BlueCross BlueShield Nebraska

GENETIC TESTING: EYE DISORDERS (REQUIRES PREAUTHORIZATION)

V.71

V.71 GENETIC TESTING: EYE DISORDERS (REQUIRES PREAUTHORIZATION)

DESCRIPTION

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 effect the eyes. Because many genes involved in ophthalmologic disorders are now mapped, 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.

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

challenges with generating evidence demonstrating that the technology results in a meaningful improvement in net health outcomes.

Dates

Original Effective
04-26-2021
Last Review
08-07-2024
Next Review
08-11-2025

REFERENCE TABLE

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

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

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RELATED POLICIES

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

- *V.74 Genetic Testing: General Approach to Genetic and Molecular Testing* for coverage criteria related to genetic testing for eye disorders that are not addressed in this or another non-general policy, including known familial variant testing.
- *V.59 Genetic Testing: Hereditary Cancer Susceptibility* for coverage criteria related to genetic testing for retinoblastoma.
- *V.35 Genetic Testing: Hereditary Hearing Loss* for coverage criteria related to genetic testing for disorders that include hearing loss, such as Usher syndrome.
- *V.62 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay* for coverage criteria related to oculocutaneous albinism and other multisystem inherited disorders.

POLICY

MACULAR DEGENERATION

I. Genetic testing for macular degeneration (81404, 81408, 81479, 81599, 0205U) is considered **investigational**.

INHERITED RETINAL DYSTROPHIES

Inherited Retinal Dystrophies Multigene Panel Analysis

I. Genetic testing for inherited retinal dystrophies via a multigene panel (81404, 81406, 81408, 81434, 81479) is considered **medically necessary** when:

A. The member has findings consistent with **one** of the following:

2. Cone-rod degeneration (e.g., achromatopsia),

OR

3. Chorioretinal degeneration, **OR**

4. Macular dysrophy, **AND**

B. The test includes, at a minimum, the *RPE65* gene.

II. Genetic testing for inherited retinal dystrophies via a multigene panel (81404, 81406, 81408, 81434, 81479) is considered **investigational** for all other indications.

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. 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 coverage criteria).

*Clinical features for a specific immune 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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blindness and irreversible vision loss among older adults (> 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 translate-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.

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 of 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.

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BACKGROUND

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.
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)

Food and Drug Administration

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 (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

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)

Quick Code Search

Use this feature to find out if a procedure and diagnosis code pair will be approved, denied or held for review. Simply put in the procedure code, then the diagnosis code, then click "Add Code Pair". If the codes are listed in this policy, we will help you by showing a dropdown to help you.

Procedure

Please type a procedure code

Enter at least the first 3 characters of the code

Diagnosis

Please type a diagnosis code

Enter at least the first 3 characters of the code

Add

+ **CPT4**

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Minor policy changes, updated references.

12-04-2023
Updated policy for 01/01/2024

09-29-2023
Removed "medically necessary" and replaced with "scientifically validated" also added "investigational when the above criteria are not met and for all other indications"

07-01-2023
Updated background and references.

07-01-2022
Updated references and minor changes in policy

01-03-2022
Added Known familiar variant analysis for Eye Disorders criteria & added code 81434 (previously in V.74 - Genetic Testing: General Approach to Genetic Testing). Minor changes to remainder of policy.