Genetic Testing for Macular Degeneration

Effect Date: May 1, 2018
Last Revised: April 3, 2018
Related Medical Policies: None

Introduction

The macula is the part of the retina that allows central vision. It's the part of the retina that lets a person see things straight ahead. Age-related macular degeneration (AMD) occurs when the macula breaks down. This is usually due to age and other risk factors like smoking, heart disease, or obesity. AMD is the leading cause of vision loss in people over 60. It affects one out of every 2,000 people in the United States. There are two types of macular degeneration, the wet form and the dry form. The wet form is the more common. It affects between 85% and 90% of people who develop AMD. The dry form develops slowly and affects both eyes, with gradual vision loss. The wet form of AMD happens when blood vessels grow beneath the macula. Vision loss is usually severe and happens quickly. A genetic test has been developed to try to predict who will develop AMD as well as how rapidly it might advance. While there are some genetic markers for AMD, genetic testing is investigational because medical studies do not show better health results after these genetic tests have been done.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

Testing | Investigational
---|---
**Genetic testing** | Genetic testing for macular degeneration is considered investigational.

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>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
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</table>
| 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). This test includes:  

- CFH/ARMS2 (complement factor H/age-related maculopathy susceptibility 2) (eg, macular degeneration), common variants (eg, Y402H [CFH], A69S [ARMS2]) |
| 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). This test includes:  

- HTRA1 (HtrA serine peptidase 1) (eg, macular degeneration), full gene sequence |
| 81408  | Molecular pathology procedure, Level 9 (eg, 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) (eg, Stargardt disease, age-related macular degeneration), full gene sequence |
| 81479* | Unlisted molecular pathology procedure                                                               |
| 81599**| 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 (MAAAA) code 81599 would be reported.
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Related Information

Commercially available tests include but are not limited to the following (see Regulatory Status):

- Macula Risk PGx® (Arctic Medical Laboratories)
- RetnaGene™ AM (Sequenom, Inc.)

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</table>
Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Evidence Review

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. 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 developing AMD and of developing the wet form is associated with genetic and nongenetic (eg, age, smoking) influences.
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). 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.

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, because 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 (eg, 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 test, a pattern of straight lines that resembles 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. The Age-Related Eye Disease Study (AREDS, 2001), a large study performed by the National Eye Institute of the National Institutes of Health, showed that, for certain individuals (those with extensive drusen or neovascular AMD in one eye), high doses of vitamins C, E, β-carotene, and zinc may provide a modest protective effect against the progression of AMD.\(^1\)

**Genetic Testing**

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 variants 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 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 and FBN2 have also been linked to AMD. Genes involved in DNA repair (RAD51B) and 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.

deCode Complete includes testing for variants in CFH, ARMS2 and 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 AMD who receive genetic testing for AMD, the evidence includes genetic association studies and risk prediction models. Relevant outcomes are test accuracy, 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 the effects of the technology on health outcomes.
For individuals who have AMD who receive genetic testing for AMD, the evidence includes genetic association studies and risk prediction models. Relevant outcomes are test accuracy, 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 the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 3.

### Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02762188</td>
<td>Genetic Biomarkers for the Response to Anti-VEGF (Vascular Endothelial Growth Factor). Treatment in Wet Age-Related Macular Degeneration (Wet ARMD)</td>
<td>501</td>
<td>Jul 2017 (ongoing)</td>
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<tr>
<td>NCT01213667</td>
<td>Genetics in Non-Response to Anti-VEGF Treatment in Exudative AMD (RESPONSE)</td>
<td>110</td>
<td>Dec 2017</td>
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<tr>
<td>NCT01310686*</td>
<td>Genetics Study of Wet Age-Related Macular Degeneration (AMD) Non-Responders to Vascular Endothelial Growth Factor (VEGF) Therapy</td>
<td>40</td>
<td>Jun 2018</td>
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<tr>
<td>NCT03024424</td>
<td>Value of Genetic Counseling and Testing for Patients Who Would Like to Know More About Their Personal Risk of AMD</td>
<td>200</td>
<td>Mar 2020</td>
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<tr>
<td>NCT01115387</td>
<td>GARM II: A Study on the Genetics of Age-related Maculopathy</td>
<td>603</td>
<td>Aug 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.
Practice Guidelines and Position Statements

American Academy of Ophthalmology

The 2014 American Academy of Ophthalmology (AAO) recommendations specific to genetic testing for complex eye disorders like age-related macular degeneration (AMD) have indicated that the presence of any one of the disease-associated variants is not highly predictive of disease development. The AAO found 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. The AAO concluded 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.

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. 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 (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.

Medicare National Coverage

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

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tr>
<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>
</tr>
<tr>
<td>07/01/16</td>
<td>Update Related Policies. Remove 9.03.20 as it was archived.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through January 2018; reference 5 was removed and reference 16 was added. Policy statement unchanged.</td>
</tr>
</tbody>
</table>

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