Genetic Testing for Macular Degeneration

Age-related macular degeneration (AMD) is a complex disease involving both genetic and environmental influences. Testing for mutations 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 risk of AMD and of the development of the wet form is associated with genetic and nongenetic (eg, age, smoking) influences.

Macular degeneration, the leading cause of severe vision loss in people over age 60, 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 (AMD). AMD has an estimated prevalence of 1 in 2,000 people in the United States, and affects individuals of European descent more frequently than African Americans in the United States.

There are two 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 one eye before the other. AMD is generally thought to progress along a continuum from dry AMD to neovascular wet AMD, with approximately 10% – 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 AMD is characterized by the growth of abnormal blood vessels from the choroid underneath the macula, and is associated with severe vision loss that can worsen rapidly. 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, as 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 that is low in certain nutrients (such as antioxidants and zinc), and obesity.

Clinical diagnosis of AMD

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, a pattern of straight lines that resemble 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
Genetic Testing for Macular Degeneration

the macula. OCT captures a cross section image of the macula and aids in identifying fluid beneath the retina and in documenting degrees of retinal thickening.

Treatment of AMD

There is currently no cure for macular degeneration, but certain treatments may prevent severe vision loss or slow the progression of the disease. For dry AMD, there is no medical treatment; however, changing certain life style risks may slow the onset and progression of AMD. 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, antiangiogenic 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. A large study performed by the National Eye Institute of the National Institutes of Health, the Age-Related Eye Disease Study (AREDS), showed that for certain individuals (those with extensive drusen or neovascular AMD in one eye) high doses of vitamins C, E, beta-carotene, and zinc may provide a modest protective effect against the progression of AMD.

Genetics of AMD

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 biological 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 polymorphisms (SNPs) contribute to the greatest AMD risk:

- the long (q) arm of chromosome 10 in a region known as 10q26 contains two genes of interest, ARMS2 and HTRA1. Changes in both genes have been studied as possible risk factors for the disease, however, because the two genes are so close together, it is difficult to tell which gene 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, HDL 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 that 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 Caucasians 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/ARMS2 genotype

Nicox offers Sequenom’s RetnaGene™ AMD in North America. RetnaGene™ evaluates the risk of a patient with early or intermediate AMD progressing to advanced choroidal neovascular disease (wet
Genetic Testing for Macular Degeneration

AMD) within 2, 5, and 10 years. The RetnaGene AMD test assesses the impact of 12 genetic variants (single nucleotide polymorphisms or SNPs) located on genes that are collectively associated with the risk of progressing to advanced disease in patients with early or intermediate stage disease (CFH/CFH region, C2, CRFB, ARMS2, C3). A risk score is generated, the patient is categorized into one of three risk groups: low, moderate, or high risk.

ARUP laboratory offers testing for mutations in the ARMS2 and CFH genes. deCode Complete includes testing for mutations in CFH, ARMS2/HTRA1, C2, DFB, and C3 genes. 23andMe includes testing for CFH, ARMS2, and C2.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Genetic testing for macular degeneration is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Macular Degeneration is covered

Not applicable.

When Genetic Testing for Macular Degeneration is not covered

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Policy Guidelines

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.

The evidence for genetic testing in individuals who are asymptomatic with risk of developing AMD includes genetic association studies and risk prediction models. Relevant outcomes are test validity, change in disease status, and functional outcomes. The analytic validity of genetic testing for AMD is high, and 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 improvement in health outcomes in patients who have been identified as being at high risk based on
Genetic Testing for Macular Degeneration

genetic testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for genetic testing in individuals who have AMD includes genetic association studies and risk prediction models. Relevant outcomes are test validity, change in disease status, and functional outcomes. The analytic validity of genetic testing for assessing the risk of progression to advanced AMD is high. 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: No specific code

If the testing is specific to particular genes that have been codified and doesn’t involve any risk algorithm, the test can be reported with the Tier 2 CPT code(s). If the specific testing is not listed in Tier 2, the unlisted molecular pathology code 81479 would be reported. If the testing involves multiple analytes and an algorithm, the unlisted multianalyte assay with algorithmic analysis (MAAA) code 81599 would be reported.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


http://www.revophth.com/content/d/retina/c/35327/.


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
Genetic Testing for Macular Degeneration


Medical director review 12/2013

Specialty Matched Consultant Advisory Panel review - 6/2014


Specialty Matched Consultant Advisory Panel review - 6/2015


Policy Implementation/Update Information

1/14/14 New medical policy issued. Genetic testing for macular degeneration is considered **investigational**. Medical director review 12/2013. (lpr)

7/15/14 Specialty matched consultant advisory panel review meeting 6/24/2014. No change to policy statement. (lpr)

1/13/15 Reference added. (lpr)

7/28/15 Specialty Matched Consultant Advisory Panel review 6/24/2015. No changes to policy statements. (lpr)

2/29/16 Updated Description and Policy Guidelines sections. Reference added. No change to policy statement. (lpr)

7/26/16 Specialty Matched Consultant Advisory Panel review 6/29/2016. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.