2.04.103 Genetic Testing for Macular Degeneration

Summary

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 (e.g., age, smoking) influences.

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. 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.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.
POLICY STATEMENT

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Genetic testing for macular degeneration is considered investigational.

POLICY GUIDELINES

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.

RATIONALE

Analytic Validity

Analytic validity is the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent.

According to a major laboratory’s website, the analytic sensitivity and specificity of testing for mutations in the ARMS2 gene and CFH gene by polymerase chain reaction is 99%.

Clinical Validity

Clinical validity is the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease.

How well can the test predict the risk of developing advanced age-related macular degeneration (AMD)?

Current models for predicting AMD risk include various combinations of epidemiologic, clinical and genetic factors, and give areas under the curve (AUC) of approximately 0.8–0.9 (By plotting the true and false positives of a test, an AUC measures the discriminative ability of the test, with a perfect test giving an AUC of 1.)

A 2009 analysis by Seddon et al demonstrated that a model of AMD risk that included age, gender, education, baseline AMD grade, smoking and body mass index had 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. In a 2015 report, Seddon et al included 10 common and rare genetic variants in their risk prediction model, resulting in an AUC of 0.911 for progression to advanced AMD. Klein et al 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 this analysis by Klein included age, family history, smoking, the AREDS Simple Scale score, presence of very large drusen, presence of advanced AMD in 1 eye, and genetic factors (CFH and ARMS2). The AUC was 0.865 without genetic factors included and 0.872 with genetic factors included.

Although these risk models suggest some small incremental increase in the ability to assess risk of developing advanced AMD based on genetic factors, the clinical utility is not established.
Clinical Utility

Clinical utility is how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

What can be done for an individual whose genetic test indicates that he or she is at high risk for vision loss from AMD? The possible clinical utility of genetic testing for AMD can be divided into disease prevention, disease monitoring and therapy guidance, as discussed in more detail next.

Prevention: Genetic testing and risk prediction for AMD would have clinical utility if a preventive therapy existed that 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 AMD risk profile for every given age would need to be established so that the decision could be made which individuals should receive those treatments and at what age to start the intervention. Currently, the only preventive measures available are high-dose antioxidants and zinc supplements.\(^1\)

Monitoring: If a patient is identified as high risk, changes in the frequency of monitoring may occur and could include the possibility of home monitoring devices, or the use of technology such as preferential hyperacuity perimetry to detect early or subclinical wet AMD. However, the impact of more frequent monitoring for high-risk patients is not known.\(^5\)

Guide therapy: There have been no consistent associations between response to vitamin supplements or anti-VEGF (vascular endothelial growth factor) therapy and VEGF gene polymorphisms.\(^{11-15}\)

Summary of Evidence

The evidence for genetic testing in individuals who are asymptomatic with risk of developing age-related macular degeneration (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. 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.
SUPPLEMENTAL INFORMATION

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

<table>
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<th>Trial Name</th>
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<th>Completion Date</th>
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<td>NCT01115387</td>
<td>GARM II: A Study on the Genetics of Age-related Maculopathy</td>
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<td>Aug 2016</td>
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<tr>
<td>Unpublished</td>
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<td>NCT01650948a</td>
<td>Evaluation of Genetic Variants in Patients Under Treatment for Choroidal Neovascular (CNV) Age-related Macular Degeneration (AMD), Receiving Intravitreal antiVEGF Injections to Evaluate the Association Between Genetic Load and Phenotypes Associated With More Aggressive Forms of Disease</td>
<td>100</td>
<td>Completed Dec 2013</td>
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NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

The 2014 American Academy of Ophthalmology (AAO) Task Force on Genetic Testing recommendations specific to genetic testing for complex eye disorders like AMD state that the presence of any one of the disease-associated variants is not highly predictive of the development of disease.11 The AAO Task Force finds that in many cases, 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. AAO concludes 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, the routine genetic testing of patients with complex eye diseases, or unaffected patients with a family history of such diseases, is not warranted.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for genetic testing for macular degeneration have been identified.

Medicare National Coverage

There is no national coverage determination (NCD).

REFERENCES

2.04.103 Genetic Testing for Macular Degeneration


POLICY HISTORY

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<tr>
<th>Date</th>
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<td>September 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review, references 9 and 11-13 added. Policy statement unchanged.</td>
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