Genetic Testing for Macular Degeneration

Policy # 00399
Original Effective Date: 01/15/2014
Current Effective Date: 04/12/2021

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

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 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.

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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 COL10A1 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.

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 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.

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 age-related macular degeneration. The Society concluded that:

- While age-related macular degeneration 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.
- Ae-related macular degeneration 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 age-related macular degeneration 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			
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) Non-Responders to Vascular Endothelial Growth Factor (VEGF) Therapy	40	Jun 2019
NCT03024424	Value of Genetic Counseling and Testing for Patients Who Would Like to Know More About Their Personal Risk of age-related macular degeneration	200	Mar 2020
NCT01115387	GARM II: A Study on the Genetics of Age-related Maculopathy	603	Aug 2020

Unpublished			
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)

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

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing for Macular Degeneration", 2.04.103, April 2020.
2. 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 degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. Oct 2001;119(10):1417-1436. PMID 11594942.
3. Gorin MB. Genetic insights into age-related macular degeneration: controversies addressing risk, causality, and therapeutics. Mol Aspects Med. Aug 2012;33(4):467-486. PMID 22561651.
4. Lim LS, Mitchell P, Seddon JM, et al. Age-related macular degeneration. Lancet. May 5 2012;379(9827):1728-1738. PMID 22559899.
5. Kim IK. Genetic testing for AMD inches forward. 2012; http://www.revophth.com/content/d/retina/c/35327/.
6. Hageman GS, Gehrs K, Lejnine S, et al. Clinical validation of a genetic model to estimate the risk of developing choroidal neovascular age-related macular degeneration. Hum Genomics. Jul 2011;5(5):420-440. PMID 21807600.
7. Jakobsdottir J, Gorin MB, Conley YP, et al. Interpretation of genetic association studies: markers with replicated highly significant odds ratios may be poor classifiers. PLoS Genet. Feb 2009;5(2):e1000337. PMID 19197355.
8. Seddon JM, Reynolds R, Maller J, et al. Prediction model for prevalence and incidence of advanced age-related macular degeneration based on genetic, demographic, and environmental variables. Invest Ophthalmol Vis Sci. May 2009;50(5):2044-2053. PMID 19117936.

9. Seddon JM, Silver RE, Kwong M, et al. Risk prediction for progression of macular degeneration: 10 common and rare genetic variants, demographic, environmental, and macular covariates. Invest Ophthalmol Vis Sci. Apr 2015;56(4):2192-2202. PMID 25655794.
10. Klein ML, Francis PJ, Ferris FL, 3rd, et al. Risk assessment model for development of advanced age-related macular degeneration. Arch Ophthalmol. Dec 2011;129(12):1543-1550. PMID 21825180.
11. Fauser S, Lambrou GN. Genetic predictive biomarkers of anti-VEGF treatment response in patients with neovascular age-related macular degeneration. Surv Ophthalmol. Mar-Apr 2015;60(2):138-152. PMID 25596882.
12. Chew EY, Klein ML, Clemons TE, et al. No clinically significant association between CFH and ARMS2 genotypes and response to nutritional supplements: AREDS report number 38. Ophthalmology. Nov 2014;121(11):2173-2180. PMID 24974817.
13. Hagstrom SA, Ying GS, Maguire MG, et al. Gene polymorphisms and response to anti-vascular endothelial growth factor therapy in age-related macular degeneration. Ophthalmology. Aug 2015;122(8):1563-1568. PMID 26028346.
14. Hagstrom SA, Ying GS, Pauer GJ, et al. VEGFA and VEGFR2 gene polymorphisms and response to anti-vascular endothelial growth factor therapy: comparison of age-related macular degeneration treatments trials (CATT). JAMA Ophthalmol. May 2014;132(5):521-527. PMID 24652518.
15. Awh CC, Lane AM, Hawken S, et al. CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. Ophthalmology. Nov 2013;120(11):2317-2323. PMID 23972322.
16. Stone EM, Aldave AJ, Drack AV, et al. Recommendations of the American Academy of Ophthamology Task Force on Genetic Testing. 2014; https://www.aao.org/clinical-statement/recommendations-genetic-testing-of-inherited-eye-d.
17. Csaky KG SA, Kaiser PK, et al. The Use of Genetic Testing in the Management of Patients with Age-Related Macular Degeneration: American Society of Retina Specialists Genetics Task Force Special Report. 2017; https://www.asrs.org/content/documents/articleasrstaskforcereportjvrd117.pdf.

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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
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.

Next Scheduled Review Date: 03/2022

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 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of

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descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

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
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.