MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR MACULAR DEGENERATION
POLICY NUMBER	MP 2.260

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**9/1/2024**

I. POLICY

Genetic testing for macular degeneration is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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 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	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in 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 of 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.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations discussed in Section VI below.

FEP PPO- Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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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. 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%).

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 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.

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. 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

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.

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 (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.

23andMe includes testing for *CFH*, *ARMS2*, and *C2*.

REGULATORY STATUS

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. Food and Drug Administration has chosen not to require any regulatory review of these tests.

IV. RATIONALE

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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 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.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any

medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational when used for Genetic Testing for Macular Degeneration. This includes Tier 2 genetic CPT codes and multianalyte assay with algorithmic analysis (MAAA), when reported:

Procedure Codes								
0205U	81401	81405	81408	81479	81599			

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.260	**02/28/2020 Consensus Review.** No changes to the policy statement. Policy guidelines and references updated.
	10/01/2020 Administrative Update. New code update. Added 0205U effective 10-1-20.
	04/14/2021 Consensus Review. No change to policy statement. References updated.
	05/25/2022 Consensus Review. Updated FEP, background, and references. No changes to coding.
	06/08/2022 Consensus Review. Updated background and references. No changes to coding.
	05/29/2024 Consensus Review. Updated background and references. No changes to coding.

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