Genetic Testing for Macular Degeneration

Policy # 00399
Original Effective Date: 01/15/2014
Current Effective Date: 04/13/2020

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.***

Policy Guidelines

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. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). 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 PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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.

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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 (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 may be performed. Angiography involves injecting a dye into the bloodstream to identify leaking blood vessels in the macula. Optical coherence tomography 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 (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 1 eye), high doses of vitamins C, E, -carotene, and zinc may provide a modest protective effect against the progression of AMD.

Genetic Testing
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 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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Rationale/Source

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 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 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 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.

Supplemental Information

Practice Guidelines and Position Statements

American Academy of Ophthalmology

The 2014 American Academy of Ophthalmology 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 Academy found that, in many cases, standard clinical diagnostic methods like

biomicroscopy, ophthalmoscopy, tonography, and perimetry would 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 Academy 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, 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.

U.S. Preventive Services Task Force Recommendations
Not applicable.

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.

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

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

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

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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.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/05/2020	Medical Policy Committee review

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03/11/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/21/2020 Coding update
Next Scheduled Review Date: 03/2021

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 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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

Code Type	Code
CPT	81401, 81405, 81408, 81479, 81599 Add code eff 10/1/2020: 0205U

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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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.