
Medical Policy



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***Current Policy Effective Date: 7/1/26**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Macular Degeneration

Description

Age-related macular degeneration is a complex disease involving both genetic and environmental influences. Testing for variants at certain genetic loci has been proposed to predict the risk of developing advanced age-related macular degeneration. Age-related macular degeneration is divided into the dry form, associated with slowly progressive vision loss, and the wet form, which may be associated with rapidly progressive and severe vision loss. The risks of age-related macular degeneration and of developing the wet form are associated with genetic and nongenetic (e.g., age, smoking) factors.

Medical Policy Statement

Genetic testing for macular degeneration is experimental/investigational. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81401

81405

81408

81479

0205U

Background

MACULAR DEGENERATION

Macular degeneration, the leading cause of severe vision loss in people older than age 60 years, occurs when the central portion of the retina, the macula, deteriorates. Because the disease develops as a person ages, it is often referred to as age-related macular degeneration (AMD). In 2019, approximately 19.8 million Americans 40 years of age and older were living with age-related macular degeneration.¹ Sex- and age-standardized rates of age-related macular degeneration were lower for non-Hispanic Black people (7.0%) than for other racial and ethnic groups (13.3%).

There are two major types of AMD, known as the dry form and the wet form. The dry form is much more common, accounting for 85% to 90% of all cases of AMD, and it is characterized by the buildup of yellow deposits called drusen in the retina and slowly progressive vision loss. The condition typically affects vision in both eyes, although vision loss often occurs in one eye before the other. AMD is generally thought to progress along a continuum from dry AMD to neovascular wet AMD, with approximately 10 to 15% of all AMD patients eventually developing the wet form. Occasionally patients with no prior signs of dry AMD present with wet AMD as the first manifestation of the condition.

The wet form of AMD is characterized by the growth of abnormal blood vessels from the choroid underneath the macula and is associated with severe vision loss that can rapidly worsen. The abnormal vessels leak blood and fluid into the retina, which damages the macula, leading to permanent loss of central vision.

Major risk factors for AMD include older age, cigarette smoking, cardiovascular diseases, nutritional factors, and certain genetic markers. Age appears to be the most important risk factor, as the chance of developing the condition increases significantly as a person gets older. Smoking is another established risk factor. Other factors that may increase the risk of AMD include high blood pressure, heart disease, a high-fat diet or one that is low in certain nutrients (e.g., antioxidants, zinc), and obesity.²

Clinical Diagnosis

Age-related macular degeneration (AMD) can be detected by routine eye exam, with one of the most common early signs being the presence of drusen or pigment clumping. An Amsler grid, a pattern of straight lines that resemble a checkerboard may also be used. In an individual with AMD, some of the straight lines may appear wavy or missing.

If AMD is suspected, fluorescein angiography and/or optical coherence tomography (OCT) may be performed. Angiography involves injecting dye into the bloodstream to identify leaking blood vessels in the macula. OCT captures a cross-section image of the macula and aids in identifying fluid beneath the retina and in documenting degrees of retinal thickening.

Treatment

There is currently no cure for macular degeneration, but certain treatments may prevent severe vision loss or slow the progression of the disease. For dry AMD, there is no medical treatment; however, changing certain lifestyle risks may slow the onset and progression of AMD. The goal for wet (advanced) AMD is early detection and treatment aimed at preventing the formation of new blood vessels or sealing the leakage of fluid from blood vessels that have already formed. Treatment options include laser photocoagulation, photodynamic therapy, surgery, anti-angiogenic drugs and combination treatments. Anti-angiogenesis drugs block the development of new blood vessels and leakage from the abnormal vessels within the eye that cause wet macular degeneration and may lead to patients regaining lost vision. A large study performed by the National Eye Institute of the National Institutes of Health, the Age-Related Eye Disease Study (AREDS), showed that for certain individuals (those with extensive drusen or neovascular AMD in one eye) high doses of vitamins C, E, beta-carotene, and zinc may provide a modest protective effect against the progression of AMD.³

Genetic Testing

It has been reported that genetic variants associated with AMD account for approximately 70% of the risk for the condition.⁴

More than 25 genes have been reported to influence the risk of developing AMD, discovered initially through family-based linkage studies, and subsequently through large-scale genome-wide association studies. Genes influencing several biological pathways, including genetic loci associated with the regulation of complement, lipid, angiogenic and extracellular matrix pathways, have been found to be associated with the onset, progression and bilateral involvement of early, intermediate and advanced stages of AMD.⁵

Loci based on common single nucleotide variants (SNVs) contribute to the greatest AMD risk:

- The long (q) arm of chromosome 10 in a region known as 10q26 contains two genes of interest, *ARMS2* and *HTRA1*. Changes in both genes have been studied as possible risk factors for the disease; however, because the two genes are so close together, it is difficult to tell which gene is associated with age-related macular degeneration risk, or whether increased risk results from variations in both genes.
- Common and rare variants in the complement factor H (*CFH*) gene.

Other confirmed genes in the complement pathway include *C2*, *C3*, *CFB* and *CFI*.⁵

On the basis of large genome-wide association studies, high-density lipoprotein (HDL) cholesterol pathway genes have been implicated, including *CETP* and *LIPC*, and possibly *LPL* and *ABCA1*.⁵ The collagen matrix pathway genes *COL10A1* and *COL8A1* and the extracellular matrix pathway gene *TIMP3* have also been linked to AMD. Genes in the angiogenesis pathway (*VEGFA*) have also been associated with AMD.

Commercially Available Testing for AMD

Commercially available genetic testing for AMD is aimed at identifying those individuals who are at risk of developing advanced AMD.

Arctic Medical Laboratories offers Macula Risk®, which uses patient clinical information and the patient's genotype for 15 associated biomarkers in an algorithm to identify Caucasians at

high risk for progression of early or intermediate AMD to advanced forms of AMD. A Vita Risk® report is also provided with vitamin recommendations based on the *CFH/ARMS2* genotype.

The AMDiGuard DNA Risk Test (Visible Genomics) uses a DNA swab combined with an individual's medical history to estimate the risk of developing age-related macular degeneration. The AMDiGuard DNA Progression Test provides additional information on the likelihood of progression to advanced age-related macular degeneration in individuals with early to intermediate disease.

Nicox offers Sequenom's RetnaGene™ AMD in North America, which evaluates the risk of a patient with early or intermediate AMD progressing to advanced choroidal neovascular disease (wet AMD) within 2, 5, and 10 years. The RetnaGene AMD test assesses the impact of 12 genetic variants (single nucleotide polymorphisms or SNPs) located on genes that are collectively associated with the risk of progressing to advanced disease in patients with early or intermediate-stage disease (*CFH/CFH* region, *C2*, *CRFB*, *ARMS2*, *C3*), along with phenotype of disease, age, and smoking history. A risk score is generated, and the patient is categorized into one of three risk groups: low, moderate, or high risk.

ARUP laboratory offers testing for mutations in the *ARMS2* and *CFH* genes. deCode Complete includes testing for variants in *CFH*, *ARMS2/HTRA1*, *C2*, *DFB*, and *C3* genes. 23andMe includes testing for *CFH*, *ARMS2*, and *C2*.

SUMMARY OF EVIDENCE

For individuals who are asymptomatic with risk of developing age-related macular degeneration (AMD) who receive genetic testing for AMD, the evidence includes genetic association studies and risk prediction models. Relevant outcomes are test validity, change in disease status, and functional outcomes. The clinical validity of genetic testing appears to provide a small, incremental benefit to risk stratification based on nongenetic risk factors. The clinical utility of genetic testing for AMD is limited, in that there are currently no preventive measures that can be undertaken. No studies have shown improvement in health outcomes in patients who have been identified as being at high risk based on genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals who have age-related macular degeneration (AMD), the evidence includes genetic association studies and risk prediction models. Relevant outcomes are test validity, change in disease status, and functional outcomes. The clinical utility of genetic testing in patients who have AMD is limited, in that genetic testing has not been shown to be superior to clinical evaluation in determining the risk of progression of disease. In addition, there is no known association with specific genotypes and specific therapies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Rationale

Evidence reviews assess clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of

life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

TESTING ASYMPTOMATIC INDIVIDUALS WITH RISK OF DEVELOPING AGE-RELATED MACULAR DEGENERATION

Clinical Context and Test Purpose

The purpose of genetic testing of asymptomatic individuals with risk of developing AMD is to identify single-nucleotide variants (SNVs) for primary prevention or earlier detection of disease for more timely intervention to affect course of disease progression.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Current models for predicting AMD risk include various combinations of epidemiologic, clinical and genetic factors, and give areas under the curve (AUC) of approximately 0.8.^{6,7} (By plotting the true and false positives of a test, an AUC measures the discriminative ability of the test, with a perfect test giving an AUC of 1).⁸

A 2009 analysis by Seddon et al demonstrated that a clinical model of AMD risk that included age, sex, education, baseline AMD grade, smoking and body mass index (BMI) had an AUC of 0.757.⁹ The addition of the genetic factors SNVs in *CFH*, *ARMS2*, *C2*, *C3* and *CFB*, increased the AUC to 0.821. In a 2015 report, Seddon et al included 10 common and rare genetic variants in their risk-prediction model, resulting in an AUC of 0.911 for progression to advanced AMD.¹⁰ Klein et al showed that an individual's macular phenotype, as represented by the Age-Related Eye Disease Study (AREDS) Simple Scale score, which rates the severity of AMD based on the presence of large drusen and pigment changes to predict the rate of advanced AMD, has the greatest predictive value.^{6,11} The predictive model used in this analysis by Klein included age, family history, smoking, the AREDS Simple Scale score, presence of very large drusen, presence of advanced AMD in one eye, and genetic factors (*CFH* and *ARMS2*). The AUC was 0.865 without genetic factors included and 0.872 with genetic factors included.¹¹ Govindaiah et al (2021) reported that a prediction model for development of age-related macular degeneration using AREDS data had an area under the curve of 0.69 using genetic data only, 0.77 using genetic and sociodemographic data, and 0.92 using genetic, sociodemographic, and retinal imaging data.¹² Ajana et al (2021) also reported an area under the curve at 5 years of 0.92 for an age-related macular degeneration model that included clinical, genetic, and lifestyle factors.¹³ de Breuk et al (2021) and the EYE-RISK consortium found that patients with late age-related macular degeneration had significantly higher genotype assay risk scores than patients with early or intermediate disease ($p<.001$) or no disease ($p<.001$) based on a European case-control population (N=4740).¹⁴

Although these risk models suggest some small incremental increase in the ability to assess risk of developing advanced AMD based on genetic factors, the clinical validity is not established.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or testing.

What can be done for an individual whose genetic test indicates that he or she is at high risk for vision loss from AMD? The possible clinical utility of genetic testing for AMD can be divided into disease prevention, disease monitoring and therapy guidance, as discussed in more detail below.

- Prevention: Genetic testing and risk prediction for AMD would have clinical utility if a preventive therapy existed that involved an intervention that went beyond good health practices (e.g., no smoking, balanced diet, exercise, nutrient supplements). If preventive therapy existed, the optimal risk-benefit point along the AMD risk profile for every given age would need to be established so that the decision could be made which individuals should receive those treatments and at what age to start the intervention. Currently, no preventive measures are available; high-dose antioxidants and zinc supplements have been shown to reduce the progression of disease.³
- Monitoring: If a patient is identified as high risk, changes in the frequency of monitoring may occur and could include the possibility of home monitoring devices, or the use of technology such as preferential hyperacuity perimetry to detect early or subclinical wet AMD. However, the impact of more frequent monitoring for high-risk patients is not known.⁶
- Direction of Therapy: No consistent associations between response to vitamin supplements and genetic variants have been established.¹⁵⁻¹⁹

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence comes from randomized controlled trials (RCTs). No such trials were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. A chain of evidence cannot be constructed.

Section Summary: Asymptomatic Individuals with Risk of Developing Age-Related Macular Degeneration

Evidence from studies has indicated that the clinical sensitivity of genetic testing for genes associated with age-related macular degeneration may have small incremental effects on assessing risk of developing age-related macular degeneration. Risk-prediction models incorporate factors such as age, sex, smoking, body mass index, and genetic factors. The true clinical specificity of genetic variants in age-related macular degeneration-related genes is uncertain because of the multifactorial nature of disease development and progression.

Direct evidence of the clinical utility of genetic testing in asymptomatic individuals at risk for developing age-related macular degeneration is lacking. While genetic variants have been used in risk-prediction models, no consistent associations between specific genetic variants and response to specific treatments have been established.

TESTING IN INDIVIDUALS WITH AMD

Clinical Context and Test Purpose

The purpose of genetic testing of individuals with AMD is to identify SNVs that potentially predict response to treatment.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Clinical validity is how the presence of specific SNVs provide accurate prognosis for disease course and predict response to treatment. Evidence to support the clinical validity of accurate disease prognosis and response to treatment was not identified.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

What can be done for an individual with AMD using genetic test results for prognosis and predicting response to treatment? The possible clinical utility of genetic testing for AMD includes disease monitoring and therapy guidance, as discussed in more detail below.

- Monitoring: There is currently no cure for macular degeneration, but genetic variants may provide more accurate prognosis on disease progression. Frequency of monitoring may be increased if a genetic variant is associated with a more rapid or severe disease course.
- Direction of therapy: No consistent association between response to vitamin supplements or anti-*VEGF* (vascular endothelial growth factor) therapy and *VEGF* gene variants polymorphisms.¹⁵⁻²⁰

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence comes from randomized controlled trials (RCTs). No such trials were identified.

Chain of Evidence

Direct evidence of the clinical utility of genetic testing in individuals with age-related macular degeneration is lacking. While genetic variants have been used in risk-prediction models, there have been no consistent associations between specific genetic variants in altering and response to treatments.

Section Summary: Individuals with Age-Related Macular Degeneration

Direct evidence of the clinical utility of genetic testing in individuals with AMD is lacking. While genetic variants have been used in risk prediction models, there have been no consistent associations between specific genetic variants in altering and response to treatments.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Ophthalmology

The 2014 American Academy of Ophthalmology (AAO) Task Force on Genetic Testing recommendations specific to genetic testing for complex eye disorders like AMD state that the presence of any one of the disease-associated variants is not highly predictive of the development of disease.²¹ The AAO Task Force finds that in many cases, standard clinical diagnostic methods like biomicroscopy, ophthalmoscopy, tonography, and perimetry will be more accurate for assessing a patient's risk of vision loss from a complex disease than the assessment of a small number of genetic loci. AAO concludes that genetic testing for complex diseases will become relevant to the routine practice of medicine when clinical trials demonstrate that patients with specific genotypes benefit from specific types of therapy or surveillance; until such benefit can be demonstrated, the routine genetic testing of patients with complex eye diseases, or unaffected patients with a family history of such diseases, is not warranted.

In 2019, AAO published a Preferred Practice Pattern on age-related macular degeneration, which noted that the routine use of genetic testing is not recommended at this time due to lack of prospective clinical evidence.²²

In 2021, the AAO published an article on genetics and AMD which noted that “gene therapy is not available for prevention or management of the disease, so there is no benefit of identifying which genes are involved in any individual's case of macular degeneration”.²³

An AAO Preferred Practice Pattern on age-related macular degeneration, last updated in 2024, notes that the routine use of genetic testing is not recommended at this time due to lack of prospective clinical evidence.²³

American Society of Retina Specialists

The American Society of Retina Specialists (2017) published special correspondence on the use of genetic testing in the management of patients with AMD.²³ The Society concluded that:

- While AMD genetic testing may provide information on progression from intermediate to advanced AMD, there is no clinical evidence that altering management of genetically

higher risk progression patients' results in better visual outcomes compared with patients' lower risk progression patients.

- AMD genetic testing in patients with neovascular AMD does not provide clinically relevant information regarding response to anti-vascular endothelial growth factor treatment and is therefore not recommended for this population.
- Currently, there is insufficient evidence to support the use of genetic testing in patients with AMD in regard to nutritional supplement recommendations.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for genetic testing for macular degeneration have been identified.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04739319	Project AMD: Comprehensive Characterization of Age-Related Macular Degeneration and Its Progression	2500	Nov 2040
NCT01115387	Genetics of Age-Related Maculopathy (GARM II)	603	Mar 2027
Unpublished			
NCT02762188	Genetic Biomarkers for the Response to Anti-VEGF (Vascular Endothelial Growth Factor). Treatment in Wet Age-Related Macular Degeneration (Wet ARMD)	501	Jan 2018
NCT01310686 ^a	Genetics Study of Wet Age-Related Macular Degeneration (age-related macular degeneration) Non-Responders to Vascular Endothelial Growth Factor (VEGF) Therapy	40	Jun 2019

NCT: national clinical trial.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Government Regulations

National/Local:

There is no national or local coverage determination on genetic testing for macular degeneration.

According to the CMS Clinical Laboratory Fee Schedule (2024), codes 81401, 81405, 81408 and 0205U all have fees attached.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 2026, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/14	2/18/14	2/28/14	Joint policy established
7/1/15	4/24/15	5/8/15	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine policy maintenance. Updated references.
7/1/17	4/18/17	4/18/17	Routine update, no change in policy status.
7/1/18	4/17/18	4/17/18	Routine policy maintenance, updated rationale added reference #16. No change in policy status.
7/1/19	4/16/19		Routine policy maintenance, no change in policy status.
7/1/20	4/14/20		Routine policy maintenance, no change in policy status.
7/1/21	4/20/21		Routine policy maintenance, added reference #15 and 16. No change in policy status.
7/1/22	4/19/22		Routine policy maintenance, no change in policy status.
7/1/23	4/18/23		Routine policy maintenance, no change in policy status. Vendor managed: N/A. (ds)
7/1/24	4/16/24		• Routine policy maintenance, added reference #23, added codes 81479 and 0205U as E/I. • RetnaGene™ testing added to policy as E/I Vendor managed: N/A (ds)
7/1/25	4/15/25		Routine policy maintenance, no change in policy status. Vendor managed: N/A (ds)
7/1/26	4/21/26		Routine policy maintenance, no change in status. Formatting changes made. Vendor managed: N/A (ds)

Next Review Date: 2nd Qtr. 2027

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR MACULAR DEGENERATION

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A