MEDICAL POLICY – 2.04.144
Gene Therapy for Inherited Retinal Dystrophy

BCBSA Ref. Policy: 2.04.144
Effective Date: April 1, 2019
Last Revised: March 19, 2019
Replaces: 8.01.536

RELATED MEDICAL POLICIES: None

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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 that there is a specific amount of healthy retina 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

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Voretigene neaparovvec-rzyl adenovirus vector-based gene therapy subretinal injection [Luxturna™ (voretigene neaparovvec)] | Voretigene neaparovvec-rzyl adenovirus vector-based gene therapy subretinal injection is considered medically necessary for patients 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) (see Related Information below for additional details)  
      - Single RPE65 pathogenic variant found in the homozygous state  
      - Two RPE65 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  
      - ≥3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole  
      - 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 |
Therapy  |  Medical Necessity
---|---
- 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 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 Luxturna™ (voretigene neparvovec-rzyl), including re-treatment of previously treated individuals, are considered investigational.

**Recommended Dosage and Quantity Limits**
- The recommended dose of voretigene neparvovec-rzyl for each eye is $1.5 \times 10^{11}$ 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) 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 patient’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 of the following for adults (age <65 years) or children (age ≥3 years):
Documentation Requirements

- Genetic testing result confirming presence pathogenic variant(s) in both copies of the RPE65 gene:
  - Single RPE65 pathogenic variant found in the homozygous state
  - Two RPE65 pathogenic variants found in the trans configuration (compound heterozygous state) by segregation analysis

- Optical coherence tomography imaging and/or ophthalmoscopy determines the patient has viable retinal cells:
  - An area of retina within the posterior pole of >100 μm thickness shown on optical coherence tomography
  - Three or more disc areas of retina without atrophy or pigmentary degeneration within the posterior pole
  - Remaining visual field within 30° of fixation as measured by III4e isopter or equivalent

- 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 study. Complicating systemic diseases would include:
    - 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 (eg, radiotherapy of the orbit; leukemia with central nervous system/optic nerve involvement)
    - Patients with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (eg, macular edema, proliferative changes)
    - Patients with immunodeficiency (acquired or congenital) because they could be susceptible to opportunistic infection (eg, cytomegalovirus retinitis)
### Related Information

#### 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 heterozygous 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 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

<table>
<thead>
<tr>
<th>Genetic Status</th>
<th>Diagram</th>
<th>Diagnosis of RPE65-Mediated Inherited Retinal Dystrophy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous</td>
<td>RPE65 gene copy #1 (- - - - - X - - - - -)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>RPE65 gene copy #2 (- - - - - X - - - - -)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X=single RPE65 pathogenic variant</td>
<td></td>
</tr>
<tr>
<td>Heterozygous (trans configuration)</td>
<td>RPE65 gene copy #1 (- - - - - X - - - - -)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>RPE65 gene copy #2 (- - O - - - - - -)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X=RPE65 pathogenic variant #1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O=RPE65 pathogenic variant #2</td>
<td></td>
</tr>
<tr>
<td>Heterozygous (cis configuration)</td>
<td>RPE65 gene copy #1 (- - O - - X - - - - -)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>RPE65 gene copy #2 (- - - - - - - - -)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X=RPE65 pathogenic variant #1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O=RPE65 pathogenic variant #2</td>
<td></td>
</tr>
</tbody>
</table>

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 (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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, 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 patients age 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 patients. Clinical studies of Luxturna for did not include patients age 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. Patients 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. 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 33,000 and 1 in 81,000 individuals in the United States.\(^4,5\) LCA subtype 2 (RPE65-associated LCA) accounts for between 5% and 16% of cases of LCA.\(^4,6-8\) 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 U.S. 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 4 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>
<thead>
<tr>
<th>Description</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated pooled prevalence of RPE65-mediated inherited retinal dystrophies (eg, LCA type 2, RPE65-mediated RP)</td>
<td>1:330,000</td>
<td>1:130,000</td>
</tr>
<tr>
<td>Estimated number of patients</td>
<td>1000</td>
<td>2500</td>
</tr>
</tbody>
</table>

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 transf ect 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 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 Food and Drug Administration-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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02781480a</td>
<td>An Open-label, Multi-centre, Phase I/II Dose Escalation Trial of an Adeno Associated Virus Vector for Gene Therapy of Adults And Children With Retinal Dystrophy Associated With Defects in RPE65 (LCA)</td>
<td>27</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCT02946879</td>
<td>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)</td>
<td>27</td>
<td>Apr 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

No guidelines or statements were identified.

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 U.S. Food and Drug Administration 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.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/01/18</td>
<td>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 patients with vision loss due to biallelic RPE65 variant-associated retinal dystrophy meeting criteria.</td>
</tr>
<tr>
<td>01/15/19</td>
<td>Coding update, added HCPCS code J3398 (new code effective 1/1/19).</td>
</tr>
</tbody>
</table>
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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, DC 20201, 1-800-368-1019, 800-537-7697 (TDD)

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