Genetic Testing for Macular Degeneration

Policy # 00399
Original Effective Date: 01/15/2014
Current Effective Date: 03/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for macular degeneration to be investigational.*

Background/Overview
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 (eg, age, smoking) influences.

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. Age-related macular degeneration 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. Age-related macular degeneration 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.
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Clinical Diagnosis of Age-Related Macular Degeneration
Age-related macular degeneration 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 Age-Related Macular Degeneration
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, 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.

Genetics of Age-Related Macular Degeneration
It has been reported that genetic variants associated with AMD account for approximately 70% of the risk for the condition.

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.

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 AMD risk, or whether increased risk results from variations in both genes.
- Two major loci in the complement factor H (CFH) gene.

Other confirmed genes in the complement pathway include C2, C3, CFB and CFI.
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. 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 Age-Related Macular Degeneration**

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.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

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.

Centers for Medicare and Medicaid Services (CMS)

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

**Rationale/Source**

**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. Data on analytic validity are lacking.
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%.

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? 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. (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. 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. Klein et al showed that an individual’s macular phenotype, as represented by the 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. 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.

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 next.

- 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 (eg, 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.
- 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.

- **Guide therapy:** There have been no consistent associations between response to vitamin supplements or anti-VEGF (vascular endothelial growth factor) therapy and VEGF gene polymorphisms.

### 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

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<thead>
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<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>NCT01115387</td>
<td>GARM II: A Study on the Genetics of Age-related Maculopathy</td>
<td>7000</td>
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<td>NCT01650948</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>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

### Summary

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.

### References

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01/09/2014 Medical Policy Committee review
01/15/2014 Medical Policy Implementation Committee approval. New policy.
01/08/2015 Medical Policy Committee review
01/21/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
03/03/2016 Medical Policy Committee review
03/16/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
03/02/2017 Medical Policy Committee review
03/15/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 03/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2016 by the American Medical Association (AMA).

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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<td>HCPCS</td>
<td>No codes</td>
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<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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