Healthy Blue

Medical Policy

Subject:	Genetic Testing for Macular Degeneration		
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Description/Scope

This document addresses genetic testing for age-related macular degeneration (AMD). Genetic testing for AMD is aimed at identifying individuals at risk of developing advanced AMD. Commercially available genetic tests for AMD include but are not necessarily limited to:

- Macula Risk® PGx (Artic Medical Laboratory, Grand Rapids, MI)
- RetnaGene™ AMD (Nicox for Sequenom, San Diego, CA)

Position Statement

Investigational and Not Medically Necessary:

Genetic testing for macular degeneration is considered **investigational and not medically necessary.**

Rationale

The leading cause of blindness in the elderly population is AMD, a complex disease. There are two major types of AMD, a dry form and wet form. The dry form is associated with slowly progressive vision loss, and the wet form may lead to rapidly progressive and severe vision loss. The risk of AMD and the risk for development of the wet form are associated with genetic factors and also non-genetic influences, such as smoking and obesity.

Genetics

Genetic variants associated with AMD account for approximately 70% of the risk for the condition (Gorin, 2012). Over 25 genes have been reported to influence the risk of developing AMD, discovered originally through family-based linkage studies, and then through large 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 associated with the onset, progression and involvement of early, intermediate and advanced stages of AMD.

Loci based on common single nucleotide polymorphisms (SNPs) contribute to the greatest AMD risk. Major AMD loci identified in different populations include complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2)/HtrA serine peptidase 1 (HTRA1). Although changes in both ARMS2 and HTRA1 have been studied as potential AMD risk factors, the two genes are located very close together, making it difficult to

determine which one is associated with AMD risk, or whether both genes cause increased risk. Other genes in the complement pathway shown to be associated with AMD include complement 2 (C2), complement 3 (C3), complement factor B (CFB), and complement factor 1 (CF1).

Large genome-wide association studies have implicated high-density lipoprotein (HDL) cholesterol pathway genes, including cholesterylester transfer protein (CETP) and hepatic lipase (LIPC), and possibly lipoprotein lipase (LPL) and ATP-binding cassette (ABCA1) (Lim, 2012). The collagen matrix pathway genes COL10A1 and COL8A1, the extracellular matrix pathway gene known as tissue inhibitor of metalloproteinase 3 (TIMP3) and genes in the angiogenesis pathway, vascular endothelial growth factor A (VEGFA) have been associated with AMD.

Clinical Validity

Current models for predicting AMD risk include various combinations of epidemiologic, clinical and genetic factors, and report areas under the curve (AUC) of approximately 0.8 (Hageman, 2011; Jakobsdottir, 2009). A multi-center prospective evaluation of 1446 participants by Seddon and colleagues (2009) demonstrated that a model of AMD risk that included age, gender, education, baseline AMD grade, smoking and body mass index gave an AUC of 0.757. The addition of the genetic factors, SNPs in CFH, ARMS2, C2, C3 and CFB, increased the AUC to 0.821. Klein and colleagues (2011) evaluated longitudinal data from 2846 study participants and showed that an individual's macular phenotype, as represented by the Age-Related Eye Disease Study (AREDS) Simple Scale score, which rates the severity of AMD based on the presence of large drusen and pigment changes to predict the rate of advanced AMD, has the greatest predictive value. The predictive model used in the Klein analysis included age, family history, smoking, the AREDS Simple Scale score, presence of very large drusen, presence of advanced AMD in one eye, and genetic factors (CFH and ARMS2). The AUC was 0.865 without genetic factors included and 0.872 with genetic factors included. These risk models suggest a small increase in the ability to assess risk of developing advanced AMD based on genetic factors. In a 2015 analysis, Seddon and colleagues included 10 rare and common genetic variants in their risk prediction model, resulting in an AUC of 0.911 for progression to advanced AMD.

Clinical Utility

The potential clinical utility of genetic testing for AMD consists of prevention and monitoring of disease, and therapy guidance. Currently, the only preventive measures available for the disease are good health practices (for example, smoking cessation) and high-dose antioxidants and zinc supplements. The impact of more frequent monitoring for those at risk for developing AMD is unknown. In regards to therapy guidance, there have been no consistent associations between response to therapy and specific genotypes. Additionally, there is a lack of a consistent association between response to vitamin supplements or anti-VEGF (vascular endothelial growth factor) therapy and VEGF gene polymorphisms (Awh, 2013; Chew, 2014; Fauser, 2015; Hagstrom, 2014, Hagstrom, 2015).

In 2015, Awh and colleagues performed a retrospective subgroup analysis of subjects from the 2001 Age-Related Eye Disease Study (AREDS). DNA was not collected from all AREDS subjects and the analysis was based on DNA from white AREDS subjects with category 3 or 4 AMD. The analysis was restricted to white subjects

"because AMD genetics has been studied best in this group." Four genotype groups based on CFH and ARM2 risks alleles were defined. The benefit of treatment with the AREDS formulation seemed to be the result of a positive response by subjects in only one genotype group, and neutral or unfavorable responses in three genotype groups. Subjects with two CFH alleles and no ARMS2 risk alleles showed more of a progression with treatment containing zinc as compared to placebo. Subjects with zero or one CFH risk alleles and one or two ARMS2 risk alleles benefited with treatment containing zinc as compared to placebo. For subjects with zero or one CFH risk alleles and no ARMS2 risk alleles, zinc containing treatment did not alter progression as compared with placebo, but antioxidant treatment decreased progression. For subjects with two CFH risk alleles and one or two AMRS2 risks alleles, no treatment was better than placebo. The authors concluded that "validation by an independent data set would be helpful, but no such data exists, and a replication trial would take many years." In reference to this analysis, Odaibo (2015) indicated that very different conclusions were drawn by Awh as compared to AREDS and pending a larger study specifically testing their hypothesis, no final conclusions can yet be drawn.

Seddon and colleagues (2016) also retrospectively analyzed data from AREDS and similarly reported that the effectiveness of antioxidant and zinc supplementation appeared to vary by genotype and that genetic factors may become relevant when selecting specific treatments. However, the authors concluded that "additional studies are needed to determine the biological mechanism for this interaction and its implications for the comprehensive management of AMD."

Other Considerations

The American Academy of Ophthalmology (AAO) Task Force on Genetic Testing (2012) includes the following recommendation for testing of inherited eye diseases:

> 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 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.

Stone (2015) re-emphasized the AAO recommendations and indicated that the clinical utility of genetic testing for AMD needs to be evaluated in a prospective randomized manner.

The 2015 AAO Preferred Practice Pattern for AMD does not recommend the routine use of genetic testing for AMD and specifically states:

> One or more prospectively designed clinical trials will need to demonstrate the value of genetic testing in AMD. Thus, the routine use of genetic testing is not supported by the existing literature and is not recommended at this time.

Similarly, the 2020 AAO Age-Related Macular Degeneration Preferred Practice Pattern® document states:

The primary risk factors for the development of advanced AMD include increasing age, northern European ancestry, and genetic factors. Cigarette smoking is the main modifiable risk factor that has been consistently identified in numerous studies. Smoking cessation is strongly recommended when advising patients who have AMD or are at risk for AMD. The routine use of genetic testing is not recommended at this time (Flaxel, 2020).

Summary

The clinical validity of genetic testing for AMD may provide a small, incremental benefit to risk stratification based on non-genetic risk factors. However, the clinical utility of genetic testing for AMD is currently limited and any association with specific genotypes and specific therapies needs to be evaluated with additional study in a prospective manner.

Background/Overview

AMD, a global disease that causes blindness, is becoming increasingly prevalent and has no effective cure (Jager, 2008). AMD affects the macula located in the center of the retina. The macula has the highest photoreceptor concentration and is where visual detail is discerned. Wet AMD occurs with the pathological formation of new blood vessels (angiogenesis) behind the retina. These new blood vessels often leak blood and fluid displacing the macula from its normal position at the back of the eye and distorting central vision as a result. Wet AMD is also known as advanced AMD.

According to the American Academy of Ophthalmology, approximately 2.1 million Americans 50 years of age or older have late AMD, the stage that can lead to severe vision impairment. An estimated 15 to 20 percent of those with AMD have at least one first-degree relative (such as a sibling) with the condition.

Commercially available genetic tests for AMD are aimed at identifying those individuals who are at risk of developing advanced AMD. Examples of these tests include but are not necessarily limited to the following:

Arctic Medical Laboratories offers Macula Risk PGx which uses 15 associated biomarkers in an algorithm to determine an individual's risk of progression to advanced AMD and aid in the selection of eye vitamin formulations for AMD based on his or her individual genetic risk profile. The Vita Risk™ pharmacogenetic result is provided as part of the Macula Risk PGx laboratory report.

Nicox offers Sequenom's RetnaGene AMD in North America, which evaluates the risk of an individual with early or intermediate AMD progressing to advanced choroidal neovascular disease (wet AMD). 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, and the individual is categorized into a low, moderate, or high risk group.

23andMe® (Sunnvale, California) offers the Age-Related Macular Degeneration Genetic Health Risk report, a retail product (sold directly to consumers) which includes testing for CFH and ARMS2 variants and assessing whether an individual of European descent is at increased risk of developing age-related macular degeneration based on their genetics.

Genetic tests for AMD are laboratory-developed and do not require United States Food and Drug Administration (FDA) approval. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Definitions

Drusen: Pale whitish-yellow deposits of extracellular material formed in a layer of the retina.

First-degree relative: Any relative who is a parent, sibling, or offspring to another.

Mutation: A permanent, transmissible change in genetic material.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. 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.

When services are Investigational and Not Medically Necessary:
For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT

81401 Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) [when specified as the following]:
- *CFH/ARMS2 (complement factor H/age-related maculopathy susceptibility 2)* (eg, macular degeneration), common variants (eg, Y402H [CFH], A69S [ARMS2])

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) [when specified as the following]:
- *HTRA1 (HtrA serine peptidase 1)* (eg, macular degeneration), full gene sequence

81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]:
- *ABCA4 (ATP-binding cassette, sub-family A [ABC1], member 4)* (eg, Stargardt disease, age-related macular degeneration), full gene sequence

81479	Unlisted molecular pathology procedure [when specified as testing for other AMD-related genes such as C2, CRFB, C3]
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a risk panel for AMD]
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 Vita Risk®, Arctic Medical Laboratories, Arctic Medical Laboratories

ICD-10 Diagnosis

H35.30-H35.3293	Age-related macular degeneration
Z13.5	Encounter for screening for eye and ear disorders

References

Peer Reviewed Publications:

1. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001; 119(10):1417-1436.
2. Assel MJ, Li F, Wang Y, et al. Genetic polymorphisms of CFH and ARMS2 do not predict response to antioxidants and zinc in patients with age-related macular degeneration: Independent statistical evaluations of data from the age-related eye disease study. Ophthalmology. 2018; 125(3):391-397.
3. Awh CC, Hawken S, Zanke BW. Treatment response to antioxidants and zinc based on CFH and ARMS2 genetic risk allele number in the Age-Related Eye Disease Study.Ophthalmology. 2015; 122(1):162-169.
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12. Jakobsdottir J, Gorin MB, Conley YP, et al. Interpretation of genetic association studies: markers with replicated highly significant odds ratios may be poor classifiers. PLoS Genet 2009; 5(2):e1000337.
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16. Odaibo SG. Re: Awh et al.: Treatment response to antioxidants and zinc based on CFH and ARMS2 genetic risk allele number in the Age-Related Eye Disease Study (Ophthalmology 2015; 122:162-9). Ophthalmology. 2015; 122(10):e58.
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Government Agency, Medical Society, and Other Authoritative Publications:

1. American Academy of Ophthalmology (AAO) Retina/Vitreous Panel. Preferred Practice Patterns® Guidelines: Age-Related Macular Degeneration. Updated January 2015. For additional information visit the AAO website: www.aao.org/ppp. Accessed on February 15, 2018.
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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Description/Scope, Rationale, Background/Overview, References, History and Index sections.
	10/01/2020	Updated Coding section with 10/01/2020 CPT changes; added PLA code 0205U.
Reviewed	11/07/2019	MPTAC review. Updated History section.
Reviewed	01/24/2019	MPTAC review. Updated History section.
Reviewed	02/27/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated the Background/Overview and References sections.
Reviewed	02/02/2017	MPTAC review. Rationale and References sections updated.
	01/01/2017	Updated Coding section with 10/01/2016 ICD-10-CM diagnosis code changes.
Reviewed	05/05/2016	MPTAC review. Description, Rationale, Background and Reference sections updated. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	Medical Policy & Technology Assessment Committee (MPTAC) review. Description, Background, Rationale and Reference sections updated.
New	05/15/2014	MPTAC review. Initial document development.