

Concert Genetic Testing: Eye Disorders

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[Coding implications](#)
[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

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)~~[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 (e.g. 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.

Inherited retinal dystrophy can be caused by biallelic variants in the [RPE65RPE65](#) gene and other genes and can result in difficulty seeing in dim light and progressive loss of vision. Historically considered untreatable, ~~gene therapy~~[gene therapy](#) has been proposed as a treatment to improve visual function. Individuals who have vision loss due to biallelic [RPE65RPE65](#) variant associated retinal dystrophy are eligible to receive ~~gene therapy~~[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

Coding Implications

CLINICAL POLICY

Eye Disorders



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NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

The tests ~~and~~, associated laboratories ~~and~~, CPT [codes](#), and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the [Concert-Genetics Platform](#) for a comprehensive list of registered tests.

Criteria Sections Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref ef
Macular Degeneration Macular Degeneration				
Macular Degeneration Macular Degeneration	Macula Risk (Arctic Medical Laboratories)	81479, 81599*	H35.30, H35.3110- H35.3194, H35.3210- H35.3293, Z13.5	2, 7
	Vita Risk (Arctic Medical Laboratories)	0205U*		
	Macular Degeneration NGS Panel (Fulgent Genetics)	81404*, 81406* , 81408*, 81479		
Inherited Retinal Dystrophies Inherited Retinal Dystrophies				
Inherited Retinal Dystrophies Multigene Panel Analysis Inherited Retinal Dystrophies Multigene Panel Analysis	Comprehensive Inherited Retinal Dystrophies Panel (PreventionGenetics, part of Exact Sciences)	81434	H35.50- H35.54	1, 3
	Leber Congenital Amaurosis Panel (PreventionGenetics, part of Exact Sciences)	81404*, 81406*, 81408*, 81479		
Other Covered Eye Disorders Other Covered Eye Disorders				

Other Covered Eye Disorders Other Covered Eye Disorders	See below	81400*-81408*		4, 5, 6, 8
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OTHER RELATED POLICIES

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

- **Genetic Testing: Hereditary Cancer Susceptibility** for criteria related to genetic testing for retinoblastoma.
- **Genetic Testing: Hearing Loss** for 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 criteria related to oculocutaneous albinism and other multisystem inherited disorders.
- **Genetic Testing: General Approach to Genetic and Molecular Testing** for criteria related to genetic testing for eye disorders that are not specifically discussed in this or another non-general policy, [including known familial variant testing](#).

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CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

MACULAR DEGENERATION

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

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INHERITED RETINAL DYSTROPHIES

Inherited Retinal Dystrophies Multigene Panel Analysis

- I. Genetic testing for inherited ~~retinal dystrophies~~retinal dystrophies via a multigene panel (81404, 81406, 81408, 81434, 81479) is considered **medically necessary** when:
 - A. The member/enrollee has findings consistent with one of the following:
 1. Rod-cone degeneration (e.g., retinitis pigmentosa), **OR**
 2. Cone-rod degeneration (e.g., achromatopsia), **OR**
 3. Chorioretinal degeneration, **OR**
 4. Macular dystrophy, **AND**
 - B. The test includes, at a minimum, the RPE65 gene.
- II. Genetic testing for inherited ~~retinal dystrophies~~retinal dystrophies via a multigene panel (81404, 81406, 81408, 81434, 81479) is considered **investigational** for all other indications.

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OTHER COVERED EYE DISORDERS

~~Genetic Testing Guidelines for Genetic 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/enrollee 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
 - ~~A. Retinitis Pigmentosa~~
 - C. Aniridia
 - D. X-linked Congenital Retinoschisis
 - E. 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 and Molecular Testing* (see policy for criteria).

***NOTE:** 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 sources.

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DEFINITIONS

1. **Age-related Macular Degeneration (AMD)** is the leading cause of blindness and irreversible vision loss among older adults (greater than age 65 years).
2. **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.
3. **RPE65 (retinal pigment epithelium-specific protein 65-kD) gene** encodes the RPE54 protein, which is an all trans-11-cis-retinyl isomerase, a key enzyme expressed in the retinal pigment epithelium (RPE) that is responsible for regeneration of 11-cis-retinol in the visual cycle.
4. **Gene therapy** ~~are treatments~~ is a treatment that ~~change~~ changes the expression of genes to treat disease, e.g., 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 [RPE65RPE65](#) gene in individuals with documented vision loss.- By definition, pathogenic or likely pathogenic variant(s) must be present in both copies of the [RPE65RPE65](#) gene to establish a diagnosis of biallelic [RPE65RPE65](#)-mediated inherited retinal dystrophy. Next-generation sequencing and Sanger sequencing typically cannot resolve the phase (e.g., *trans* vs. *cis* configuration) when two [RPE65RPE65](#) 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.

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BACKGROUND AND RATIONALE

Macular Degeneration

American Society of Retina Specialists

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

1. Age-related macular degeneration (AMD) 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.

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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. (p. 75)

American Academy of Ophthalmology

A Preferred Practice Pattern published in 2020 concluded that there is no evidence to support the need for genotyping to guide recommendations for use of supplements containing antioxidants and zinc in AMD (age related macular degeneration). (p. P15) In addition they state that routine use of genetic testing is not supported by existing literature and is not recommended at this time. (p. P16)

Inherited Retinal Dystrophies 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.” (p. 1)

American Academy of Ophthalmology (AAO)

The American Academy of Ophthalmology Clinical Statement (2022) provides recommendations and clinical genetic assessments of patients with inherited retinal degenerations. Next generation sequencing using a retinal dystrophy panel is an efficient first step for genetic testing and should include genes for syndromic forms of retinal disease even in patients without syndromic features. Patients would also need to have genetic testing to determine eligibility for the FDA- approved voretigene neparvovec or be considered for clinical trials. -Genetic testing is recommended in patients with any of four major types of inherited retinal degenerations (rod-cone degenerations, cone-rod degenerations, chorioretinal degenerations and inherited macular dystrophies).

OTHER COVERED EYE DISORDERS

~~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 (2012, revised 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. (p. 4 and 5)

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Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Policy developed.	09/23	11/27/23	
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced “coverage criteria” with “criteria. For Policy Reference Table: removed “Stargardt Disease...” and added “Macular Degeneration...”; under RPE-Associated Retinal Dystrophy/Leber Congenital Amaurosis and Glaucoma: added “part of Exact Sciences”; added “Other” to Covered Eye Disorders. For Other Related Policies: added “Molecular” to Genetic Testing: General Approach to Genetic Testing. For RPE65-Associated Retinal Dystrophy/Leber Congenital Amaurosis: in II. added “81479”. For Notes and Definitions: 1. added “on the same side of the family”. For Clinical	12/23	2/27/24	

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Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Considerations: removed “In all cases, the patient should receive...”. For Background and Rationale: removed “inheritance patterns” and replaced with “genetic testing”.			
Semi-annual review. Updated title to reflect V2.2024 version. In Known Familial Variant Analysis for Eye Disorders criteria, moved criteria to policy “Genetic Testing: General Approach to Genetic and Molecular Testing” to consolidate criteria for known familial variant tests. In Inherited Retinal Dystrophies Multigene Panel Analysis criteria, criteria set name changed (formerly “RPE65 Sequencing and/or Deletion/Duplication Analysis”). Clinical criteria updated to be more consistent with guidelines. In Glaucoma criteria, retired criteria set based on rarity of testing (low order volume and low claim volume). Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	06/24	10/23/24	11/22/24
Semi-annual review. Updated title to reflect V1.2025 version. Macular Degeneration: Removed CPT code 81406 from Fulgent Genetics test in Policy Reference Table and within criteria; Updated access date for online reference. Inherited Retinal Dystrophies Multigene Panel Analysis: Updated access date for online reference. Other Covered Eye Disorders: Removed "Retinitis Pigmentosa" from disorders list, as this condition is covered in the criteria section called "Inherited Retinal Dystrophies Multigene Panel Analysis."; Removed unnecessary header ("Genetic Testing Guidelines for Genetic Eye Disorders") from the Background and Rationale; Updated GeneReviews copyright dates in Reference list.	1/25		

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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