Policy

Genetic testing for macular degeneration is considered investigational.

Related Policies

None

Policy Guidelines

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

If the testing is specific to particular genes that have been codified and does not involve any risk algorithm, the test can be reported with the Tier 2 CPT code(s).

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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</table>
| 81401 | Molecular pathology procedure, Level 2 (e.g., 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). This test includes:  
  - APOE (apolipoprotein E) (e.g., hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (e.g., *2, *3, *4)  
  - CFH/ARMS2 (complement factor H/age-related maculopathy susceptibility 2) (e.g., macular degeneration), common variants (e.g., Y402H [CFH], A69S [ARMS2]) |
| 81405 | Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis). This test includes:  
  - HTRA1 (HtrA serine peptidase 1) (e.g., macular degeneration), full gene sequence |
Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis). This test includes:

- ABCA4 (ATP-binding cassette, sub-family A [ABC1], member 4) (e.g., Stargardt disease, age-related macular degeneration), full gene sequence

Unlisted molecular pathology procedure

Unlisted multianalyte assay with algorithmic analysis

* If the specific testing is not listed in Tier 2, the unlisted molecular pathology code 81479 would be reported.
** If the testing involves multiple analytes and an algorithm, the unlisted multianalyte assay with algorithmic analysis (MAAA) code 81599 would be reported.

Commercially available tests include but are not limited to the following (see Regulatory Status):
- Macula Risk PGx® (Arctic Medical Laboratories)
- RetnaGene™ AM (Sequenom, Inc.)

**Description**

Age-related macular degeneration (AMD) is a complex disease involving both genetic and environmental influences. Testing for mutations at certain genetic loci has been proposed to predict the risk of developing advanced AMD. AMD 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 risk of AMD and of the development of the wet form is associated with genetic and nongenetic (e.g., age, smoking) influences.

The evidence for genetic testing in individuals who are asymptomatic with risk of developing AMD includes genetic association studies and risk prediction models. Relevant outcomes are test validity, change in disease status, and functional outcomes. The analytic validity of genetic testing for AMD is high, and 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 the effects of the technology on health outcomes.

The evidence for genetic testing in individuals who have AMD includes genetic association studies and risk prediction models. Relevant outcomes are test validity, change in disease status, and functional outcomes. The analytic validity of genetic testing for assessing the risk of progression to advanced AMD is high. 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 the effects of the technology on health outcomes.

**Background**

**Description of the Disease**

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 2 major types of AMD, known as the dry form and the wet form.

1. 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.
2. 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.

**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 life style 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, antiangiogenic 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 (NCT00345176) 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. (1)

- Slideshow: Essential Screening Tests Every Man Needs
- Eye Health Check - Take the WebMD Eye Health Assessment
- Coping With Vision Loss
- Low Vision and Your Eyes
- Blind/Visually Impaired
- How Well Can Newborn Babies See?
- Computer Vision Syndrome
- See All Vision Loss & Changes Topics

**Genetics of AMD**

It has been reported that genetic variants associated with AMD account for approximately 70% of the risk for the condition. (2)

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. (3)

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. (3)

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. (3) The collagen matrix pathway genes COL10A1 and COL8A1 and the extracellular matrix pathway gene TIMP3 have also been linked to AMD. (3) 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.

Nicox offers Sequenom’s RetnaGene™ AMD in North America. RetnaGene™ 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) 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). A risk score is generated, and the patient is categorized into one of 3 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.

### Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

### Benefit Application

N/A

### Rationale

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• Who are asymptomatic with</td>
<td></td>
<td></td>
<td>• Test validity</td>
</tr>
</tbody>
</table>
risk of developing age-related macular degeneration

- Genetic testing
- No genetic testing
- Change in disease status
- Functional outcomes

| Individuals: |
| With age-related macular degeneration |
| Interventions of interest |
| Genotyping |
| Comparators of interest |
| Standard clinical care |
| Relevant outcomes include: |
| Test validity |
| Change in disease status |
| Functional outcomes |

This evidence review was created in 2013 and has been updated with a search of the MEDLINE database through November 10, 2015. Literature that describes the analytic validity, clinical validity, and clinical utility of genetic testing for macular degeneration was sought (see Appendix Table 1 for genetic testing categories).

**Analytic Validity**

Analytic validity is the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent.

According to a major laboratory’s website, the analytic sensitivity and specificity of testing for mutations in the *ARMS2* gene and *CFH* gene by polymerase chain reaction is 99%.(4)

**Clinical Validity**

Clinical validity is the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease.

*How well can the test predict the risk of developing advanced age-related macular degeneration (AMD)?* 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. (4-7) (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.)

A 2009 analysis by Seddon et al demonstrated that a model of AMD risk that included age, gender, education, baseline AMD grade, smoking and body mass index had an AUC of 0.757.8 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 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.9 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.5,10 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 1 eye, and genetic factors (*CFH* and *ARMS2*). The AUC was 0.865 without genetic factors included and 0.872 with genetic factors included. (5)

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 utility is not established.

**Clinical Utility**

Clinical utility is 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.

*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 a 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, the only preventive measures available are high-dose antioxidants and zinc supplements. (1)

- **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. (4)

- Guide therapy: There have been no consistent associations between response to anti-VEGF (vascular endothelial growth factor) therapy and VEGFA or VEGFR2 gene polymorphisms. (9) CFH and ARMS2 polymorphisms have been shown to predict response to antioxidants and zinc. (10) No studies were identified that assessed the clinical utility of commercially available algorithms.

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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT01115387</td>
<td>GARM II: A Study on the Genetics of Age-related Maculopathy</td>
<td>7000</td>
<td>Aug 2016</td>
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<tr>
<td>Unpublished</td>
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<tr>
<td>NCT01650948a</td>
<td>Evaluation of Genetic Variants in Patients Under Treatment for Choroidal Neovascular (CNV) Age-related Macular Degeneration (AMD), Receiving Intravitreal antiVEGF Injections to Evaluate the Association Between Genetic Load and Phenotypes Associated With More Aggressive Forms of Disease</td>
<td>100</td>
<td>Completed Dec 2013</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

Summary of Evidence

The evidence for genetic testing in individuals who are asymptomatic with risk of developing age-related macular degeneration (AMD) includes genetic association studies and risk prediction models. Relevant outcomes are test validity, change in disease status, and functional outcomes. The analytic validity of genetic testing for AMD is high, and 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 the effects of the technology on health outcomes.

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Practice Guidelines and Position Statements

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.16 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.

**U.S. Preventive Services Task Force Recommendations**

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

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**

Coding

<table>
<thead>
<tr>
<th>Codes</th>
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<tbody>
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<td>81405</td>
<td>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)</td>
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<td>81479</td>
<td>Unlisted molecular pathology code</td>
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<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis (MAAA)</td>
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Appendix

N/A

History

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<td>12/09/13</td>
<td>New Policy. New policy developed with review of the literature through September 2013. Genetic testing for AMD is considered investigational.</td>
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<tr>
<td>02/09/16</td>
<td>Annual Review. Policy updated with literature review through November 10, 2015; references 9 and 11-13 added. Policy statement unchanged.</td>
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<tr>
<td>07/01/16</td>
<td>Update Related Policies. Remove 9.03.20 as it was archived.</td>
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200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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