

Genetic Testing for Macular Degeneration

Effective: January 1, 2024

Next Review: July 2024

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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

Age-related macular degeneration (AMD) 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 AMD or to guide treatment.

MEDICAL POLICY CRITERIA

Genetic testing for macular degeneration is considered **investigational**.

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

CROSS REFERENCES

1. [Preimplantation Genetic Testing of Embryos](#), Genetic Testing, Policy No. 18
2. [Evaluating the Utility of Genetic Panels](#), Genetic Testing, Policy No. 64

BACKGROUND

AGE-RELATED MACULAR DEGENERATION (AMD)

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). AMD has an estimated prevalence of 1 in 2,000 people in the United States and affects individuals of European descent more frequently than African Americans in the United States.

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 (such as antioxidants and zinc), and obesity. Observational data (n=17,174) from the European EYE-RISK Consortium suggest that the odds of AMD increases by at least 2 times in patients with both genetic risk and predisposing lifestyle factors (e.g., smoking and low dietary intake of vegetables, fruit, and fish).^[1]

CLINICAL DIAGNOSIS OF AMD

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 a 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 OF AMD

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.^[2]

GENETICS OF AMD

It has been reported that genetic variants associated with AMD account for approximately 70% of the risk for the condition.^[3]

More than 25 genes have been reported in association with an increased 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.^[4]

Loci based on common single nucleotide polymorphisms (SNPs) 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*.^[4] 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*.^[4, 5] The collagen matrix pathway genes *COL10A1* and *COL8A1*, apolipoprotein E *APOE* and the extracellular matrix pathway gene *TIMP3* and *FBN2* have also been linked to AMD.^[4] Genes involved in DNA repair (*RAD51B*) and in the angiogenesis pathway (*VEGFA*) have also been associated with AMD as have specific SNPs.^[6] Recently Fang (2021) presented a systematic review on use of genetic biomarkers different than those mentioned above for early AMD and intermediate AMD, which are more reproducible and less invasive than the other classes of biomarkers.^[7]

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 PGx®, which uses patient clinical information (age, BMI, smoking history, education) and the patient's genotype for 15 genetic markers across 12 AMD-associated genes, 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.

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 mutations in *CFH*, *ARMS2/HTRA1*, *C2*, *DFB*, and *C3* genes. 23andMe includes testing for *CFH*, *ARMS2*, and *C2*.

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.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature^[8] 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.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test indicating how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of the literature search was on evidence related to the ability of genetic test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

ANALYTIC VALIDITY

According to the manufacturer, the Macula Risk® PGx test is noted as having a 10-year predictive accuracy of 89.5%, with a sensitivity and specificity both > 80%.^[9, 10] Data regarding the predictive accuracy of the RetnaGene™ AMD test was not identified in the peer-reviewed literature.

Genetic testing for single or multiple genes associated with advanced AMD may be requested through a number of laboratories which are typically validated in-house and are subject to CLIA regulatory standards.

CLINICAL VALIDITY

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.^[11-16] (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). An analysis by Seddon (2015) demonstrated that a model of AMD risk that included age, gender, education, baseline AMD grade, smoking and body mass index had an AUC of 0.757.^[14] The addition of the genetic factors SNPs in CFH, ARMS2, C2, C3 and CFB, increased the AUC to 0.821. In a 2015 report, Seddon included 10 common and rare genetic variants in their risk prediction model, resulting in an AUC of 0.911 for progression to advanced AMD.^[17]

Klein (2011) evaluated macular phenotype, utilizing the Age-Related Eye Disease Study (AREDS) Simple Scale score, which rated the severity of AMD based on the presence of large drusen and pigment changes, to predict the rate of advanced AMD.^[11, 18] This predictive model 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 (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.^[19] Ajana (2021) also reported an area under the curve at five years of 0.92 for an age-related macular degeneration model that included clinical, genetic, and lifestyle factors.^[20] de Breuk (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 ($p < 0.001$) or no disease ($p < 0.001$) based on a European case-control population ($n = 4,740$).^[21] In addition to the biomarkers mentioned in this policy, a recent publication reported microRNAs, urinary proinflammatory cytokines, and proteins in the aqueous and vitreous humor; apolipoprotein A1 (APOA1), complement factor H R2 (CFHR2), and clusterin (CLUS) proteins, kallistatin (SERPINA4), lumican (LUM), and keratan (KERA) as an indication of early AMD.^[7]

Although these risk models suggest some small incremental increase in the ability to assess risk of developing advanced AMD based on genetic factors, they do not demonstrate how results from testing alter treatment decisions or improve overall health outcomes.

CLINICAL UTILITY

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

The clinical utility of predictive genetic testing for AMD rests in the availability of preventative therapies and interventions which go beyond good health practices (e.g., abstinence from smoking, balanced diet, exercise, nutrient supplements). In addition, once a preventive therapy was established, the optimal risk-benefit treatment strategy would need to be validated to ensure appropriate age-related AMD interventions. However, the only preventive measures currently available are high-dose antioxidants and zinc supplements which have been shown to reduce the progression of disease.^[2, 22-25]

Monitoring

The clinical utility of genetic testing for AMD could also rest in the tests ability to identify a patient as high risk, which may increase the frequency of monitoring. This could include the use of home monitoring devices or the use of technology such as preferential hyperacuity perimetry to detect early or subclinical wet AMD. However, there is insufficient evidence demonstrating how more frequent monitoring of high-risk patients slows the progression of AMD or improves overall outcomes.^[11]

Treatment

Finally, the clinical utility of genetic testing for AMD could also rest in the tests ability to identify patients who would benefit from specific gene-based treatment which may slow, halt, or resolve AMD symptoms. There is insufficient evidence demonstrating how genetic test results have been used to guide treatment decisions in patients with advanced AMD. A recent systematic review showed that anti-VEGF therapy may produce significant improvement at 12 months in patients with neovascular AMD.^[26] However, there have been no consistent associations between response to vitamin supplements or anti-VEGF (vascular endothelial growth factor) therapy and *VEGF* gene polymorphisms.^[23, 24, 27-32]

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF OPHTHALMOLOGY (AAO)

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.^[33] 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.^[34]

AMERICAN SOCIETY OF RETINA SPECIALISTS^[35]

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

SUMMARY

The current evidence is insufficient in demonstrating how genetic testing for age-related macular degeneration (AMD) improves treatment decisions or health outcomes. Currently, there are no preventive measures that can be undertaken, outside of good health practices. Therefore, genetic testing for AMD is considered investigational.

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CODES

Codes	Number	Description
CPT	0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements
	81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
	81479	Unlisted molecular pathology procedure

Codes	Number	Description
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

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