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Perspectives and Debates Contesting the Justification for Genetic Testing for AMD-Specific Nutritional Supplementation Based on AREDS Data

Julie Adams Poteet, OD, MS, CNS, FONS

Research brings clarity and/or confusion to genomic testing and nutritional therapy

To test or not to test; to be or not to be. When Shakespeare wrote his famous soliloquy in Hamlet, with Prince Hamlet contemplating suicide or life, I doubt he would have imagined that some 400 years later his phrase would be used in an article about eye disease. Indeed, this is not an article about life and death but rather an exploration of data and recommendations used to prevent vision loss, a fate to some that is almost as severe.

Age-related macular degeneration (AMD) remains the leading cause of irreversible visual loss among the elderly in developed nations. (1) In 2004, the prevalence of AMD in the US was estimated to be 1.47%, indicating approximately 1.75 million patients, and was projected to increase to 2.95 million by 2020. (2) Depending on one’s definition of the disease, AMD will affect about 1 in 3 people older than 75 years of age. (3)

All eye-care professionals are familiar with the National Eye Institute’s Age-Related Eye Disease Study (AREDS). This double-blind randomized controlled trial (RCT) evaluating nutritional supplementation on the progression of AMD showed that treatment with antioxidants plus zinc was associated with a statistically significant reduction in disease progression in patients with intermediate or advanced AMD by about 25% after 5 years. (4) This was exciting news for anyone in the business of caring for patients with macular degeneration. Before this trial, all we as optometrists had to offer patients was Amsler grids for home monitoring, consultations on quitting smoking, protecting eyes from UV radiation, and—vaguely—eating a more healthy diet. To have a treatment that would reduce disease progression in intermediate or advanced AMD by about 25% after 5 years was transformative. (4) This was exciting news for anyone in the business of caring for patients with macular degeneration.

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The Age-Related Eye Disease Study 2 (AREDS 2), a subsequent RCT, was then performed to determine if adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formula would further reduce the risk to advanced AMD. From this trial, though not truly placebo-controlled as the control group was taking the original AREDS formula, the National Eye Institute recommended replacing the beta-carotene in the original formula (over concerns of increasing the risk of lung cancer in smokers) with 10 mg of lutein and 2 mg of zeaxanthin. (22) Adding lutein/zeaxanthin to the original AREDS formula resulted in an additional beneficial effect of about 20% beyond the effects of AREDS in reducing the progression to advanced AMD.

Substantial inter-patient variability in disease progression rates suggests a potential pharmacogenetic/nutrigenetic component in treatment response. Pharmacogenetics/nutrigenetics is the study of inherited genetic differences in metabolic pathways which can affect individual responses to drugs/nutrients, both in terms of therapeutic effect as well as adverse effects.

The Genetics of AMD

AMD is not a Mendelian, or monogenetic, disorder like Stargardt disease or X-linked retinitis pigmentosa, where the development of clinically detectable disease is very likely if a disease-causing genotype is present in a single gene. AMD is considered a complex genetic disease where the presence of one or more risk alleles does not necessarily result in a more affected phenotype, and the absence of risk alleles does not necessarily result in a less affected phenotype. (23,24) In AMD, the genotypes of many genes will advise my patients fully and honestly of all which may serve to restore, maintain or enhance their vision and general health.” (See textbox “Zinc and the Eye” for continuity of citations.)

The Genetics of AMD

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appear to interact with each other and with the environment to determine whether a patient will develop clinically significant disease.(24) However, of all human multi-genetic diseases, AMD has been shown to have the strongest genetic influence.(25) The Human Genome Project cataloged and identified single nucleotide polymorphisms (SNPs) which are genetic variations that influence disease risk; since then, SNPs involving at least 19 genes have been shown to be involved in AMD. Of those 19 genes, two major susceptibility genes for AMD, CFH and ARMS2, have been shown to have a substantial contribution to the heritability of AMD.(26) Complement factor H (CFH) is the main regulator of the alternate complement pathway of the immune system and multiple independent genetic studies have shown that dysfunction of the complement system is a key factor in AMD development.(27) The age-related maculopathy susceptibility 2 (ARMS2) gene is involved with energy metabolism in the mitochondria.(26) Despite advances in genetic research related to AMD, the current recommendation of the American Academy of Ophthalmology’s task force on genetic testing is to avoid routine genetic testing for AMD until specific treatment or surveillance strategies have been shown in prospective studies to be of benefit to people with specific genotypes.(24,28)

Pharmacogenetics and AREDS

Recent pharmacogenetic studies using the original AREDS data have reported differences in treatment outcomes with respect to variants in genes for CFH and ARMS2. In 2008, Klein et al published a study using AREDS data that showed an observed interaction between CFH and antioxidants + zinc.(29) Their analysis was based on genetic data from 876 white participants of the original AREDS trial who at baseline had intermediate AMD or unilateral advanced AMD. Using multivariate analysis, after controlling for age, sex, education, smoking and body mass index (BMI), a greater reduction effect in AMD progression was reported with the CFH non-risk genotype compared to the CFH risk genotype. However, antioxidants + zinc reduced progression to advanced AMD (compared to placebo) in all 6 genotype subgroups tested. Neither zinc alone or antioxidants alone were superior to antioxidants + zinc in any genotype sub-group; therefore, these researchers did not recommend genetic screening.(29)

In 2013, Awh et al analyzed AREDS data but reached different conclusions.(30) These authors studied 989 white AREDS patients with intermediate AMD in at least one eye. They estimated AMD progression rates for 9 CFH/ARM52 genotypes. They reported—using multivariate analysis, after controlling for age, sex, education, smoking, and BMI—statistically significant differences in outcomes based on CFH and ARMS2 genotypes. For 23% of patients, the original AREDS formulation was the best treatment. For 49% of patients, a formulation other than AREDS was more beneficial. For 13% of patients, the AREDS combination was harmful and accelerated vision loss significantly faster than placebo, thought to be due to too much zinc.(30)

Following this publication, the AREDS investigators (Chew et al) reported an “unplanned retrospective evaluation” of 1,237 white AREDS study participants, AREDS report #38, published in 2014.(31) They tested the response to the original AREDS supplement using genotypes described by Klein et al and then by Awh et al. They refuted Awh et al by finding no significant interactions and concluded that AREDS supplementation reduces the rate of progression across all genotype groups.(31)

Awh et al then went on to dispute AREDS report #38, claiming that the 27 comparisons made by Chew et al, many with small sample sizes, were not clinically interpretable.(31,32) They subsequently analyzed 989 white study participants from the same AREDS trial and defined four categories of risk variants, based on alleles at CFH and ARMS2. Their findings showed that patients with a high CFH risk and no ARMS2 risk allele had a 135% increased AMD progression compared to those treated with a placebo. Patients with a low CFH risk allele and a high ARMS2 risk allele had a 37% decreased AMD progression if treated with the AREDS formula compared to the placebo. They presented their research at the American Society of Retinal Specialists annual meeting September 4, 2014 and then later published their findings in 2015.(32) They recommended using genotype-directed nutritional supplementation to patients.

Recently, Chew et al have responded, criticizing Awh et al for presenting results that are biased and therefore difficult to interpret.(33) Awh et al had acknowledged the following in their conclusions, “Validation by an independent data set would be helpful, but no such data set exists, and a replication trial would take years.”(30,32) A data set was recently made available, however, to the AREDS researchers. Chew et al had access to an additional 526 patients from the AREDS trial with the same qualifications used by Awh et al, a residual cohort, whose DNA had recently become available. The demographics from the Awh et al’s test data and Chew et al’s validation set are comparable. If Awh et al were correct in their conclusions, then the findings from the residual cohort would serve to validate their findings. Chew et al analyzed the 526 patients in the residual cohort using the same 4 genetic groupings developed and used by Awh et al and their findings did not, in fact, validate the findings by Awh et al. They reported that the combination of antioxidants plus zinc was beneficial in all genetic subtypes described by Awh et al.(33) Based on the latest findings by Chew et al, the NEI concluded that because the findings by Awh et al were not verified by the results of the residual cohort, genetic testing prior to treatment with AREDS supplements is not recommended.(33)
Zinc and the Eye
Too much, too little, and/or induction of iatrogenic copper deficiency

The concentration of zinc in the eye is higher than in most tissues of the body. Zinc is a cofactor for enzymes involved in visual function, and it plays an important role in regulating enzymes that are involved in the oxidative process. One of the major problems in assessing the need for zinc in AMD is the lack of information about its biological role in the retina and surrounding tissues. Like other tissues, the retina can be damaged by too much or too little zinc. Newsome et al demonstrated that levels of zinc are reduced in human eyes with signs of AMD. Depletion of zinc increases oxidative stress, may cause deficits in phagocytic and lysosomal functions and induce macro-molecule synthesis and caspase-dependent apoptosis; mechanisms that are all implicated in AMD. Zinc depletion also markedly increases the vulnerability of retinal pigment epithelial cells to UV radiation through UV-induced DNA damage. In addition, inflammation has been associated with AMD and we know that zinc supplementation raises plasma zinc concentration which then supports immune function and provides better protection in AMD and in general aging. The role of zinc depletion and its consequences have been established, but what has recently been suggested by Lengyel et al is that excess zinc may be just as harmful in AMD. Lengyel et al have shown that drusen—asymptomatic yellow deposits that develop under the retina between the retinal pigment epithelium and the choroid layer of blood vessels that supply nutrients to the macula—are filled with anomalous deposits of zinc some of which are free or weakly protein bound. This is also true of amyloid plaques in Alzheimer's disease. A hypothesis has been made that while zinc (along with antioxidants) has been shown to be protective during the intermediate to late stage of AMD (as was shown in the AREDS trial), excessive zinc may contribute to the development of AMD at the early stages. In a 2013 paper in the Journal of Biological Chemistry, "Zinc-induced Self-association of Complement C3b and Factor H: Implications for Inflammation and Age-Related Macular Degeneration", a potential molecular mechanism for zinc-induced drusen formation was clarified. Excess zinc induces precipitation of immune factors that may contribute to the initial development of drusen as well as reducing the progression to advanced age-related macular degeneration in higher risk patients. Obviously more research needs to be done to further elucidate the role of zinc regulation or dysregulation in retinal tissue and AMD. The pathways to drusen formation and from drusen to advanced disease may be different. In the AREDS2 trial, the version of AREDS2 with reduced zinc was shown to be as efficacious as the AREDS2 formula with higher zinc and is therefore arguably the safer choice in a well-nourished population. The recommended dietary allowance (RDA) for zinc in adults is 12-15 mg/day. However, some elderly people appear to require zinc intakes above the RDA in order to maintain positive zinc balance. Elderly people below the poverty line or people with certain food preferences (i.e. vegetarians or people who only eat fish or chicken meat) are likely to be zinc deficient. Therefore, the AREDS2 formulation with the original zinc dosage would be a better choice in this population. Of note, copper is necessary with long-term high zinc supplementation above the RDA to avoid a copper-zinc imbalance. Supplementation with quantities of zinc above the suggested upper limit can result in copper deficiency, suppress the immune system, increase the risk for metastatic prostate cancer and impair behavior. The original AREDS formulation provides copper in the form of cupric oxide. Animal studies have shown that the bioavailability of this form of copper “is not significantly different from zero”. In summary, zinc is necessary for proper retinal functioning, and AMD patients are often deficient in zinc; however, excessive levels of zinc supplementation can have adverse consequences as well. Practitioners that are still recommending the original AREDS formula or AREDS 2 with the higher zinc levels (80 mg versus 25 mg) to patients with AMD without taking into consideration the stage of the disease (early, intermediate, or advanced) or the nutritional status of the patient could theoretically be doing more harm than good. My recommendation as an optometrist as well as a Certified Nutrition Consultant (CNS) is that practitioners consider the nutritional status of the patient and opt for an AREDS 2 formulation with lower zinc and a form of copper other than cupric oxide when indicated.
Conflicts of Interest
This debate between Awh et al and Chew et al that is playing out in meetings and journals has been a focus of much confusion and frustration for clinicians. From a commercial point of view, AMD represents a sizeable market for profit by companies making targeted interventions, and conflicts of interest have been made public on both sides. Carl Awh MD and another researcher on his team, Brent Zanke MD PhD both have strong financial ties to Arctic DX, which is the only provider of the personalized genetic test for AMD supplementation and is available by prescription only. Dr Awh is an equity owner, consultant, and member of the advisory board of Arctic DX. Dr Zanke is the medical oncologist and geneticist who founded and chairs Arctic DX and has equity ownership. Both are involved with Arctic DX patents. On the other side of the debate, the AREDS trial, which was sponsored by National Eye Institute (NEI) and National Institutes of Health (NIH), received additional funding from Bausch and Lomb Inc which holds the patent for the original AREDS formula. Emily Chew MD led the AREDS study. She is currently the deputy director of the Division of Epidemiology and Clinical Applications and the deputy clinical director at the National Eye Institute (NEI), a division of the National Institutes of Health (NIH). Dr Chew denies the institute has been influenced by Bausch and Lomb, and she says the money barely offsets the millions the NEI has spent on research in the area.(34)

Deciphering the Data/Clinical Applications
Both sides of the debate are quick to point out flaws in the other side’s analysis of the data. How should practicing clinicians, who are not experts in clinical trial design, genetics, or statistical analysis interpret these conflicting results? To answer this question, information from three credible resources is cited:

1. The first source, a 2015 review in Clinical Ophthalmology by a team of doctors at Bascom Palmer Eye Institute titled “Pharmacogenetics and nutritional supplementation in age-related macular degeneration” concluded that in their opinion the balance of available evidence does not support the use of genetic screening to guide clinical decisions in AMD patients at this time.(35) The doctors from Bascom Palmer pointed out that many of the sub-groups analyzed on both sides of the debate were too small for statistical significance. They also noted that retrospective sub-group analysis is not equivalent to a prospective RCT such as the AREDS trial. The likelihood of inadvertent selection bias, resulting in statistically significant but clinically meaningless associations, increases with the number of sub-groups. They also noted that the original AREDS formula and not AREDS2 was used in the studies.

2. The second source is an article by Edwin Stone MD PhD. Dr Stone is a researcher and professor with the University of Iowa Carver College of Medicine. For more than 25 years, the central premise of his professional career has been the evaluation of genes that will lead to improved diagnosis and treatment of eye disease. He is the director of the University’s Center for Macular Degeneration and the Nonprofit Genetic Testing Laboratory. Dr Stone also headed the AAO’s task force on genetic testing. In an article he published in JAMA Ophthalmology May 2015 titled, “Genetic testing for age-related macular degeneration not indicated now”, he notes the following: “I think that it is very important for all ophthalmologists (and optometrists) to recognize that the burden of proof of this hypothesis (that specific genotypes are associated with different responses to antioxidants plus zinc) lies with Awh and his colleagues; there is no burden of disproof for the AREDS investigators or, for that matter, anyone else in the scientific community. I continue to recommend AREDS vitamin supplementation to my patients with AMD regardless of their genotype. I believe that all hypothesis about the clinical utility of genetic testing for AMD should be tested in a prospective fashion, with participants randomly assigned to groups that receive either conventional care or genotyped-guided care. If, in such a prospective study, the clinical outcomes of the genotype-guided groups are significantly better than the clinical outcomes of the conventionally managed groups, this, and only this, will be meaningful evidence in favor of using genetic testing to help care for patients with AMD.”(24) Dr Stone has no financial conflicts of interests. He does have a personal interest in AMD as both of his maternal grandparents lost a lot of their vision to the disease.

Recently, a Canadian online journal reported that a University of Toronto biostatistician, Rafal Kustra, concluded that the raw data in the NEI’s AREDS report #38 actually supported Arctic DX’s contention that 19% of patients had the genotypes that appear to fare worse on the supplement than placebo.(34) Kustra was hired to do the analysis by a competitor of Bausch and Lomb. His conclusions were confirmed by Bernard Rosner, a Harvard biostatistician hired by Arctic DX.(34) In light of this recent development, I (JAP) emailed Dr Stone to inquire if he was aware of this latest development and to see if his 2015 position on genetic testing to guide AMD supplementation still stands. Dr Stone wrote that he was also aware of the data from Kustra and Rosner. (E Stone, personal communication, March 17, 2016) He stated that his thoughts on this topic are still 100% in line with his article in JAMA and he restated his quote above from the May 2015 article.

The third source cited to answer the question of genetic testing and AMD supplementation is a lecture given at the October 2015 American Academy of Ophthalmology’s annual meeting. Stuart Richer, OD, PhD, FAAO gave an informative, unbiased lecture
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As a clinician on the front lines caring for patients with AMD, I am frustrated by the conflicting data. I look into the eyes of a favorite patient, an 81-year-old retired school teacher with moderate AMD, who spends her days reading and corresponding with former students. She has entrusted me with caring for her eyes, her way of life. In deciding on her treatment, the following considerations come to mind: 1) the original AREDS study was a prospective RCT that showed a benefit for patients with intermediate to advanced AMD, 2) the AREDS 2 formula with lutein and zeaxanthin was shown to have an additional beneficial effect beyond that of the original AREDS, 3) the studies by Awh et al and Chew et al were conducted on the original AREDS formula with the higher zinc levels, and 4) lowering the zinc dosage in the AREDS 2 formula did not decrease the efficacy.

**Conclusion and Author’s Perspective**

Clearly more research is needed to further elucidate the very important roles of selective testing and nutritional supplementation in the clinical management of AMD.

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"Throughout the centuries there were men who took first steps down new roads armed with nothing but their own vision. .... The great creators—the thinkers, the artists, the scientists, the inventors—stood alone against the men of their time. Every great new thought was opposed. Every great new invention was denounced. .... But the men of unborrowed vision went ahead. They fought, they suffered and they paid. But they won."

Chapter XVIII; testimony of Howard Roark in *The Fountainhead* by Ayn Rand