Dynamic Developments in AMD Diagnosis and Treatment (2014)

The Dawn of:
Pharmaco-Genetics (aka Nutrigenomics)

Jerome Sherman, OD
Disclosures: Jerome Sherman

- Dr. Sherman has lectured, received honorarium and/or consulted with Carl Zeiss Meditec, Topcon, Optovue, Optos, Eye Solutions, MacuHealth, PHP, Diopsys, Annidis, Arctic, Quantel, Heidelberg DGH, and AMD iManager.

- All of the above have supported RR (www.retinarevealed.com) Retina Revealed
- Sherman is divested from the Arctic group. - Mar 2014
Welcome to Review of Optometry’s “Retina Revealed,” a weekly, thought-provoking series providing doctors/clinicians with the latest technology in Retina via online case presentations. Gain valuable clinical insights into high tech, retinal diagnosis and treatment as you observe various retinal disorders and learn how others are utilizing new technology to provide optimal patient care.

Review thanks the leading technology companies for their support of “Retina Revealed.” Following each case presentation, we provide you with a direct link to the company, or companies, website to gain more knowledge on the technologies used in that week’s case presentation.
Building an “AMD Center of Excellence”

is based upon the

Evolving Standard of Care in AMD

New knowledge and new technology creates additional opportunity but also new responsibility.
Dad’s Scar

OD’s Drusen
AMD Genetic Testing

Macula Risk NXG
Identifies AMD patients who may progress to vision loss within:

• 2 years
• 5 years
• 10 years

Cheek Swab
The Macula Risk score

Risk of Progression from early / intermediate AMD to advanced AMD with vision loss

- MR1: 50%
- MR2: 30%
- MR3: 16.8%
- MR4: 2.2%
- MR5: 1%

20% of the population
Angelina Jolie obviously understands the importance of genetic testing...

But, does the average patient?

“Can’t tell the difference!” –Brad Pitt
“You don’t look anything like the long haired, skinny kid I married 25 years ago. I need a DNA sample to make sure it’s still you.”
Great Science - Key AMD genes

Macula Risk NXG – 12 genes

- CFH
- CFI
- CFB
- C2
- C3
- ARMS2
- TIMP3
- COL8A1
- LIPC
- APOE
- CETP
- ABCA1

Key AMD genes:
- Complement
- Oxygen Metabolism
- Extracellular Matrix
- Cholesterol Metabolism
Dynamic Developments in AMD Diagnosis and Treatment (2014)

The Dawn of: Pharmaco-Genetics (aka Nutrigenomics)

Jerome Sherman, OD
More than double the benefit of AREDS:
“We estimate that genotype-directed therapy of the study population would have more than doubled the reduction in AMD progression rate compared with treatment with the AREDS formulation.”

A clear role for genetic testing – Ivana Kim (co-author)
“This data demonstrates that the composition of supplements recommended to AMD patients should be guided by an individual’s genetic risk profile, indicating a clear role for genetic testing in clinical management.”
CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration

Published Study:
includes 995 subjects from AREDS 1 with intermediate disease (AREDS Category 3) and Category 1-4 in fellow eye with 12 year follow-up.
Low CFH Risk

High CFH Risk
GDT more than doubles the efficacy of progression to vision loss.
Age Related Eye Disease Study (AREDS)

AMD Patients

- **Antioxidants***: 17% risk reduction
- **Zinc Oxide**: 21% risk reduction
- **Antioxidants*** + **Zinc Oxide**: 25% risk reduction

* AREDS Study (2001)
Risk reduction in developing advanced disease, as compared to placebo

4750 Patients - Vitamin C, Vitamin E, Beta Carotene, Zinc
49% derive more benefit from treatment other than AREDS

Estimated probabilities of progression to Advanced AMD as a function of genotype, treatment group, and time (years).

Genetic Profile 1: 0 CFH and 2 ARMS2
Genetic Profile 2: 1 CFH and 1 ARMS2
Genetic Profile 3: 2 CFH and 0 ARMS2

Recommended treatment:
- Genetic Profile 1: Zinc Alone
- Genetic Profile 2: AREDS Formulation
- Genetic Profile 3: Antioxidants Alone

Figure modified from Awh et al., CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. *Ophthalmology* (In press).

Macula Risk®
PREDICT AND PROTECT®
### Suggested Treatments*

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<th>CFH Alleles</th>
<th>ARMS2 Alleles</th>
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</table>

* no statistical treatment benefit observed
Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration
The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial

The Age-Related Eye Disease Study 2 (AREDS2) Research Group*

Age-related macular degeneration (AMD), the leading cause of blindness in the developed world, accounts for more than 50% of all blindness in the United States. In 2004, it was estimated that 8 million individuals had intermediate AMD, defined as bilateral drusen, and approximately 2 million had advanced AMD, either neovascular AMD or geographic atrophy. Although intraocular drugs that inhibit vascular endothelial growth factor are currently available for treatment of neovascular AMD, no effective therapies are proven for atrophic AMD. Without more effective ways of slowing progression, the number of persons with advanced AMD is expected to double over the next 20 years, resulting in increasing socioeconomic burden.

The Age-Related Eye Disease Study (AREDS) demonstrated that daily oral supplementation with antioxidant vitamins and minerals reduced the risk of developing advanced AMD by 25% at 5 years. Animal studies and epidemiologic studies provide a rationale for a clinical trial of antioxidant vitamins and omega-3 fatty acids.

Importance Oral supplementation with the Age-Related Eye Disease Study (AREDS) formulation (antioxidant vitamins C and E, beta-carotene, and zinc) has been shown to reduce the risk of progression to advanced age-related macular degeneration (AMD). Observational data suggest that increased dietary intake of lutein + zeaxanthin (carotenoids), omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] + eicosapentaenoic acid [EPA]), or both might further reduce this risk.

Objectives To determine whether adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of eliminating beta-carotene, lowering zinc doses, or both in the AREDS formulation.

Design, Setting, and Participants The Age-Related Eye Disease Study 2 (AREDS2), a multicenter, randomized, double-masked, placebo-controlled phase 3 study with a 2×2 factorial design, conducted in 2006-2012 and enrolling 4203 participants aged 50 to 85 years at risk for progression to advanced AMD with bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye.

Interventions Participants were randomized to receive lutein (10 mg) + zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), lutein + zeaxanthin and DHA + EPA, or placebo. All participants were also asked to take the original AREDS formulation or accept a secondary randomization to 4 variations of the AREDS formulation, including elimination of beta-carotene, lowering of zinc dose, or both.

Main Outcomes and Measures Development of advanced AMD. The unit of analyses used was by eye.

Results Median follow-up was 5 years, with 1940 study eyes (1608 participants) progressing to advanced AMD. Kaplan-Meier probabilities of progression to advanced AMD by 5 years were 31% (493 eyes [406 participants]) for placebo, 29% (468 eyes [399 participants]) for lutein + zeaxanthin, 31% (507 eyes [416 participants]) for DHA + EPA, and 30% (472 eyes [387 participants]) for lutein + zeaxanthin and DHA + EPA. Comparison with placebo in the primary analyses demonstrated no statistically significant reduction in progression to advanced AMD (hazard ratio [HR], 0.90 [98.7% CI, 0.76-1.07]; P = .12 for lutein + zeaxanthin; 0.97 [98.7% CI, 0.82-1.16]; P = .70 for DHA + EPA; 0.89 [98.7% CI, 0.75-1.06]; P = .10 for lutein + zeaxanthin and DHA + EPA). There was no apparent effect of beta-carotene elimination or lower-dose zinc on progression to advanced AMD. More lung cancers were noted in the beta carotene vs no beta carotene groups.
Zinc: 80mg or 25mg?  (RDA is 9-15mg)

Increase in lung cancer rates and associated mortality in cigarette smokers assigned to receive beta carotene. AREDS2 participants who were not current smokers or who had stopped smoking more than 1 year prior to enrollment, and those assigned to one of the 2 groups receiving the AREDS formulation with beta carotene, showed an increased incidence of lung cancers (23 [2.0%] and 11 [0.9%], respectively; nominal P = .04). Thirty-one (91%) of those participants developing lung cancer were former smokers. AREDS2 found no increased risk of lung cancer with lutein + zeaxanthin supplementation.

Previous randomized controlled clinical trials of lutein + zeaxanthin, of short duration and with limited sample sizes, suggested improved visual function, but AREDS2 showed no evidence that treatment affected visual acuity. One randomized trial of DHA and EPA found no effect on AMD progression.

The limitations of this study include a complicated study design involving a secondary randomization, which may have affected our ability to evaluate the role of adding lutein + zeaxanthin and DHA + EPA to equivalency between low-dose zinc and high-dose zinc and between no beta carotene and beta carotene.

Another limitation would be our inability to assess the effect of the potential increased risk of lung cancer associated with beta carotene on our analyses of mortality. The number of lung cancers was small, and the analyses of competing risk showed essentially no change in our mortality results.

These study results may not be generalizable, because the study population is a highly selected group of highly educated and well-nourished people. The strengths of this study include the low rates of loss to follow-up and consistently good adherence to the treatment regimen.

In summary, addition of lutein + zeaxanthin, DHA + EPA, or lutein + zeaxanthin and DHA + EPA to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD. Comparison of low-dose zinc vs high-dose zinc showed no evidence of a statistically significant effect, and there is insufficient evidence to provide a clinical recommendation. Based on apparent risks of beta carotene and possible benefits that are only evident within exploratory analyses, the AREDS2 formulation appears to be the preferred option for AMD prevention. The AREDS2 formulation is an aqueous suspension custom made, and is only available from AREDS2 formulation.

Author Contributions: Drs Chew and Clemons had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chew, Clemons, Danis, Ferris, Sperduto.

Acquisition of data: SanGiovanni, Danis, Elman, Antoszyk, Ruby, Orth, Bressler, Fish, Hubbard, Klein, Chandra, Blodi, Domalpally, Friberg, Wong, Rosenfeld, Toth, Bernstein.

Analysis and interpretation of data: Chew, Clemons, SanGiovanni, Danis, Ferris, Elman, Antoszyk, Orth, Fish, Klein, Domalpally, Wang, Rosenfeld, Agron, Toth, Bernstein, Sperduto.

Drafting of the manuscript: Chew, Clemons, Danis, Friberg, Agron.

Critical revision of the manuscript for important intellectual content: Chew, Clemons, SanGiovanni, Danis, Ferris, Elman, Antoszyk, Ruby, Orth, Bressler, Fish, Hubbard, Klein, Chandra, Blodi, Domalpally, Friberg, Wong, Rosenfeld, Agron, Toth, Bernstein, Sperduto.

Statistical analysis: Clemons, Ferris, Agron.

Obtained funding: Chew, Danis, Ferris.

Administrative, technical, or material support: Chew, Danis, Ferris, Elman, Ruby, Bressler, Chandra, Domalpally, Wong, Rosenfeld, Sperduto.

Study supervision: Chew, Clemons, Danis, Ferris, Bressler, Domalpally, Friberg.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ferris reported holding a patent for the Age-Related Eye Disease Study (AREDS) formulation with Bausch & Lomb. Dr Anto-
Why does NEI recommend 80mg?

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Previous randomized controlled clinical trials of lutein + zeaxanthin, of short duration and with limited sample sizes, suggested improved visual function.30-34 but AREDS2 showed no evidence that treatment affected visual acuity. One randomized trial of DHA and EPA found no effect on AMD progression.35

The limitations of this study include a complicated study design involving a secondary randomization, which may have affected our ability to evaluate the role of adding lutein + zeaxanthin and DHA + EPA to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD. Comparison of low-dose zinc vs high-dose zinc showed no evidence of a statistically significant effect, and there is insufficient evidence to provide a clinical recommendation. Based on apparent risks of beta carotene and possible benefits that are only evident within exploratory. University of Wisconsin; Thomas Friberg, MD, University of Pittsburgh Medical Center Eye Center, Pittsburgh, Pennsylvania; Wai Wong, MD, PhD, Division of Epidemiology and Clinical Applications, NEI/NHI; Philip Rosenfeld, MD, PhD, Bascom Palmer Eye Institute, Miami, Florida; Elvira Agron, MA, Division of Epidemiology and Clinical Applications, NEI/NHI; Cynthia Toth, MD, Duke University, Durham, North Carolina; Paul Bernstein, MD, PhD, University of Utah Moran Eye Center, Salt Lake City; and Robert Sperduto, MD, EMMES Corporation.

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NUTRITIONAL SUPPLEMENT TO TREAT MACULAR DEGENERATION

Inventors: Stephen Paul Bartels, Wyckoff, NJ (US); Cara Lorraine Baustian, Palisades, NY (US); George Edwin Bunce, Blacksburg, VA (US); Leon Ellenbogen, New City, NY (US); Frederick L. Ferris, III, Columbia, MD (US); Jin Kinoshita, El Macero, CA (US); James Cecil Smith, Jr., Glenn Dale, MD (US); David A. Souerwine, Pittsford, NY (US)

Assignee: Bausch & Lomb Incorporated, Rochester, NY (US)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

Appl. No.: 09/816,284
Filed: Mar. 23, 2001
Prior Publication Data

References Cited
A61K 9/20
424/464; 424/451; 424/489; 424/400; 424/427

PreserVision

BAUSCH + LOMB

Eye Vitamin & Mineral Supplement

AREDS 2 FORMULA

Based on The ONLY Clinically Proven Formula*

Sample NOT FOR RESALE

Now 2 per day

*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
**PreserVision**

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**Supplement Facts**

**Serving Size:** 1 Soft Gel

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*Percent Daily Values (DV) are based on a 2,000 calorie diet. **Daily Value (DV) not established.*

**Ingredients:** Ascorbic acid, gelatin, dl-alpha tocopheryl acetate, glycerin, soybean oil with peanut oil, zinc oxide, marigold flower extract, soy lecithin with peanut oil, yellow beeswax, silicon dioxide, titanium dioxide, cupric oxide, FD&C red 40, FD&C blue 1.

§ May be sourced from paprika fruit extract.

**COMPLETE AREDS 2 FORMULA**

This advanced PreserVision AREDS 2 Formula contains the exact same levels of all six nutrients based on the latest clinical evidence from the AREDS2 study.

**ALL 6 CLINICALLY PROVEN NUTRIENTS**

See inside package for Supplement Facts, product information, and to report serious side effects.
Technology Requirements

(if you are serious about an AMD Center of Excellence)

Must have:
- Genetic Testing and SD OCT?
- Fundus photography and/or optos panoramic imaging?
- Multi Spectral Imaging?

Very nice to have:
- Maia microperimetry
- Fundus Auto-fluorescence
- PHP and PHP Home Device
- MPOD instrument

Which Genetic Test? There is only one at present
Which SD OCT: all are great!

Cirrus HD-OCT (Zeiss)

3D-OCT-2000 (Topcon)
iVue (Optovue)
Spectralis (Heidelberg)
The RHA is a Multi-spectral digital ophthalmoscope generating spectral image data (from blue to deep IR) and data maps including 3D Stereo, color, and oxy/deoxy maps which facilitate visualization of the retina, the vitreomacular interface and the deep choroid.

*The Annidis RHA is currently available for sale in Canada. The RHA is currently not available for sale in the United States and is intended to be commercially available pending U.S. FDA approval.*
Multi-Spectral Imaging (MSI) Fundus Spectral Slices
AMD

Six Slices: Spectral Dissection

Green  Amber  Yellow

Red  Deep Red  Infrared
Targeting AMD with a Critical Carotenoid

Richard A. Bone, PhD, John T. Landrum, PhD, Miami, and Stephen Beatty, MD, John Nolan, PhD, Waterford, Ireland

meso-zeaxanthin
• Ocular Carotenoids (Triplets)
  • Lutein
  • Zeaxanthin
  • Meso-Zeaxanthin
• See the Carotenoid triplets

If Sherman is going to pop a pill, and I do, it’s going to contain all three carotenoids.
Localization is different

Meso-Z

Zeaxanthin

Lutein
As in the previous case, is this early AMD? It certainly could be and gives the clinician ammunition to strongly advise the patient to stop smoking and to improve his diet. Genetic testing and supplemental nutriceuticals are a consideration.
Figure 2. Aβ in drusen in GA retina
Eyes may hold answer for method of early Alzheimer’s detection, treatment

Primary Care Optometry News, August 2013

Presently, diagnosis of Alzheimer’s disease begins with symptoms patients exhibit, namely memory loss. Unfortunately, by the time patients become symptomatic, the disease has already progressed to its later stages. Like age-related macular degeneration, treating Alzheimer’s disease at such an advanced stage is difficult, if not altogether impossible. However, recent advances in Alzheimer’s research have yielded the potential for a method of detecting the disease in its developmental stages, possibly decades before patients become symptomatic.

What is now generally agreed upon by neurologists as being a biomarker of Alzheimer’s disease (AD) is the presence of amyloid beta protein deposits in the brain. Moreover, amyloid also accumulates in the eye, and it has been theorized that if a correlation can be made between the amyloid in the eye and the amyloid in the brain, then it would be possible to diagnose AD by looking into the eye.

Retinal Amyloid Index
Amyloid protein in the back of the eye – indicated here with the Retinal Amyloid Index – is believed to correlate with the presence of amyloid protein in the brain, which is a biomarker for Alzheimer’s disease.
• If a correlation can be made between the amyloid in the eye and the amyloid in the brain, then it would be possible to diagnose AD by looking into the eye.

• Two companies, Cognoptix and NeuroVision, have been developing simple tests to detect amyloid beta plaques in the eye.

• Working title for this test is NeuroVision
  • Uses orally administered curcumin
  • Curcumin crosses the blood-brain and blood-retina barrier and binds with high affinity to amyloid beta plaque
  • Curcumin is also a fluorochrome and naturally generates a fluorescent signal that is captured by imaging device
Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model

Maya Koronyo-Hamaoui a,*,1, Yosef Koronyo a,f,1, Alexander V. Ljubimov b, Carol A. Miller c, MinHee K. Ko a, Keith L. Black a, Michal Schwartz d,2, Daniel L. Farkas e,f,*,2

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b Ophthalmology Research Laboratories, Cedars-Sinai Medical Center, and David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
c Departments of Pathology, Neurology and Program in Neuroscience, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
d Department of Neurobiology, The Weizmann Institute of Science, Rehovot, Israel
e Department of Biomedical Engineering, University of Southern California, Los Angeles, CA, USA
f Departments of Surgery and Biomedical Sciences and Minimally Invasive Surgical Technologies Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

ABSTRACT

Noninvasive monitoring of β-amyloid (Aβ) plaques, the neuropathological hallmarks of Alzheimer's disease (AD), is critical for AD diagnosis and prognosis. Current visualization of Aβ plaques in brains of live patients and animal models is limited in specificity and resolution. The retina as an extension of the brain presents an appealing target for a live, noninvasive optical imaging of AD if disease pathology is manifested there. We identified retinal Aβ plaques in postmortem eyes from AD patients (n = 8) and in suspected early stage cases (n = 5), consistent with brain pathology and clinical reports; plaques were undetectable in age-matched non-AD individuals (n = 5). In APPswe/PS1ΔE9 transgenic mice (AD-Tg; n = 18) but not in non-Tg wt mice (n = 10), retinal Aβ plaques were detected following systemic administration of curcumin, a safe plaque-labeling fluorochrome. Moreover, retinal plaques were detectable earlier than in the brain and accumulated with disease progression. An immune-based therapy effective in reducing brain plaques, significantly reduced retinal Aβ plaque burden in immunized versus non-immunized AD mice (n = 4 mice per group). In live AD-Tg mice (n = 24), systemic administration of curcumin allowed noninvasive optical imaging of retinal Aβ plaques in vivo with high resolution and specificity; plaques were undetectable in non-Tg wt mice (n = 11). Our discovery of Aβ specific plaques in retinas from AD patients, and the ability to noninvasively detect individual retinal plaques in live AD mice establish the basis for developing high-resolution optical imaging for early AD diagnosis, prognosis assessment and response to therapeutics.

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AMD: The Evolving Standard of Care

OPTOMETRIC LEGAL ISSUES: THE EVOLVING STANDARD OF CARE by Jerome Sherman, OD
Technology, Therapeutics and Genetics Increase Opportunity and Responsibility to Prevent Vision Loss from AMD

Today, most ODs recognize how to minimize the risk of vision loss in glaucoma suspects. Patient risk factors such as family history, high IOPs and thin corneas (in a patient with normal appearing discs and normal visual fields) warrant more frequent monitoring. Such a patient with IOPs in the high 20’s and corneas under 500 u is typically evaluated several times a year. Nerve fiber layer thickness (measured with either OCT or GDx), OCT ganglion cell assessment (GCC or GCA), SWAP and Matrix Visual Fields, pattern VEPs and pERGs should be obtained when available. Early detection and early treatment of glaucoma results in significantly better outcomes while dramatically decreasing the risk of malpractice allegations.

Although ODs have been sued, frequently and successfully, for failure to diagnose glaucoma for decades, AMD lawsuits were nonexistent until very recently. Suits are only successful if the issue of causation is met.

Since effective treatment is not available for retinal degenerations such as RP, missing these early diagnoses does not change the patient outcome and the issue of causation is not met.

What is it like to be badgered by a plaintiff’s attorney?

“What question might the plaintiff’s attorney ask in such a case during the deposition and how should the defendant prepare for it?”

Doctor:

- Please describe risk factors in glaucoma and do these risk factors alter the care you render?
- In others words, do you evaluate a glaucoma suspect more often and in more depth (with advanced diagnostic equipment) if they have multiple risk factors?
- Do you do this in order to arrive at a timely diagnosis, knowing that early diagnosis and treatment lead to better outcomes and the prevention of vision loss?
- Is it correct that your record on the date in question indicates that Mrs. Jones had drusen in both eyes?
- Are drusen early indicators of possible loss of vision due to AMD?
- Why didn’t you discuss the implications of drusen and counsel her?
- Do you know the results of the nationally funded, multi-million dollar AREDS study concerning AMD?
PreserVision

Eye Vitamin & Mineral Supplement

AREDS 2 FORMULA

Based on The ONLY Clinically Proven Formula*

Sample NOT FOR RESALE

*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.
49% derive more benefit from treatment other than AREDS

Estimated probabilities of progression to Advanced AMD as a function of genotype, treatment group, and time (years).

Genetic Profile 1: 0 CFH and 2 ARMS2
- Recommended treatment: Zinc Alone

Genetic Profile 2: 1 CFH and 1 ARMS2
- Recommended treatment: AREDS Formulation

Genetic Profile 3: 2 CFH and 0 ARMS2
- Recommended treatment: Antioxidants Alone

Figure modified from Awh et al., CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. *Ophthalmology* (In press).