

# GENETIC TESTING: EYE DISORDERS

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## OVERVIEW

In the past 15 years, genetics experts have identified approximately 500 genes that contribute to inherited eye diseases. Approximately 4,000 diseases affect humans, and nearly one-third of these diseases may affect the eyes. Because many genes involved in ophthalmologic disorders are now identified, scientists have developed a better understanding of how these genes influence vision and eye health.

Age-related macular degeneration (AMD) is an eye condition that causes damage to the central portion of the retina (the macula), affecting the ability to see objects straight ahead. It is a complex disease and is the leading cause of blindness and irreversible vision loss among adults over the age of 65 years. The etiology of AMD is multifactorial and includes both genetic and environmental (eg, age, smoking) factors. Genetic testing has been proposed to predict the risk of developing advanced AMD in asymptomatic individuals, however, the clinical utility of genetic testing for age-related macular degeneration is limited. No studies have shown improvements in patients identified as being high-risk based on genetic testing, and evidence is insufficient to determine the effects of genetic testing on health outcomes. For individuals who have age-related macular degeneration, the clinical utility of genetic testing is limited and has not shown to be superior to clinical evaluation.

The molecular genetic basis for glaucoma has not been clearly elucidated, however a small subset of genes have been identified in very rare forms of congenital glaucoma.

Inherited retinal dystrophy can be caused by biallelic variants in the *RPE65* gene and other genes and can result in difficulty seeing in dim light and progressive loss of vision. Historically considered untreatable, [gene therapy](#) has been proposed as a treatment to improve visual function. Individuals who have vision loss due to biallelic *RPE65* variant associated retinal dystrophy are eligible to receive gene therapy. Because this is a rare condition, there are challenges with generating evidence demonstrating that the technology results in a meaningful improvement in net health outcomes.

## POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

<a href="#">Coverage Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	<a href="#">Ref</a>
<b><a href="#">Known Familial Variant Analysis for Eye Disorders</a></b>				
<a href="#">Known Familial Variant Analysis</a>	Targeted Mutation Analysis for a Known Familial Variant	81403		
<b><a href="#">Macular Degeneration</a></b>				
<a href="#">Macular Degeneration</a>	Macula Risk® (Arctic Medical Laboratories)	81401, 81479, 81599	H35.30, H35.3110-H35.3194, H35.3210-H35.3293, Z13.5	1, 2
	Vita Risk® (Arctic Medical Laboratories)	0205U		
	Stargardt Disease (STGD) and Macular Dystrophies Panel (PreventionGenetics)	81404, 81406, 81408, 81479		
<b><a href="#">RPE-Associated Retinal Dystrophy/Leber Congenital Amaurosis</a></b>				
<a href="#">RPE65 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel Analysis</a>	RPE65-Association Disorders via the RPE65 Gene (PreventionGenetics)	81406, 81479	H35.50-H35.54	3, 4
	Leber Congenital Amaurosis Panel (PreventionGenetics)	81404, 81406, 81408, 81479		
<b><a href="#">Glaucoma</a></b>				
<a href="#">Glaucoma</a>	Glaucoma Panel (PreventionGenetics)	81404, 81406, 81408, 81479	H40	1
	Glaucoma Panel (Blueprint Genetics)	81404, 81406, 81407, 81408, 81479		
<b><a href="#">Covered Eye Disorders</a></b>				

<a href="#">Covered Eye Disorders</a>	See below	81400-81408		1
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## OTHER RELATED POLICIES

This policy document provides coverage criteria for Genetic Testing for Eye Disorders. Please refer to:

- **Genetic Testing: Hereditary Cancer Susceptibility** for coverage criteria related to genetic testing for retinoblastoma.
- **Genetic Testing: Hearing Loss** for coverage criteria related to genetic testing for disorders that include hearing loss, such as Usher syndrome.
- **Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay** for coverage criteria related to other multisystem inherited disorders.
- **Genetic Testing: General Approach to Genetic Testing** for coverage criteria related to genetic testing for eye disorders that are not specifically discussed in this or another non-general policy.

## COVERAGE CRITERIA

### KNOWN FAMILIAL VARIANT ANALYSIS FOR EYE DISORDERS

- I. Targeted mutation analysis for a known familial variant (81403) for an eye disorder is considered **medically necessary** when:
  - A. The member has a [close relative](#) with a known pathogenic or likely pathogenic variant causing the condition.
- II. Targeted mutation analysis for a known familial variant (81403) for an eye disorder is considered **investigational** for all other indications.

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## MACULAR DEGENERATION

- I. Genetic testing for [macular degeneration](#) (81401, 81404, 81406, 81408, 81479, 81599, 0205U) is considered **investigational**.

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## RPE65-ASSOCIATED RETINAL DYSTROPHY / LEBER CONGENITAL AMAUROSIS

### **RPE65 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel Analysis**

- I. Genetic testing for [RPE65-associated retinal dystrophy](#) / Leber congenital amaurosis via *RPE65* sequencing and/or deletion/duplication analysis (81406, 81479) or a multigene panel (81404, 81406, 81408, 81479) that includes *RPE65* is considered **medically necessary** when:
  - A. The member has a diagnosis of a retinal dystrophy or Leber Congenital Amaurosis, **AND**
  - B. The member is being considered for treatment with voretigene neparovec (Luxturna®).
- II. Genetic testing for *RPE65*-associated retinal dystrophy / Leber congenital amaurosis via *RPE65* sequencing and/or deletion/duplication analysis (81406) or a multigene panel (81404, 81406, 81408, 81479) that includes *RPE65* is considered **investigational** for all other indications

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## GLAUCOMA

- I. Genetic testing for glaucoma (81404, 81406, 81407, 81408, 81479) is considered **investigational**.

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## OTHER COVERED EYE DISORDERS

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to approve claims for these tests to establish or confirm a diagnosis.

- I. Genetic testing to establish or confirm one of the following eye disorders to guide management is considered **medically necessary** when the member demonstrates clinical features\* consistent with the disorder (the list is not meant to be comprehensive, see II below):
  - A. [Duane Syndrome](#)
  - B. Familial Exudative Vitreoretinopathy
  - C. [Retinitis Pigmentosa](#)
  - D. [Aniridia](#)
  - E. [X-linked Congenital Retinoschisis](#)
  - F. Presenile Cataracts
  
- II. Genetic testing to establish or confirm the diagnosis of all other eye disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic Testing* (see policy for coverage criteria).

\*Clinical features for a specific disorder may be outlined in resources such as [GeneReviews](#), [OMIM](#), [National Library of Medicine](#), [Genetics Home Reference](#), or other scholarly source.

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## NOTES AND DEFINITIONS

Close relatives include first, second, and third degree blood relatives:

**First-degree relatives** are parents, siblings, and children

**Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

**Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

**Age-related Macular Degeneration (AMD)** is the leading cause of blindness and irreversible vision loss among older adults (older than 65 years).

**Retinal dystrophies (RDs)** are degenerative diseases of the retina which have marked clinical and genetic heterogeneity. Vision impairment may vary from poor peripheral or night vision to complete blindness, and severity usually increases with age.

**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.

**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.

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## CLINICAL CONSIDERATIONS

The purpose of genetic testing of asymptomatic individuals with risk of developing age-related macular degeneration is to identify single nucleotide variants for primary prevention or earlier detection of disease for more timely intervention to affect course of disease progression. Patients may be referred from primary care to an ophthalmologist or medical geneticist for investigation and management of age-related macular degeneration. In all cases, the patient should receive counseling from a physician with expertise in inherited disease or a genetic counselor. Whenever clinical findings suggest the presence of an inherited eye disease, the treating ophthalmologist should either discuss the potential value of genetic testing with their patient and order the appropriate tests (if any) or should offer a referral to another physician or counselor with expertise in the selection and interpretation of genetic tests. Treating physicians should also ensure that their patients receive a written copy of their genetic test results.

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. Next-generation sequencing and Sanger sequencing typically cannot resolve the phase (eg, *trans* vs. *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.

In all cases, the patient should receive counseling from a physician with expertise in inherited disease or a genetic counselor. Whenever clinical findings suggest the presence of an inherited eye disease, the treating ophthalmologist should either discuss the potential value of genetic testing with their patient and order the appropriate tests (if any) or should offer a referral to another physician or counselor with expertise in the selection and interpretation of genetic tests. Treating physicians should also ensure that their patients receive a written copy of their genetic test results.

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## BACKGROUND AND RATIONALE

### Macular Degeneration

*American Society of Retina Specialists*

American Society of Retina Specialists published special correspondence on the use of genetic testing in the management of patients with age-related macular degeneration (2017), which made the following conclusions:

1. Age-related macular degeneration genetic testing may provide information on the progression rates from intermediate to advanced AMD. However, before ordering this testing, retina specialists should be aware of the following:
  - a. Testing should be performed only at Clinical Laboratory Improvement Amendments–certified laboratories with expertise in genetic sequencing. Because of the high variability in the results, direct-to-consumer (DTC) AMD genetic testing that does not meet this standard is not recommended.
  - b. Interpretation of the results of AMD genetic testing is complex.
  - c. At present, there is no clinical evidence that altering the management of genetically higher risk progression patients, for example, with more frequent office visits and/or improved lifestyle changes, results in better

visual outcomes for these patients compared with individuals of lower genetic susceptibility. As such, prospective studies are needed before patient care is modified.

2. Age-related macular degeneration genetic testing at present in patients with neovascular AMD does not provide clinically relevant information regarding response to anti-vascular endothelial growth factor (VEGF) treatment and is not recommended for this purpose.
3. Although genetic testing to determine the optimal nutritional supplementation may in the future prove useful, at present there is insufficient data to support the use of genetic testing in patients with AMD prior to recommendation of current Age-Related Eye Disease Study (AREDS) nutritional supplement use.

#### *American Academy of Ophthalmology (AAO)*

The American Academy of Ophthalmology (AAO) Task Force on Genetic Testing published recommendations for genetic testing of inherited eye diseases (2014) which stated, in part: “Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published prospective clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies.”

#### **RPE64 Sequencing and/or Deletion/Duplication Analysis or Multigene Panel Analysis**

##### *US Food and Drug Administration (FDA)*

The FDA issued an approval letter on December 18, 2017 for Luxturna stating, “Under this license, you are authorized to manufacture the product voretigene neparvovec-rzyl, which is indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.”

##### *National Institute for Health and Care Excellence*

The National Institute for Health and Care Excellence published guidance in 2019 for the use of voretigene neparvovec for treating inherited retinal dystrophies caused by *RPE65* gene mutations, which stated the following:

- 1.1 Voretigene neparvovec is recommended, within its marketing authorisation, as an option for treating *RPE65*-mediated inherited retinal dystrophies in people with vision loss caused by inherited retinal dystrophy from confirmed biallelic *RPE65*



mutations and who have sufficient viable retinal cells. It is recommended only if the company provides voretigene neparvovec according to the commercial arrangement.

The committee noted that, “*RPE65*-mediated inherited retinal dystrophies are rare and serious. They involve progressive loss of vision. This ultimately leads to near-total blindness, and severely affects the quality of life of people with the condition, and their families and carers. Current treatment is supportive care. Clinical trial evidence shows that, in the short term, voretigene neparvovec improves vision and prevents the condition from getting worse. There is no long-term clinical evidence, but it is biologically plausible that the treatment effect is likely to continue for decades. Some assumptions in the economic modelling are uncertain, particularly around the utility values and how long the treatment effect lasts. Despite the uncertainties, voretigene neparvovec is likely to provide important clinical benefits for people with *RPE65*-mediated inherited retinal dystrophies, and is considered an appropriate use of NHS resources within the context of a highly specialised service. It is therefore recommended for use in the NHS.”

## **Glaucoma**

### *American Academy of Ophthalmology (AAO)*

The American Academy of Ophthalmology (AAO) Task Force on Genetic Testing published recommendations for genetic testing of inherited eye diseases (2014) which stated, in part: “Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published prospective clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies.”

## **General Testing Guidelines for Genetic Eye Disorders**

### *American Academy of Ophthalmology (AAO)*

The American Academy of Ophthalmology (AAO) Task Force on Genetic Testing published the following recommendations for genetic testing of inherited eye diseases (2014):

1. Offer genetic testing to patients with clinical findings suggestive of a Mendelian disorder whose causative gene(s) have been identified. If unfamiliar with such testing, refer the patient to a physician or counselor who is. In all cases, ensure

that the patient receives counseling from a physician with expertise in inherited disease or a certified genetic counselor.

2. Use Clinical Laboratories Improvement Amendments– approved laboratories for all clinical testing. When possible, use laboratories that include in their reports estimates of the pathogenicity of observed genetic variants that are based on a review of the medical literature and databases of disease-causing and non–disease-causing variants.
3. Provide a copy of each genetic test report to the patient so that she or he will be able independently to seek mechanism-specific information, such as the availability of gene-specific clinical trials, should the patient wish to do so.
4. Avoid direct-to-consumer genetic testing and discourage patients from obtaining such tests themselves. Encourage the involvement of a trained physician, genetic counselor, or both for all genetic tests so that appropriate interpretation and counseling can be provided.
5. Avoid unnecessary parallel testing— order the most specific test(s) available given the patient’s clinical findings. Restrict massively parallel strategies like whole-exome sequencing and whole-genome sequencing to research studies conducted at tertiary care facilities.
6. Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published prospective clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies.
7. Avoid testing asymptomatic minors for untreatable disorders except in extraordinary circumstances. For the few cases in which such testing is believed to be warranted, the following steps should be taken before the test is performed: (1) the parents and child should undergo formal genetic counseling, (2) the certified counselor or physician performing the counseling should state his or her opinion in writing that the test is in the family’s best interest, and (3) all parents with custodial responsibility for the child should agree in writing with the decision to perform the test.

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## REFERENCES

1. American Academy of Ophthalmology Task Force on Genetic Testing. Recommendations for Genetic Testing of Inherited Eye Diseases - 2014. Accessed 11/11/2021. <https://www.aaopt.org/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d>
2. Csaky KG SA, Kaiser PK, et al. The Use of Genetic Testing in the Management of Patients with Age-Related Macular Degeneration: American Society of Retina Specialists Genetics Task Force Special Report. 2017. Accessed November 2, 2020. <https://www.asrs.org/content/documents/articleasrstaskforcereportjvrd117.pdf>.
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