2.04.103	Genetic Testing for Macular Degeneration		
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Section:	2.0 Medicine	**Page:**	Page 1 of 14

Policy Statement

I. Genetic testing for macular degeneration is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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	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 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.

Coding

See the Codes table for details.

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 degeneration and of developing the wet form are associated with genetic and nongenetic (e.g., 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.

Additional Information

Not applicable.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

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

Background

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.[1,]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 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.

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 (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 (e.g., smoking and low dietary intake of vegetables, fruit, and fish).[2,]

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.[3,]

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.[4,]

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.[5,]

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*.[5,]
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*.[5,] 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*.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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Testing Asymptomatic Individuals with Risk of Developing Age-Related Macular Degeneration

Clinical Context and Test Purpose

The purpose of genetic testing in asymptomatic individuals with risk of developing age-related macular degeneration is to identify single nucleotide variants for primary prevention or earlier detection of disease for more timely intervention to affect course of disease progression.
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is asymptomatic individuals with risk of developing age-related macular degeneration.

Interventions

The test being considered is genetic testing for age-related macular degeneration.

Comparators

The following practice is currently being used to make decisions about the risk of developing age-related macular degeneration: standard clinical management without genetic testing.

Outcomes

The general outcomes of interest are improvements in disease status and functional outcomes. Additional outcomes of interest are test accuracy and the initiation and frequency of monitoring for assessing changes in disease status.

Potential harmful outcomes would be those resulting from false-positive or false-negative test results. False-positive test results can lead to clinical management changes that may not be beneficial. False-negative test results can lead to absence of clinical management changes

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for macular degeneration, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.

- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Current models for predicting age-related macular degeneration risk include various combinations of epidemiologic, clinical, and genetic factors, and give areas under the curve of approximately 0.8.[6,7,] By plotting the true- and false-positives of a test, an area under the curve measures the discriminative ability of the test, with a perfect test giving an area under the curve of 1.[8,]

An analysis by Seddon et al (2009) demonstrated that a clinical model of age-related macular degeneration risk, which included age, sex, education, baseline age-related macular degeneration grade, smoking, and body mass index, had an area under the curve of 0.757.[9,] The addition of the genetic factors (single nucleotide variants) in *CFH, ARMS2, C2, C3*, and *CFB* increased the area under the curve to 0.821. In a later report, Seddon et al (2015) included 10 common and rare genetic variants in their risk-prediction model, resulting in an area under the curve of 0.911 for progression to advanced age-related macular degeneration.[10,] The Age-Related Eye Disease Study (AREDS) Simple Scale, which rates the severity of age-related macular degeneration based on the presence of large drusen and pigment changes to predict the rate of advanced age-related macular degeneration, is considered to have the greatest predictive value.[6,11,] Klein et al (2011) constructed a predictive model that included age, family history, smoking, the AREDS Simple Scale score, presence of very large drusen, presence of advanced age-related macular degeneration in one eye, and genetic factors *(CFH, ARMS2)*. The area under the curve was 0.865 without genetic factors included and 0.872 with genetic factors included.[11,] Govindaiah et al (2021) reported that a prediction model for development of age-related macular degeneration using AREDS data had an area under the curve of 0.69 using genetic data only, 0.77 using genetic and sociodemographic data, and 0.92 using genetic, sociodemographic, and retinal imaging data.[12,] Ajana et al (2021) also reported an area under the curve at 5 years of 0.92 for an age-related macular degeneration model that included clinical, genetic, and lifestyle factors.[13,] de Breuk et al (2021) and the EYE-RISK consortium found that patients with late age-related macular degeneration had significantly higher genotype assay risk scores than patients with early or intermediate disease (p<.001) or no disease (p<.001) based on a European case-control population (N=4740).[14,]

Although these risk models suggest some small incremental increase in the ability to assess risk of developing advanced age-related macular degeneration based on genetic factors, the clinical validity is not established.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

What can be done for an individual whose genetic test indicates that they are at high risk for vision loss from age-related macular degeneration? The possible clinical utility of genetic testing for age-related macular degeneration can be divided into disease prevention, disease monitoring, and therapy guidance, as discussed below.

- Prevention: Genetic testing and risk prediction for age-related macular degeneration would have clinical utility if a preventive therapy involved an intervention that went beyond good health practices (e.g., no smoking, balanced diet, exercise, nutrient supplements). If a preventive therapy existed, the optimal risk-benefit point along the age-related macular degeneration risk profile for every given age would need to be established so that it could be determined which individuals should receive those treatments and at what age to start the

intervention. Currently, no preventive measures are available; high-dose antioxidants and zinc supplements have been shown to reduce disease progression.[3,]

- Monitoring: If a patient is identified as high-risk, changes in the frequency of monitoring may occur and could include home monitoring devices or the use of technology such as preferential hyperacuity perimetry to detect early or subclinical wet age-related macular degeneration. However, the impact of more frequent monitoring for high-risk patients is not known.[6,]
- Direction of therapy: No consistent associations between response to vitamin supplements and genetic variants have been established.[15,16,17,18,19,]

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs). No such trials were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. A chain of evidence cannot be constructed.

Section Summary: Asymptomatic Individuals with Risk of Developing Age-Related Macular Degeneration

Evidence from studies has indicated that the clinical sensitivity of genetic testing for genes associated with age-related macular degeneration may have small incremental effects on assessing risk of developing age-related macular degeneration. Risk-prediction models incorporate factors such as age, sex, smoking, body mass index, and genetic factors. The true clinical specificity of genetic variants in age-related macular degeneration-related genes is uncertain because of the multifactorial nature of disease development and progression.

Direct evidence of the clinical utility of genetic testing in asymptomatic individuals at risk for developing age-related macular degeneration is lacking. While genetic variants have been used in risk-prediction models, no consistent associations between specific genetic variants and response to specific treatments have been established.

Testing Individuals with Age-Related Macular Degeneration

Clinical Context and Test Purpose

The purpose of genetic testing in individuals who have age-related macular degeneration is to identify single nucleotide variants that potentially predict response to treatment.
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is symptomatic individuals with age-related macular degeneration.

Interventions

The test being considered is genetic testing to determine prognosis or predict response to therapy.

Comparators

The following practice is currently being used to make decisions about managing age-related macular degeneration: standard clinical management without genetic testing.

Outcomes

The general outcomes of interest are improvements in disease status and functional outcomes. Additional outcomes of interest are test accuracy and the initiation and frequency of monitoring for

assessing changes in disease status and effects of management decisions on short-term and long-term functional outcomes.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to clinical management changes that may not be beneficial. False-negative test results can lead to absence of clinical management changes.

Study Selection Criteria

For the evaluation of clinical validity of the genetic test for macular degeneration, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Clinical validity is how the presence of specific single nucleotide variants provides accurate prognosis for disease course and predicts response to treatment. Evidence supporting the clinical validity of accurate disease prognosis and response to treatment was not identified.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

What can be done for an individual with age-related macular degeneration using genetic test results for prognosis and prediction of response to treatment? The possible clinical utility of genetic testing for age-related macular degeneration includes disease monitoring and therapy guidance, as discussed below.

- Monitoring: There is currently no cure for macular degeneration, but genetic variants may provide more accurate prognosis on disease progression. Frequency of monitoring may be increased if a genetic variant is associated with a more rapid or severe disease course.
- Direction of therapy: No consistent associations between response to vitamin supplements or anti-vascular endothelial growth factor therapy and *VEGF* gene variants have been established.[15,16,17,18,19,20,]

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No such trials were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. A chain of evidence cannot be constructed.

Section Summary: Individuals with Age-Related Macular Degeneration

Direct evidence of the clinical utility of genetic testing in individuals with age-related macular degeneration is lacking. While genetic variants have been used in risk-prediction models, there have been no consistent associations between specific genetic variants and response to treatments.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 have indicated that the presence of any 1 of the disease-associated variants is not highly predictive of disease development.[21,] 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.[22,]

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.[23,] 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.

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	Pharmacogenetics in Anti-VEGF Treatment Non-responders Suffering Exudative Age-related Macular Degeneration (AMD): Genetic Correlations and Intraocular Cytokine Concentrations	110	Dec 2017
NCT01310686[a]	Genotypic Evaluation of Chronic Exudative Macular Degeneration Despite Monthly Anti-Vascular Endothelial Growth Factor (VEGF) Therapy	40	Jun 2019
NCT05265624	A Phase 2 Study of the Value of Pre-symptomatic Genetic Risk Assessment for Age-Related Macular Degeneration	76	Jul 2024

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

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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements
	81401	Molecular pathology procedure level 2
	81405	Molecular pathology procedure level 6
	81408	Molecular pathology procedure level 9
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/01/2016	BCBSA Medical Policy adoption
05/01/2017	Policy revision without position change
05/01/2018	Policy revision without position change
05/01/2019	Policy revision without position change
05/01/2020	Annual review. No change to policy statement. Literature review updated.
12/01/2020	Coding update.
05/01/2021	Annual review. No change to policy statement. Literature review updated.
05/01/2022	Annual review. No change to policy statement. Policy guidelines and literature review updated.
05/01/2023	Annual review. No change to policy statement. Literature review updated.
10/01/2025	Policy reactivated. Previously archived from 12/01/2023 to 09/30/2025

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) 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 the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing for Macular Degeneration 2.04.103** **Policy Statement:** I. Genetic testing for macular degeneration is considered **investigational**.