis of RPE65-mediated inherited retinal dystrophy.

Table 1. 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	No

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 2**). 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 3** shows the recommended

standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table 2. 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 3. 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.

Consideration of Age

Luxturna (voretigene neparvovec) is indicated for treatment of individuals aged 3 and older. The manufacturer recommends that it not be used in children less than 1 year old, because their retinal cells are still dividing, and subsequently formed cells will not incorporate the voretigene DNA. The safety and effectiveness of Luxturna have not been established in geriatric individuals. Clinical studies of Luxturna did not include individuals aged 65 years and over.

Benefit Application

Luxturna (voretigene neparvovec) is administered by a complex intraocular surgical procedure. It is managed under the Medical benefit.

Evidence Review

Description

Inherited retinal dystrophy can be caused by recessive variants in the RPE65 gene. Individuals with biallelic variants have difficulty seeing in dim light and have a 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.

Background

Inherited Retinal Dystrophies

Inherited retinal dystrophies are a diverse group of disorders with overlapping phenotypes characterized by progressive degeneration and dysfunction of the retina.[1] The most common subgroup is retinitis pigmentosa, which is characterized by a loss of retinal photoreceptors, both

cones and rods.[2] The hallmark of the condition 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.

RPE65 Gene

Retinitis pigmentosa (RP) and Leber congenital amaurosis (LCA) both have subtypes related to pathogenic variants in RPE65. The RPE65 (retinal pigment epithelium-specific protein 65-kD) gene encodes the RPE65 protein, which is an all-trans retinal isomerase, a key enzyme expressed in the retinal pigment epithelium (RPE) that is responsible for regeneration of 11-cis-retinol in the visual cycle.[3] The RPE65 gene is located on the short (p) arm of chromosome 1 at position 31.3 (1p31.3). Individuals with biallelic variations in RPE65 lack the RPE65 enzyme; this lack leads to build-up of toxic precursors and damage to RPE cells, loss of photoreceptors, and eventually complete blindness.[4]

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.[5,6] LCA subtype 2 (RPE65-associated LCA) accounts for between 5% and 16% of cases of LCA.[5,7-9] The prevalence of RP in the United States is approximately 1 in 4000[2], with approximately 1% of individuals with RP having RPE65 variants.[10] **Table 4** summarizes the estimated pooled prevalence of RPE-associated inherited retinal dystrophy and the range of estimated cases based on the estimated 2017 United States population.

Table 4. Estimated Pooled Prevalence of RPE65-Associated Inherited Retinal Dystrophy and Estimated Number of Individuals

Description	Low	High
Estimated pooled prevalence of RPE65-mediated inherited retinal dystrophies (e.g., LCA type 2, RPE65-mediated RP)	1:330,000	1:130,000
Estimated number of individuals	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, for example, 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 individual.[4] There are over 100 different AAVs, and 12 serotypes have been identified so far, labeled AAV1 to AAV12; of these, AAV2, AAV5, and AAV8 have been most extensively studied in ocular gene therapies.[11]. The recombinant AAV2 is the most used AAV serotype in gene therapy.[12]

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.

Summary of Evidence

For individuals with vision loss due to biallelic RPE65 variant-associated retinal dystrophy who receive gene therapy, the evidence includes systematic reviews, randomized controlled 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 long-term data on safety and durability. While gene therapy with voretigene neparvovec is approved by the U.S. Food and Drug Administration (FDA), there are no other approved pharmacologic treatments for this condition. A recent systematic review found statistically significant improvements in full-field stimulus threshold test (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 two 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. Therefore, the long-term efficacy and safety are unknown. Based on a small number of individuals from both early and phase three studies, voretigene neparvovec appears to have durable effects to at least four years. Other gene therapies tested in early phase trials have shown improvements in retinal function but variable durability of effect; some individuals from two cohorts who initially experienced improvements have subsequently experienced declines after one to three years. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Interest in gene therapy for inherited retinal dystrophies has grown enormously in recent years; numerous gene therapy treatments (with various targets) are now in different stages of clinical development. Some currently ongoing and unpublished trials that might influence this review are listed in **Table 5**.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04123626[a]	A Prospective First-In-Human Study to Evaluate the Safety and Tolerability of QR-1123 in Subjects With Autosomal Dominant Retinitis Pigmentosa (adRP) Due to the P23H Mutation in the RHO Gene (AURORA)	11	Jun 2022 (ongoing)
NCT03913143[a]	Double-masked, Randomized, Controlled, Multiple-dose Study to Evaluate Efficacy, Safety, Tolerability and Syst. Exposure of QR-110 in Leber's Congenital Amaurosis (LCA) Due to c.2991+1655A>G Mutation (p.Cys998X) in the CEP290 Gene (ILLUMINATE)	36	Mar 2023 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04671433[a]	Phase 3 Randomized, Controlled Study of AAV5-RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	97	Sep 2024
NCT03597399[a]	A Post-Authorization, Multicenter, Longitudinal, Observational Safety Registry Study for Patients Treated with Voretigene Neparvovec in US	87	Jun 2025 (ongoing)
NCT03328130[a]	Safety and Efficacy of a Unilateral Subretinal Administration of HORA-PDE6B in Patients with Retinitis Pigmentosa Harbouring Mutations in the PDE6B Gene Leading to a Defect in PDE6ß Expression	23	Dec 2029 (recruiting)
NCT03316560[a]	An Open-Label Dose Escalation Study to Evaluate the Safety and Efficacy of AGTC-501 (rAAV2tYF-GRK1-RPGR) in Subjects With X-linked Retinitis Pigmentosa Caused by RPGR Mutations	29	Mar 2025
NCT00481546	Phase I Trial of Ocular Subretinal Injection of a Recombinant Adeno-Associated Virus (rAAV2-CBSB-hRPE65) Gene Vector to Patients with Retinal Disease Due to RPE65 Mutations (Clinical Trials of Gene Therapy for Leber Congenital Amaurosis) (LCA)	15	Jun 2026 (ongoing)
NCT04794101[a]	Follow-up Phase 3 Randomized, Controlled Study of AAV5-RPGR for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	97	Sep 2029
NCT04517149[a]	An Open-Label, Phase 1/2 Trial of Gene Therapy 4D-125 in Males With X-linked Retinitis Pigmentosa (XLRP) Caused by Mutations in the RPGR Gene	21	May 2029 (ongoing)
NCT00999609[a]	A Safety and Efficacy Study in Subjects with Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-301]	31	Jul 2029 (ongoing)
NCT03602820[a]	A Long-Term Follow-Up Study in Subjects Who Received an Adenovirus-Associated Viral Vector Serotype 2 Containing the Human RPE65 Gene (AAV2-hRPE65v2, Voretigene Neparvovec-rzyl) Administered Via Subretinal Injection	41	Jun 2030 (ongoing)
NCT01208389[a]	A Follow-On Study to Evaluate the Safety of Re-Administration of Adeno-Associated Viral Vector Containing the Gene for Human RPE65 [AAV2-hRPE65v2] to the Contralateral Eye in Subjects With Leber Congenital Amaurosis (LCA) Previously Enrolled in a Phase 1 Study	12	Jun 2030 (ongoing)

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02435940	Foundation Fighting Blindness Registry, My Retina Tracker	20,000	Jun 2037 (recruiting)
Unpublished			
NCT02946879[a]	Long-term Follow-up Study of Participants Following an Open-Label, Multi-centre, Phase I/II Dose Escalation Trial of an Adeno-associated Virus Vector (AAV2/5-OPTIRPE65) for Gene Therapy of Adults and Children with Retinal Dystrophy Owing to Defects in RPE65 (LCA2)	14	Jun 2023 (completed)
NCT03252847[a]	An Open-Label, Multi-centre, Phase I/II Dose Escalation Trial of a Recombinant Adeno-associated Virus Vector (AAV2-.RPGR) for Gene Therapy of Adults and Children With X-linked Retinitis Pigmentosa Owing to Defects in Retinitis Pigmentosa GTPase Regulator (RPGR)	49	Nov 2021 (completed)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion 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, the 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.

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

On December 19, 2017, the AAV2 gene therapy vector voretigene neparvovec-rzyl (Luxturna Spark Therapeutics) was approved by the FDA for use in individuals with vision loss due to confirmed biallelic RPE65 variant-associated retinal dystrophy.[13] Spark Therapeutics received breakthrough therapy designation, rare pediatric disease designation, and orphan drug designation.

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History

Date	Comments
11/01/18	New policy, approved October 9, 2018. This policy replaced policy 8.01.536. Voretigene neparvovec-rzyl adeno-associated virus vector-based gene therapy subretinal injection (Luxturna) is considered medically necessary for individuals with vision loss due to biallelic RPE65 variant-associated retinal dystrophy meeting criteria.
01/15/19	Coding update, added HCPCS code J3398 (new code effective 1/1/19).
04/01/19	Annual Review, approved March 19, 2019. Policy updated with literature review through December 2018; no references added. Policy statements unchanged. Removed unlisted HCPC codes J3490 and J3590.
08/20/19	Minor formatting updates only.
07/01/20	Annual Review, approved June 18, 2020. Policy updated with literature review through June 2020 and references were updated. Policy criteria updated to include coverage for "likely pathogenic variants" in the RPE65 gene.
03/01/21	Annual Review, approved February 18, 2021. Policy updated with literature review through October 19, 2020; references added. Policy statements unchanged.
04/01/22	Annual Review, approved March 7, 2022. Policy updated with literature review through December 8, 2021; reference added. Policy statements unchanged.
04/01/23	Annual Review, approved March 6, 2023. Policy updated with literature review through November 10, 2022; reference added. Minor editorial refinements to policy statements;

Date	Comments
	intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/24	Annual Review, approved March 25, 2024. Policy updated with literature review through November 17, 2023; reference added. Policy statements unchanged except for minor edits; policy intent unchanged. Added CPT code 67036 and 67299.
07/01/24	Minor correction with no changes to policy statements.
05/01/25	Annual Review, approved April 21, 2025. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.