Genetic Testing for Macular Degeneration

Policy # 00399
Original Effective Date: 01/15/2014
Current Effective Date: 03/21/2018

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

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 (e.g., 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 life style 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.

Genetics
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 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.

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*.

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*. 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*.

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 Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA 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

GENETIC TESTING IN ASYMPTOMATIC INDIVIDUALS WITH RISK OF DEVELOPING AGE-RELATED MACULAR DEGENERATION

Clinical Context and Test Purpose
The purpose of genetic testing of asymptomatic individuals with risk of developing AMD is to identify SNVs for primary prevention or earlier detection of disease for more timely intervention to affect course of disease progression.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in asymptomatic individuals with risk of developing AMD?

The following PICOTS were used to select literature to inform this review.

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Patients
The relevant population of interest is asymptomatic individuals with risk of developing AMD.

Interventions
The relevant intervention is genetic testing for AMD.

Comparators
The relevant comparator is standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are test validity, change in disease status, and functional outcomes. The potential beneficial outcomes of primary interest would be improvements in disease status and functional outcomes.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to clinical management changes. False-negative test results can lead to absence of clinical management changes.

Timing
The primary outcomes of interest are the initiation and frequency of monitoring for assessing changes in disease status.

Setting
Patients may be referred from primary care to an ophthalmologist or medical geneticist for investigation and management of AMD. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

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

According to a major laboratory's website, the analytic sensitivity and specificity of testing for variants in the *ARMS2* and *CFH* genes 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 risk assessment for predicting disease development in asymptomatic individuals. In other words, how well can the test predict the risk of developing advanced 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. (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, which included age, sex, education, baseline AMD grade, smoking, and body mass index, had an AUC of 0.757. The addition of the genetic factors (SNVs) 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 (2011) 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 validity is not established.

Section Summary: Clinical Validity
Evidence from studies has indicated that the clinical sensitivity of genetic testing for genes associated with AMD may have small incremental effects on assessing risk of developing AMD. Risk-prediction models incorporate factor such as age, sex, smoking, body mass index, and genetic factors. The true clinical specificity of genetic variants in AMD-related genes is uncertain because of the multifactorial nature of disease development and progression.

Clinical Utility
Clinical utility is how the results of the risk assessment/susceptibility test will be used to change patient management 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 below.

- Prevention: Genetic testing and risk prediction for AMD would have clinical utility if a preventive therapy 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 it could be determined which individuals should receive those treatments and at what age to start the intervention. Currently, no preventive measures are available; high-dose antioxidants and zinc supplements have been shown to reduce disease progression.
- Monitoring: If a patient is identified as high risk, changes in the frequency of monitoring may occur and could include 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.

- Direction of therapy: No consistent associations between response to vitamin supplements and genetic variants have been established.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from randomized controlled trials (RCTs). No such trials were identified.

Chain of Evidence
A chain of evidence for clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Clinical Utility
Direct evidence of the clinical utility of genetic testing in asymptomatic individuals at risk for developing AMD is lacking. While genetic variants have been used in risk-prediction models, no consistent associations between specific genetic variants and response to specific treatments have been established.

GENETIC TESTING IN INDIVIDUALS WITH AMD

Clinical Context and Test Purpose
The purpose of genetic testing of individuals with AMD is to identify SNVs that potentially predict response to treatment.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals with AMD?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is symptomatic individuals with AMD.

Interventions
The relevant intervention is genetic testing to determine prognosis or predict response to therapy.

Comparators
The relevant comparator is standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are test validity, change in disease status, and functional outcomes. The potential beneficial outcomes of primary interest would be improvements in disease status and functional outcomes.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to clinical management changes. False-negative test results can lead to absence of clinical management changes.

Timing
The primary outcomes of interest are the initiation and frequency of monitoring for assessing changes in disease status and effects of management decisions on short-term and long-term functional outcomes.

Setting
Patients may be referred from primary care to an ophthalmologist or medical geneticist for investigation and management of AMD. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
See the previous section on Analytic Validity.

Clinical Validity
Clinical validity is how the presence of specific SNVs provide accurate prognosis for disease course and predict response to treatment.

Clinical Utility
Clinical utility is how the results of the genetic test will be used to change patient management and whether these changes in management lead to clinically important improvements in health outcomes.

What can be done for an individual with AMD using genetic test results for prognosis and predicting response to treatment? The possible clinical utility of genetic testing for AMD includes disease monitoring and therapy guidance, as discussed below.

- Monitoring: There is currently no cure for macular degeneration, but genetic variants may provide more accurate prognosis on disease progression. Frequency of monitoring may be increased if a genetic variant is associated with a more rapid or severe disease course.
- Direction of therapy: No consistent associations between response to vitamin supplements or anti-vascular endothelial growth factor (VEGF) therapy and *VEGF* gene variants have been established.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from RCTs. No such trials were identified.

Chain of Evidence
A chain of evidence for clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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Section Summary: Clinical Utility
Direct evidence of the clinical utility of genetic testing in individuals with AMD is lacking. While genetic variants have been used in risk-prediction models, there have been no consistent associations between specific genetic variants in altering and response to treatments.

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 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.

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Policy History

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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.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 03/2019

Coding

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Code Type	Code
CPT	81401, 81405, 81408, 81479, 81599
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*****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 U.S. Food and Drug Administration (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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