FEP Medical Policy Manual

FEP 2.04.103 Genetic Testing for Macular Degeneration

Effective Policy Date: July 1, 2022

Original Policy Date: June 2015

Related Policies:

None

Genetic Testing for Macular Degeneration

Description

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

OBJECTIVE

The objective of this evidence review is to determine whether use of genetic testing improves the net health outcome in patients with suspected age-related macular degeneration or disease progression in those with age-related macular degeneration.

POLICY STATEMENT

Genetic testing for macular degeneration is considered **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 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<97>"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"<97>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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

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

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.

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 has indicated that the presence of any 1 of the disease-associated variants is not highly predictive of disease development.[20,] 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.[21,]

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.[22,] 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.

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2015	New policy	
September 2016	Replace policy	Policy updated with literature review, references 9 and 11-13 added. Policy statement unchanged.
March 2017	Replace policy	Policy updated with literature review through January 25, 2017; no references added. ARUP test reference removed. The policy is revised with updated genetics nomenclature. Policy statement unchanged.
June 2018	Replace policy	Policy updated with literature review through January 8, 2018; reference 16 was added. Policy statement unchanged. Summary of Evidence edited to reflect Benefit Application information of "existing medical condition€□.
June 2019	Replace policy	Policy updated with literature review through January 9, 2019; no references added. Policy statement unchanged.
June 2020	Replace policy	Policy updated with literature review through January 13, 2020; no references added. Policy statement unchanged.
June 2021	Replace policy	Policy updated with literature review through January 20, 2021; reference added. Policy statement unchanged.
June 2022	Replace policy	Policy updated with literature review through January 14, 2022; references added. Policy statement unchanged.