

Test Specific Guidelines

Macula Risk

MOL.TS.300.A**v1.0.2023**

Introduction

Macula Risk testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

<u>Procedures addressed by this guideline</u>	<u>Procedure code</u>
<u>CFH/ARMS2 common variants</u>	<u>81401</u>
<u>Unlisted molecular pathology procedure (e.g. ABCA1, ApoE, C2, C3, CETP, CFB, CFI, COL8A1, LIPC, TIMP3)</u>	<u>81479</u>

What Is Age-Related Macular Degeneration?

Definition

Age-related macular degeneration (AMD) is the leading cause of blindness and irreversible vision loss among older adults (>65 years).

The etiology of AMD is believed to be multifactorial, and includes modifiable and non-modifiable genetic risk factors that affect the progression of AMD to more advanced stages. The Age-Related Eye Disease Study (AREDS) evaluated the effects of supplements with antioxidants (vitamin E, C, and beta-carotene) and zinc. Results showed that individuals taking these supplements experienced a 25% reduced risk of disease progression to advanced AMD in at least one eye over a period of 5 years. More recent data from the AREDS2 study found that omega-3 acids or lutein and zeaxanthin added to the original AREDS formulation had no additional treatment effect on AMD progression to advanced disease. However, some clinical study results of genetic subgroup analyses have shown a differential treatment effect of supplementation on progression based on genotype.¹ For example, some results suggest that complement factor H gene (CFH) and age-related maculopathy susceptibility 2 gene (ARMS2) genetic polymorphisms have different effects on the progression risk of AMD in different treatment groups of AREDS, while other studies fail to report any differential

effect. As a result, there is ongoing controversy regarding the impact of nutritional supplementation on disease progression to advanced AMD for those individuals with specific genotypes.^{2,3}

Test Information

Introduction

According to the manufacturer (ArcticDx, Inc.), Macula Risk testing is intended to assist in the selection of eye supplement formulations for individuals diagnosed with intermediate dry age-related macular degeneration (AMD).

Macula Risk is a combined pharmacogenetic and prognostic DNA test that assesses an individual's risk of progression to advanced AMD based on their individual risk profile and is designed to aid in the selection of eye supplement formulations.⁴

Guidelines and Evidence

Introduction

The following section includes relevant guidelines and evidence pertaining to Macula Risk testing.

American Academy of Ophthalmology

The American Academy of Ophthalmology (AAO, 2020) published an update to their Preferred Practice Pattern. It stated that routine genetic testing is not supported by the literature and is not currently recommended, citing the need for prospectively designed clinical trials to demonstrate clinical value.⁵

American Society of Retina Specialists

In a Genetics Task Force Special Report, the American Society of Retina Specialists (ASRS, 2017) stated:⁶

“At present, there is no clinical evidence that altering the management of genetically higher risk progression patients, for example, with more frequent office visits and/or improved lifestyle changes, results in better visual outcomes for these patients compared with individuals of lower genetic susceptibility. As such, prospective studies are needed before patient care is modified.”

“Although genetic testing to determine the optimal nutritional supplementation may in the future prove useful, at present there is insufficient data to support the use of genetic testing in patients with AMD prior to recommendation of current Age-Related Eye Disease Study (AREDS) nutritional supplement use.”

Selected Relevant Publications

Several retrospective post-hoc subgroup analyses evaluated the clinical usefulness of identifying specific genotypes to guide optimal nutritional supplementation among individuals with ARMD.^{1-3,7-11}

Most, if not all, available studies are association studies conducting retrospective post-hoc analyses of the same population sample of the previous RCT evaluating the efficacy of the AREDS formulation on AMD progression. These studies conducted several repeat analyses using differing methodologies of various subsets of the study population enrolled in the AREDS Study. Results of these studies are conflicting and inconsistent. One study that conducted a re-analysis of the AREDS data failed to detect an association between genetics and nutritional supplements in AMD prophylaxis.⁸ Another study showed a treatment benefit of zinc to reduce progression to advanced AMD among individuals without risk alleles for CFH and 1 or 2 risk alleles for ARMS2.⁷ Another analysis by the same author found that among individuals treated with zinc, the risk increased for those with a CFH allele, while the risk lessened for individuals with ARMS2 allele.²

More recently, three studies found that CFH and ARMS gene variants either do or do not influence progression of disease to advanced AMD, further demonstrating inconsistent study results.^{3,9,10} Thus, there is considerable uncertainty regarding the clinical usefulness of genotyping to guide use of nutritional supplements.

There is also a lack of direct evidence regarding the clinical utility of genetic testing for AMD progression. Well-designed research that consistently replicates findings of significant associations between genotype and disease progression following AREDS supplementation is needed before genotype testing is used to guide decisions regarding nutritional supplementation in clinical practice.

Criteria

Introduction

Requests for Macula Risk are reviewed using the following criteria.

This test is considered investigational and/or experimental.

Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

References

Introduction

This guideline cites the following references.

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