

The Use of Genetic Testing in the Management of Patients With Age-Related Macular Degeneration: American Society of Retina Specialists Genetics Task Force Special Report

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Our understanding of the role that genetics play in age-related macular degeneration (AMD) is rapidly evolving. DNA polymorphisms in various genes continue to be identified that associate with the disease. Clinicians are frequently asked by their patients about the role of genetic testing and the utility of that testing in the management of the disease. While the present recommendations are contemporary and pertinent, it is clear that the field continues to provide new insights that require clinicians to follow this field closely.

1. Age-related macular degeneration genetic testing may provide information on the progression rates from intermediate to advanced AMD. However, before ordering this testing, retina specialists should be aware of the following:
 - a. Testing should be performed only at Clinical Laboratory Improvement Amendments–certified laboratories with expertise in genetic sequencing. Because of the high variability in the results, direct-to-consumer (DTC) AMD genetic testing that does not meet this standard is not recommended.
 - b. Interpretation of the results of AMD genetic testing is complex.
 - c. 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.
2. Age-related macular degeneration genetic testing at present in patients with neovascular AMD does not provide clinically relevant information regarding response to anti-vascular endothelial growth factor (VEGF) treatment and is not recommended for this purpose.

3. 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.

Over the last decade, multiple genetic markers that associate with AMD have been identified.^{1,2} Variant DNA changes within the complement activation cascade, in particular, complement factor H (*CFH*), as well as mutations in other non-complement-related genes such as age-related maculopathy susceptibility 2 (*ARMS2*), have been demonstrated to show a strong association with AMD.

Although initial research focused on association studies, newer work using longitudinal data has shown that many of these genetic variants have a strong predictive value for AMD progression from intermediate to advanced AMD, characterized by the development of choroidal neovascularization and/or geographic atrophy.³⁻⁵ Subsequently, several AMD risk assessment models were developed using environmental, demographic, and phenotypic data from the AREDS study, incorporated with genetic information.⁶⁻⁸

The predictive algorithms evolved to add additional genetic information. One algorithm incorporated a set of 10 genetic loci with rare variants, 3 variants in *CFH*, and 6 variants in *ARMS2*, as well as variants that appear to be inversely associated with AMD.⁹ These models provided additional

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information about progression beyond what could be seen with funduscopic findings alone.

However, it is important to remember that a fundus examination alone provides significant information about the stage of AMD and the risk of progression as determined by the presence or absence of intermediate or large drusen along with pigmentary changes.¹⁰⁻¹² These findings can direct a discussion with a patient, not just on the use of nutritional supplementation but also on the risk of disease progression.

Incorporating genetic information using the progression models outlined above provides additional data that could be helpful for research, selection of high-risk individuals for clinical trials, and identifying individuals at highest risk of progression. However, there is no clinical data that support changes to the therapeutic approaches of such patients beyond current clinical management.

Is there a role for genetic testing in the management of patients with neovascular AMD using intravitreal anti-VEGF agents? Several large clinical trials examined the association of response to anti-VEGF injections and DNA variants commonly found in patients with AMD. To date, no consistent and reliable genetic marker of response to anti-VEGF intravitreal injections has been identified.¹³⁻¹⁷ Therefore, at this time, it is not recommended that patients presenting with choroidal neovascularization and AMD undergo genetic testing to inform aspects of the response to anti-VEGF therapy.

Another aspect of genetic testing for patients with AMD regards the need for genetic testing prior to initiation of nutritional supplement therapy. Klein et al¹⁸ provided evidence that the benefit of nutritional supplementation seen in the AREDS cohort, particularly with the use of zinc supplementation, was statistically diminished in participants with 2 *CFH* risk alleles. Importantly, no statistically significant negative effect of nutritional supplementation in relation to genetic mutations was demonstrated, and these authors did not recommend routine genetic testing prior to initiation of nutritional supplementation.

Additionally, a recent study of a large cohort of AREDS participants found that the effectiveness of the combination antioxidant and zinc supplement on progression to advanced AMD differed significantly according to the genotype. No significant treatment effect with nutritional supplementation was seen among individuals with 2 *CFH* risk alleles, but a protective effect remained among high-risk *ARMS2* carriers.¹⁹

However, Awh and colleagues have provided evidence from a retrospective analysis of the AREDS data that suggested patients who were homozygous for the *CFH* risk alleles were at an increased risk of progression of AMD if zinc supplements were taken—those who had either 0 or 1 *CFH* risk allele but no *ARMS2* risk allele benefited only from antioxidants—while no nutritional benefit was seen in patients with 2 *CFH* risk alleles and 1 or 2 *ARMS2* risk alleles.^{20,21}

Their conclusion was that genetic testing was important and should be used to tailor the nutritional supplement formulation for patients with AMD. However, several concerns regarding this conclusion have been raised. One concern was

based on the type of analysis employed in these studies. Awh et al^{20,21} performed a post hoc analysis of subgroups within the larger AREDS cohort using a retrospective regression analysis. This approach is traditionally used to generate a working hypothesis but requires subsequent analysis using more stringent methods and additional data sets before any conclusions can be made.^{22,23}

Another concern about the Awh et al manuscripts was a lack of appropriate adjustment for the number of genotypes examined. For example, Wittes and Musch, in their editorial, felt that Awh et al did not correct adequately for multiple statistical testing.^{24,25}

The AREDS study group examined a slightly larger but similar subgroup and DNA data set as Awh et al. Using a similar retrospective analysis, they found no interaction between genetics of the participants and components of the AREDS formulation.²⁶ In other words, the AREDS study group found a favorable treatment response to AREDS supplements including zinc in all participants with AMD independent of genotype class and were unable to find any association or interaction with genotype.

Most importantly, this finding was further supported by the DNA analysis of a smaller residual cohort of AREDS participants who were not part of the cohort on whose results both Awh et al and the AREDS study group were based.²⁷ This subgroup analysis further supported the conclusion that the benefit of AREDS supplementation remained, regardless of the genotype.

How should a clinician approach the issue of genetic testing in patients at risk for, or who present with, AMD? The newest data do support performing genetic testing for patients and families who wish a more accurate prognosis of the progression of intermediate to advanced AMD. This may be useful for patients and doctors and motivating for patients to adhere to the AREDS recommendations.

However, it is important to note the absence of data confirming that altering current clinical care demonstrates improved outcomes in high-risk genetic patients. Although some genetic groups may benefit from the combination antioxidant and zinc supplement more than others, current data are not strong enough to recommend routinely using genetic testing to alter nutritional supplement composition.

Finally, it is important for clinicians interested in genetic testing for their patients with AMD to recognize the importance of where and how the genetic testing should be performed. To date, the majority of published results of genetic testing have been performed in laboratories with specific expertise in genetic testing of DNA mutants associated with AMD. While DTC testing is becoming more available, caution is advised with this approach.

In a 2014 study by Buitendijk et al,²⁸ considerable variations in the predicted risks of progression were obtained from several commercial DTC genetic analyses when compared with results obtained in an academic genetic laboratory. And, as described above, models that predict rates of progression of AMD require assessment of several genetic variants and careful

interpretation. Therefore, prior to undertaking genetic testing for their patients with AMD, clinicians should understand that the output for predicted rates of progression are based on complex algorithms.

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