Medical Policy Manual Genetic Testing, Policy No. 21

Genetic Testing for Biallelic RPE65 Variant-Associated Retinal Dystrophy

Effective: June 1, 2024

Next Review: February 2025
Last Review: April 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

RPE65 genetic testing can be used to predict treatment response to targeted therapy in patients with biallelic RPE65 variant-associated retinal dystrophy.

MEDICAL POLICY CRITERIA

I. Genetic testing for the *RPE65* variant may be considered **medically necessary** to confirm a diagnosis of biallelic *RPE65* variant-associated retinal dystrophy when Luxturna (voretigene neparvovec-rzyl) is being considered as a treatment option.

II. Genetic testing for the *RPE65* variant is considered **investigational** for all other indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Strategies for testing may include testing for individual genes or in combination, such as in a panel.

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

However, if two different *RPE65* pathogenic variants are detected (e.g., compound heterozygous state), confirmatory testing such as linkage analysis by family studies may be required to determine the *trans* vs *cis* configuration (e.g., whether the two different pathogenic variants are found in different copies or in the same copy of the *RPE65* gene). The presence of two different *RPE65* 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 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* 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.

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 (FDA) for use in patients with vision loss due to confirmed biallelic *RPE65* variant-associated retinal dystrophy. Spark Therapeutics received breakthrough therapy designation, rare pediatric disease designation, and orphan drug designation.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION:

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutation(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
    - o History and physical exam including any relevant diagnoses related to the genetic testing
    - o Conventional testing and outcomes
    - o Conservative treatments, if any

CROSS REFERENCES

None

BACKGROUND

INHERITED RETINAL DYSTROPHIES

Inherited retinal dystrophies (IRDs) 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 IRD 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 LCA4[6-8]. The prevalence of RP in the United States is approximately 1 in 3500 to 1 in 4000 with approximately 1% of patients with RP having *RPE65* variants[9, 10]. Assuming a U.S. population of approximately 326.4 million at the end of 2017, the prevalence of *RPE65*-associated retinal dystrophies in the United States would therefore be roughly 1000 to 3000 individuals[11].

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[12] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

LITERATURE REVIEWS AND SUMMARY OF THE EVIDENCE TO SUPPORT OUR POSITION

Systematic Reviews

There are no systematic reviews for this indication.

Randomized Controlled Trials

One gene therapy (voretigene neparvovec) for patients with biallelic *RPE65* variant-associated retinal dystrophy has RCT evidence. The pivotal RCT (NCT00999609) for voretigene neparvovec was an open-label trial of patients ages three or older with biallelic *RPE65* variants, VA worse than 20/60, and/or a VF less than 20o in any meridian, with sufficient viable retinal cells[13, 14]. Those patients meeting these criteria were randomized 2:1 to intervention (n=21) or control (n=10). The trial was conducted at a children's hospital and university medical center. Patients were enrolled between 2012 and 2013. The intervention treatment group received sequential injections of 1.5E11 vg AAV2-hRPE65v2 (voretigene neparvovec) to each eye no more than 18 days apart (target, 12 days; standard deviation [SD], 6 days). The injections were delivered in a total subretinal volume of 0.3 mL under general anesthesia. The control treatment group received voretigene neparvovec one year after the baseline evaluation. Patients received prednisone 1 mg/kg/d (max, 40 mg/d) for seven days starting three days before injection in the first eye and tapered until three days before injection of the second eye at which point the steroid regimen was repeated. During the first year, follow-up visits occurred at 30, 90, 180 days, and one year. Extended follow-up is planned for 15 years. The efficacy outcomes were compared at 1 year. The primary outcome was the difference in mean bilateral MLMT score change. MLMT graders were masked to treatment group. The trial was powered to have greater than 90% power to detect a difference of one light level in the MLMT score at a two-sided type I error rate of 5%. Secondary outcomes were hierarchically ranked: (1) difference in change in full-field light sensitivity threshold (FST) testing averaged over both eyes for white light; (2) difference in change in monocular (first eye) MLMT score change; (3) difference in change in VA averaged over both eyes. Patient-reported vision-related activities of daily living (ADLs) using a Visual Function Questionnaire (VFQ) and VF testing (Humphrey and Goldmann) were also reported. The VFQ has not been validated.

At baseline, the mean age was about 15 years old (range, 4-44 years) and approximately 42% of the participants were male. The MLMT passing level differed between the groups at baseline; about 60% passed at less than 125 lux in the intervention group vs 40% in the control group. The mean baseline VA was not reported but appears to have been between approximately 20/200 and 20/250 based on a figure in the manufacturer briefing document. One patient in each treatment group withdrew before the year one visit; neither received voretigene neparvovec. The remaining 20 patients in the intervention treatment and nine patients in the control treatment groups completed the year one study visit. The intention-to-treat (ITT) population included all randomized patients. The efficacy outcome results at year one for the ITT population are shown in Table 3. In summary, the differences in change in MLMT and FST scores were statistically significant. No patients in the intervention group had worsening MLMT scores at one year compared with three patients in the control group. Almost two-thirds of the intervention arm showed maximal improvement in MLMT scores (passing at one lux) while no participants in the control arm were able to do so. Significant improvements were also observed in Goldmann III4e and Humphrey static perimetry macular threshold VF exams. The difference in change in VA was not statistically significant although the changes correspond to an improvement of about eight letters in the intervention group and a loss of one letter in the control group. The original VA analysis used the Holladay method to assign values to off-chart results. Using, instead the Lange method for off-chart results, the treatment effect estimate was similar but variability estimates were reduced (difference in change, 7.4 letters; 95% confidence interval [CI], 0.1 to 14.6 letters). No control patients experienced a gain of 15

or more letters (≤0.3 logMAR) at year one while 6 of 20 patients in the intervention group gained 15 or more letters in the first eye and four patients also experienced this improvement in the second eye. Contrast sensitivity data were collected but were not reported.

The manufacturer briefing document reports results out to two years of follow-up21. In the intervention group, both functional vision and visual function improvements were observed for at least two years. At year one, all 9 control patients received bilateral injections of voretigene neparvovec. After receiving treatment, the control group experienced improvement in MLMT (change score, 2.1, SD=1.6) and FST (change, -2.86, SD=1.49). VA in the control group improved an average of 4.5 letters between years 1 and 2. Overall, 72% (21/29) of all treated patients achieved the maximum possible MLMT improvement at one year following injection.

Two patients (one in each group) experienced serious adverse events, both were unrelated to study participation. The most common ocular adverse events in the 20 patients treated with voretigene neparvovec were mild to moderate: elevated intraocular pressure, four (20%) patients; cataract, three (15%) patients; retinal tear, two (10%) patients; and eye inflammation, two (10%) patients. Several ocular adverse events occurred only in one patient each: conjunctival cyst, conjunctivitis, eye irritation, eye pain, eye pruritus, eye swelling, foreign body sensation, iritis, macular hold, maculopathy, pseudopapilledema, and retinal hemorrhage. One patient experienced a loss of VA (2.05 logMAR) in the first eye injected with voretigene neparvovec; the eye was profoundly impaired at 1.95 logMAR (approximately 20/1783 on a Snellen chart) at baseline.

Maguire (2019) recently published the results of the open-label follow-on phase 1 study at year four and the phase 3 study at year two.[15] Mean (SD) MLMT lux score change was 2.4 (1.3) at four years compared with 2.6 (1.6) at one year after administration in phase 1 follow-on subjects (n=8). Mean (SD) MLMT lux score change was 1.9 (1.0) at two years and 1.9 (1.0) at one year post-administration in the original intervention group (n=20). The mean (SD) MLMT lux score change was 2.1 (1.6) at one year post-administration in control subjects (n=9). Therefore, durability for up to four years has been reported, with observation ongoing.

Evidence Summary

In the pivotal RCT, patients in the voretigene neparvovec group demonstrated greater improvements on the MLMT, which measures the ability to navigate in dim lighting conditions, compared with patients in the control group. The difference in mean improvement was both statistically significant and larger than the a priori defined clinically meaningful difference. Most other measures of visual function were also significantly improved in the voretigene neparvovec group compared with the control group, with the exception of VA. Improvements seemed durable over a period of two years. The adverse events were mostly mild to moderate; however, one patient lost 2.05 logMAR in the first eye treated with voretigene neparvovec by the one year visit. There are limitations in the evidence. There is limited follow-up available, therefore, long-term efficacy and safety are unknown. The primary outcome measure has not been used previously in RCTs and has limited data to support its use. Only the MLMT assessors were blinded to treatment assignment, which could have introduced bias assessment of other outcomes. The modified VFQ is not validated, so effects on quality of life remain uncertain.

PRACTICE GUIDELINE SUMMARY

There are no evidence-based clinical practice guidelines that recommend RPE65 variant

testing to confirm a diagnosis of biallelic RPE65 variant-associated retinal dystrophy.

SUMMARY

There is enough research to show that testing for RPE65 variants can help to identify patients with biallelic RPE65 variant-associated retinal dystrophy who are likely to benefit from certain gene therapies. Therefore, RPE65 genetic variant testing may be considered medically necessary for patients that meet the policy criteria.

There is not enough research to show that this testing improves health outcomes for patients who do not meet policy criteria, and therefore, RPE65 variant testing is considered investigational for all other indications.

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CODES

Codes	Number	Description
CPT	81406	Molecular pathology procedure level 7
	81479	Unlisted molecular pathology procedure
HCPCS	None	

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