Medical Policy
Genetic Testing for Macular Degeneration

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Policy Number: 665
BCBSA Reference Number: 2.04.103
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
- Intravitreal Angiogenesis Inhibitors for Choroidal Vascular Conditions, #343

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genetic testing for macular degeneration is considered INVESTIGATIONAL.

Medicare HMO Blue℠ and Medicare PPO Blue℠ Members
Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>This is not a covered service.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>This is not a covered service.</td>
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<tr>
<td>Medicare HMO Blue℠</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

According to the policy statement above, the following CPT codes are considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), and PPO, Indemnity.

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81401</td>
<td>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)</td>
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<tr>
<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>
</tr>
<tr>
<td>81408</td>
<td>Molecular pathology procedure, Level 9 (eg, analysis of &gt;50 exons in a single gene by DNA sequence analysis)</td>
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Description
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 2000 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. 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 1 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, 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 low in certain nutrients (eg, antioxidants, zinc), and obesity.
Clinical Diagnosis
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-sectional 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 disease progression. For dry AMD, there is no medical treatment; however, changing certain lifestyle risks may slow AMD onset and progression. 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. The Age-Related Eye Disease Study (AREDS), 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 1 eye), high doses of vitamins C, E, β-carotene, and zinc may provide a modest protective effect against the progression of AMD.¹

Genetics
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 biologic 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 (SNVs) contribute to the greatest risk of AMD:
- the long (q) arm of chromosome 10 in a region known as 10q26 contains 2 genes of interest, ARMS2 and HTRA1. Changes in both genes have been studied as possible risk factors for the disease; however, because the 2 genes are so close together, it is difficult to tell which is associated with AMD 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 cholesterol pathway genes have been implicated, including CETP and LIPC, and possibly LPL and ABCA1.³ The collagen matrix pathway genes COL10A1 and COL8A1, apolipoprotein E APOE, and the extracellular matrix pathway genes TIMP3 and FBN2 have also been linked to AMD. Genes involved in DNA repair (RAD51B) and 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 whites 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 and 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
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 risks of AMD and of developing the wet form are associated with genetic and nongenetic (eg, age, smoking) factors.

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 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 improvements in health outcomes in patients 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 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.

Policy History

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<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>5/2017</td>
<td>BCBSA National medical policy review. Policy clarified.  5/1/2017</td>
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<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<td>7/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<td>12/2014</td>
<td>New references added to BCBSA National medical policy.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References
1. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular


