

Corporate Medical Policy

Genetic Testing for Macular Degeneration AHS-M2083

File Name: genetic_testing_for_macular_degeneration
Origination: 1/1/2019
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Description of Procedure or Service

Age-related macular degeneration (AMD) is an eye condition that causes damage to the central portion of the retina (the macula), impacting the ability to see objects straight ahead. It can lead to complete vision loss, and is the leading cause of blindness in industrialized countries (Arroyo, 2018).

*****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

Genetic testing for macular degeneration is considered **investigational** for all applications.

Policy Guidelines

Two major types of age-related macular degeneration, dry form and wet form. The dry form accounts for 85 to 90 percent of all cases of age-related macular degeneration, and typically has a slower progression. Although accounting for only 10 percent of cases, the wet form results in 90% of legal blindness (Arroyo, 2018).

Age-related macular degeneration is caused by a combination of genetic and environmental factors. Age, smoking, hypertension, and heart disease are risk factors associated with AMD. Several genetic mutations are associated with age-related macular degeneration. The strongest association comes from genes involved in complement pathways (Arroyo, 2018) "A common polymorphism of the complement factor H (CFH) gene

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predisposes to the development of AMD This polymorphism is involved in regulation of the alternate complement pathway that results in increased inflammation. Individuals with one allele with a histidine substitution for tyrosine in position 402 of the CFH gene (CFH Y402H) on chromosome 1 appear to have 2.5 to 4.6 times the risk of AMD, and individuals with both alleles affected appear to have 3.3 to 7.4 times the risk” (Arroyo, 2018). Increased risk of AMD is also associated with changes on the long arm of chromosome 10 in 10q26. *ARMS2* and *HTRA1* have also been studied for possibility of increasing risk for the disease.

The substantial contribution of environmental factors to AMD raises the possibility of altering patient lifestyle in response to genetic testing. Although the dietary intake of a number of substances, notably those with antioxidant properties such as the carotenoids β -carotene, lutein, and zeaxanthin and vitamins C and E, is known to affect progression to advanced AMD, studies attempting to prove that modifying dietary intake of such substances is significantly preventive of AMD have so far been inconclusive (Black & Clark, 2016).

Clinical Validity and Utility

Fauser and Lambrou (2015) analyzed potential biomarker candidates identified that could be used in a clinical setting to predict response to anti-VEGF treatment of neovascular age-related macular degeneration. The authors found that a number of studies supported an association between anti-VEGF treatment response and two SNPs, CFH rs1061170 and VEGFA rs699947, but results from randomized controlled trials found no such association.

Chew et al (2014) determined whether genotypes at 2 major loci associated with late age-related macular degeneration (AMD), complement factor H (CFH) and age-related maculopathy susceptibility 2 (*ARMS2*), influenced the relative benefits of Age-Related Eye Disease Study (AREDS) supplements. The investigators found that the genotypes at the CFH and *ARMS2* loci did not statistically significantly alter the benefits of AREDS supplements. The investigators concluded that genetic testing remains a valuable research tool, but these analyses suggest it provides no benefits in managing nutritional supplementation for patients at risk of late AMD.

Hagstrom et al (2015) evaluated the pharmacogenetic relationship between genotypes of single nucleotide polymorphisms (SNPs) in the VEGF signaling pathway and response to treatment with ranibizumab or bevacizumab for neovascular age-related macular degeneration (nAMD). For each of the measures of visual equity evaluated, there was no association with any of the genotypes or with the number of risk alleles. The investigators concluded that there are no pharmacogenetic associations between the studied *VEGFA* and *VEGFR-2* SNPs and response to anti-VEGF therapy.

Casella et al (2018) aimed to characterize exudative AMD in the Italian population and to identify the susceptibility/protective factors (genetic variants, age, sex, smoking and dietary habits) which are specific for the onset of disease. The study involved a cohort of 1976 subjects, including 976 patients affected with exudative AMD and 1000 control subjects who underwent genotyping analysis of 20 genetic variants which are known to be associated with AMD. This analysis revealed that 8 genetic variants (*CFH*, *ARMS2*, *IL-8*, *TIMP3*, *SLC16A8*, *RAD51B*, *VEGFA* and *COL8A1*) were significantly associated with AMD susceptibility. Following a multivariate analysis, considering both genetic and non-genetic data available age, smoking, dietary habits and sex, together with the genetic variants, were significantly associated with AMD.

Applicable Federal Regulations

This test is considered a laboratory developed test (LDT); developed, validated and performed by individual laboratories.

LDTs are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

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Practice Guidelines and Position Statements

In 2014, The American Academy of Ophthalmology (AAO) Task Force on Genetic Testing published recommendations for genetic testing of inherited eye diseases. The Task Force stated that standard clinical diagnostic methods like biomicroscopy, ophthalmoscopy, tonography, and perimetry will 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. Until the benefit of genetic testing can be demonstrated, the AAO task force stated that "the routine genetic testing of patients with complex eye diseases, or unaffected patients with a family history of such diseases, is not warranted." The recommendations include:

- "Avoid unnecessary parallel testing— order the most specific test(s) available given the patient's clinical findings. Restrict massively parallel strategies like whole-exome sequencing and whole-genome sequencing to research studies conducted at tertiary care facilities."
- "Avoid routine genetic testing for genetically complex disorders like age-related macular degeneration and late-onset primary open-angle glaucoma until specific treatment or surveillance strategies have been shown in 1 or more published prospective clinical trials to be of benefit to individuals with specific disease-associated genotypes. In the meantime, confine the genotyping of such patients to research studies."
- These guidelines as updated in 2015 continue to recommend against genetic testing (AAO, 2015).

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 service codes: 81401, 81405, 81408, 81479, 81599

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

AAO. (2015). Age-Related Macular Degeneration PPP - Updated 2015. Retrieved 1/29/2015, from American Academy of Ophthalmology <https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp-2015>

Arroyo, J. (2018). Age-related macular degeneration: Clinical presentation, etiology, and diagnosis - UpToDate. In D. Sullivan (Ed.), UpToDate. Retrieved from https://www.uptodate.com/contents/age-related-macular-degeneration-clinical-presentation-etiology-and-diagnosis?search=macular%20degeneration&source=search_result&selectedTitle=2~63&usage_ty pe=default&display_rank=2#H9.

Black, J. R., & Clark, S. J. (2016). Age-related macular degeneration: genome-wide association studies to translation. *Genet Med*, 18(4), 283-289. doi:10.1038/gim.2015.70

Cascella, R., Strafella, C., Longo, G., Ragazzo, M., Manzo, L., De Felici, C., . . . Giardina, E. (2018). Uncovering genetic and non-genetic biomarkers specific for exudative age-related macular degeneration: significant association of twelve variants. *Oncotarget*, 9(8), 7812-7821. doi:10.18632/oncotarget.23241

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Chew, E. Y., Klein, M. L., Clemons, T. E., Agron, E., Ratnapriya, R., Edwards, A. O., Abecasis, G. R. (2014). No clinically significant association between CFH and ARMS2 genotypes and response to nutritional supplements: AREDS report number 38. *Ophthalmology*, *121*(11), 2173-2180. doi:10.1016/j.ophtha.2014.05.008

Fausser, S., & Lambrou, G. N. (2015). Genetic predictive biomarkers of anti-VEGF treatment response in patients with neovascular age-related macular degeneration. *Surv Ophthalmol*, *60*(2), 138-152. doi:10.1016/j.survophthal.2014.11.002

Hagstrom, S. A., Ying, G. S., Maguire, M. G., Martin, D. F., Gibson, J., Lotery, A., & Chakravarthy, U. (2015). VEGFR2 Gene Polymorphisms and Response to Anti-Vascular Endothelial Growth Factor Therapy in Age-Related Macular Degeneration. *Ophthalmology*, *122*(8), 1563-1568. doi:10.1016/j.ophtha.2015.04.024

Specialty Matched Consultant Advisory Panel review 6/2019

Medical Director review 9/2019

Policy Implementation/Update Information

- 1/1/2019 New policy developed. Genetic testing for macular degeneration is considered investigational for all applications. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
- 7/16/19 Specialty Matched Consultant Advisory Panel review 6/19/2019. No change to policy statement. (lpr)
- 10/1/19 Reviewed by Avalon 2nd Quarter 2019 CAB. Deleted coding table from Billing/Coding section. Medical Director review 9/2019. (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.