MASSACHUSETTS

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Medical Policy

Gene Therapy for Inherited Retinal Dystrophy

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Policy Number: 911

BCBSA Reference Number: 2.04.144
NCD/LCD: NA

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Preauthorization Request Form: Gene Therapy for Inherited Retinal Dystrophy
This form must be completed and faxed to: Medical and Surgical: 1-888-282-0780; Medicare Advantage: 1-800-447-2994.
Click here for Gene Therapy for Inherited Retinal Dystrophy Preauthorization Request Form, #926

Voretigene neparvovec-rzyl adeno-associated virus vector-based gene therapy subretinal injection is considered **MEDICALLY NECESSARY** for patients with vision loss due to biallelic *RPE65* pathogenic or likely pathogenic[1] 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 bilallelic RPE65 pathogenic or likely pathogenic[1] variant(s)*
    - Single RPE65 pathogenic or likely pathogenic[1] variant found in the homozygous state
    - Two RPE65 pathogenic or likely pathogenic[1] 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

        - Any remaining visual field within 30° of fixation as measured by III4e/V4e isopter equivalent, OR
        - Measureable full-field light sensitivity threshold (FST).
- Do not have any of the following:
    - Pregnancy in females.
    - Breastfeeding.
    - Use of prescription retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme; individuals who discontinue use of these compounds for 3 months may become eligible.
    - Prior intraocular surgery within 3 months.
    - Preexisting eye conditions or complicating systemic diseases that would eventually lead to irreversible vision loss and prevent the patient from receiving full benefit from Voretigene neparvovec-rzyl (eg, leukemia with central nervous system/optic nerve involvement, severe diabetic retinopathy).
    - Patients with immunodeficiency (acquired or congenital) because they could be susceptible to opportunistic infection (eg, cytomegalovirus retinitis).

***Diagnosis of Biallelic *RPE65*-Mediated Inherited Retinal Dystrophies**
Genetic testing is required to detect the presence of pathogenic(s) variants in the *RPE65* gene. By definition, 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 variant found in the homozygous state (eg, 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* pathogenic 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* 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 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 two *RPE65* 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 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 (- - - - - - - - - - - - -)	**No**

	X=RPE65 pathogenic variant #1 O=RPE65 pathogenic variant #2	

Other applications of voretigene neparvovec-rzyl are considered **INVESTIGATIONAL**.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	*Prior authorization is **required**.
Commercial PPO and Indemnity	*Prior authorization is **required**.
Medicare HMO Blue℠	*Prior authorization is **required**.
Medicare PPO Blue℠	*Prior authorization is **required**.

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CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

HCPCS Codes

HCPCS codes:	Code Description
C9399	Unclassified drugs or biological
J3398	Injection, voretigene neparvovec-rzyl, 1 billion vector genomes
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
3E0C3GC	Introduction of Other Therapeutic Substance into Eye, Percutaneous Approach
3E0CXGC	Introduction of Other Therapeutic Substance into Eye, External Approach

Description

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. 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*. *RPE65* (retinal pigment epithelium-specific protein 65-kD) gene encodes the RPE54 protein 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. [2,]

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.[3,]

Epidemiology

RPE65-associated inherited retinal dystrophy is rare. The prevalence of LCA has been estimated to be between 1 in 33000 and 1 in 81000 individuals in the United States.[4,5,] LCA subtype 2 (*RPE65*-associated LCA) accounts for between 5% and 16% of cases of LCA.[4,6,7,8,] 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.[10,] Assuming a United States population of approximately 326.4 million at the end of 2017,[11,] 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 United States 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.[12,] 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.[3,] 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.[13,]

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

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

For individuals who have vision loss due to biallelic *RPE65* variant-associated retinal dystrophy who receive gene therapy, the evidence includes 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 and, as such, it is recognized that there will be particular challenges in generating evidence, including recruitment for adequately powered RCTs, validation of novel outcome measures, and obtaining longer-term data on safety and durability. There are no other FDA-approved pharmacologic treatments for this condition. One RCT (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 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 a meaningful improvement in the net health outcome.

Policy History

Date	Action
3/2020	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
3/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2019	Clarified coding information.
9/2018	Policy criteria clarified. 9/13/2018
7/2018	Clarified coding information.
2/1/2018	New medical policy describing medically necessary and investigational indications. Effective 2/1/2018.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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Endnotes

[1] Based on expert opinion and MPRM #2.04.144