Genetic Testing for Macular Degeneration

Policy # 00399
Original Effective Date: 01/15/2014
Current Effective Date: 04/08/2024

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.

When 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.***

When Services Are Not Covered

Based on review of available data, the Company considers repeat germline testing to be **not covered****.

Note:
Repeat germline testing that investigates the same genetic information is not reasonable and necessary as it is duplicative and not required for medical treatment decisions. Examples of germline tests include, but are not limited to, single gene testing, gene panel tests, and whole exome or whole genome sequencing for inherited disorders and pharmacogenomic/cytochrome P450 testing.

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 was 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

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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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors

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can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

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. In 2019, approximately 19.8 million Americans 40 years of age and older were living with age-related macular degeneration. Sex- and age-standardized rates of age-related macular degeneration were lower for non-Hispanic Black people (7.0%) than for other racial and ethnic groups (13.3%). Age-related macular degeneration 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 age-related macular degeneration, 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 age-related macular degeneration, 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. Age-related macular degeneration is generally thought to progress along a continuum from dry age-related macular degeneration to neovascular wet age-related macular degeneration, with approximately 10% to 15% of all age-related macular degeneration patients eventually developing the wet form. Occasionally patients with no prior signs of dry age-related macular degeneration present with wet age-related macular degeneration as the first manifestation of the condition.

The wet form of age-related macular degeneration, sometimes referred to as "vision-threatening" or "late stage" age-related macular degeneration, 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.

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Major risk factors for age-related macular degeneration 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 age-related macular degeneration include high blood pressure, heart disease, a high-fat diet or a diet low in certain nutrients (eg, antioxidants, zinc), and obesity. Observational data (N=17,174) from the European EYE-RISK Consortium suggest that the odds of age-related macular degeneration increase by at least 2 times in patients with both genetic risk and predisposing lifestyle factors (eg, smoking and low dietary intake of vegetables, fruit, and fish).

Clinical Diagnosis
Age-related macular degeneration can be detected by routine eye exams, 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 age-related macular degeneration, some of the straight lines may appear wavy or missing.

If age-related macular degeneration 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 age-related macular degeneration, there is no medical treatment; however, changing certain lifestyle risks may slow age-related macular degeneration onset and progression. The goal for wet (advanced) age-related macular degeneration 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

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with extensive drusen or neovascular age-related macular degeneration in 1 eye), high doses of vitamins C, E, beta-carotene, and zinc may provide a modest protective effect against the progression of age-related macular degeneration.

Genetic Testing
It has been reported that genetic variants associated with age-related macular degeneration account for approximately 70% of the risk for the condition.

More than 25 genes have been reported to influence the risk of developing age-related macular degeneration, 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 age-related macular degeneration.

Loci based on common single nucleotide variants contribute to the greatest risk of age-related macular degeneration:

- 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 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.*

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 *COL10A* and *COL8A1*, apolipoprotein E (APOE), and the extracellular matrix pathway genes, *TIMP3* and *FBN2,* have also been linked to age-related macular degeneration. Genes involved in DNA repair *(RAD51B)* and in the angiogenesis pathway *(VEGFA)* have also been associated with age-related macular degeneration.

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Commercially Available Testing for Age-Related Macular Degeneration
Commercially available genetic testing for age-related macular degeneration is aimed at identifying those individuals who are at risk of developing advanced age-related macular degeneration.

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 age-related macular degeneration to advanced forms of age-related macular degeneration. A Vita Risk®‡ report is also provided with vitamin recommendations based on the *CFH* and *ARMS2* genotype.

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 (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Description
Age-related macular degeneration 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 age-related macular degeneration. Age-related macular degeneration 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 age-related macular

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degeneration and of developing the wet form are associated with genetic and nongenetic (eg, age, smoking) factors.

Summary of Evidence
For individuals who are asymptomatic with risk of developing age-related macular degeneration who receive genetic testing for age-related macular degeneration, 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 age-related macular degeneration 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 that the technology results in an improvement in the net health outcome.

For individuals with age-related macular degeneration who receive genetic testing for age-related macular degeneration, 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 age-related macular degeneration 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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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 have indicated that the presence of any 1 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 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 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, routine genetic testing of patients with complex eye diseases, or unaffected patients with a family history of such diseases, is not warranted.

In 2019, AAO published a Preferred Practice Pattern on age-related macular degeneration, which noted that the routine use of genetic testing is not recommended at this time due to lack of prospective clinical evidence.

American Society of Retina Specialists
In 2017, the American Society of Retina Specialists published special correspondence on the use of genetic testing in the management of patients with age-related macular degeneration. The Society concluded that:

- While age-related macular degeneration genetic testing may provide information on progression from intermediate to advanced age-related macular degeneration, there is no clinical evidence that altering management of patients with genetically higher risk for progression results in better visual outcomes compared with patients with genetically lower risk for progression.
- Age-related macular degeneration genetic testing in patients with neovascular age-related macular degeneration does not provide clinically relevant information regarding response to anti-vascular endothelial growth factor treatment and is therefore not recommended for this population.
- Currently, there is insufficient evidence to support the use of genetic testing in patients with age-related macular degeneration in regard to nutritional supplement recommendations.

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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 ongoing and 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			
NCT04739319	Project AMD: Comprehensive Characterisation of Age-Related Macular Degeneration and Its Progression	2500	Nov 2040
NCT01115387	Genetics of Age Related Maculopathy (GARM II)	603	Mar 2027
Unpublished			
NCT02762188	Genetic Biomarkers for the Response to Anti-VEGF (Vascular Endothelial Growth Factor). Treatment in Wet Age-Related Macular Degeneration (Wet ARMD)	501	Jan 2018
NCT01213667	Genetics in Non-Response to Anti-VEGF Treatment in Exudative age-related macular degeneration (RESPONSE)	110	Dec 2017
NCT01310686[a]	Genetics Study of Wet Age-Related Macular Degeneration (age-related macular degeneration)	40	Jun 2019

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	Non-Responders to Vascular Endothelial Growth Factor (VEGF) Therapy		

NCT: national clinical trial.

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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

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03/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/21/2020	Coding update
03/04/2021	Medical Policy Committee review
03/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/03/2022	Medical Policy Committee review
03/09/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/25/2022	Coding update
03/02/2023	Medical Policy Committee review
03/08/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/07/2024	Medical Policy Committee review
03/13/2024	Medical Policy Implementation Committee approval. Added a "When Services Are Not Covered" section with a not covered statement and a *Note* for repeat germline testing,

Next Scheduled Review Date: 03/2025

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 2023 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
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 technology evaluation center(s);

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ 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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

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