The Influence of Nutrition and Genetics on AMD Pathogenesis

Date: June 16, 2019
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Dennis Ruskin

- Past Chair - Ocular Nutrition - Special Interest Group of the AAO (SIG)
- Current member - Nutrition, Disease Prevention and Wellness AAO – (SIG)
- Ocular Wellness and Nutrition Society – Founding Director, Secretary
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- Past President of the College of Optometrists of Ontario
- Past Chair of the Clinical Practice Committee (CPC) of the College of Optometrists
- Current committee member of CPC
- Independent Medical Examiner

Disclosure: Relevant financial relationships.

Consultant to:

Bausch & Lomb
Alcon/ Novartis
Bayer
AMD Insight

The content and format of this course is presented without commercial bias and does not claim any superiority of any commercial product or service
Optometry and Integrative Medicine
Understanding Impact of Nutrition and Lifestyle on NVAMD
Course Objectives -
Exudative AMD = Environmental and Genetic Factors

- Factors contributing to exudative macular degeneration (nvAMD)
- Role that diet and food intake has upon nvAMD
- Understanding the relationship between the Gut Microbiome and nvAMD
- Review the AREDS controversy
- Recent interpretation of AREDS data by investigators Seddon and Vavass.
- Review of July 2019 ASRS Paper - demonstrating that AREDS influences our genetics in cases of nvAMD.
Reducing or delaying progression to nvAMD over time with personalized lifestyle-health strategies is safer and less costly to society than antivegf injections.
Macronutrients and Micronutrients

Nutrition

Calories
- Carbohydrates
  - Simple Sugars
    - Glucose
    - Fructose
    - Galactose
    - Lactose
  - Complex Carbohydrates
    - Starch
    - Cellulose
    - Glycogen
- Fats
- Protein
  - Non Essential Amino Acids
  - Essential Amino Acids
    - Histidine
    - Isoleucine
    - Leucine
    - Lysine
    - Methionine
    - Phenylalanine
    - Threonine
    - Tryptophan
    - Valine
- Saturated
- Unsaturated
  - Monounsaturated
  - Polyunsaturated
    - Omega 3
    - Omega 6

Non-Calories
- Water
- Vitamins
  - Vitamin A
  - Vitamin C
  - Vitamin D
  - Vitamin E
  - Vitamin K
  - B complex Vitamins
    - Thiamine (B₁)
    - Riboflavin (B₂)
    - Niacin (B₃)
    - Pantothenic Acid (B₅)
    - Pyridoxine (B₆)
    - Biotin (B₇)
    - Folic Acid (B₉)
    - Cyanocobalamin (B₁₂)
    - Pangamic Acid (B₁₃)
    - Choline
    - Inositol
    - PABA
    - Bioflavonoids (Vitamin P)
- Minerals
  - Calcium
  - Chlorine
  - Chromium
  - Cobalt
  - Copper
  - Fluorine
  - Iodine
  - Iron
  - Magnesium
  - Manganese
  - Molybdenum
  - Nickel
  - Phosphorus
  - Potassium
  - Selenium
  - Sodium
  - Sulfur
  - Vanadium
  - Zinc
Nutrient deficiency or excess with ageing

- Orange arrow: Aging causes poorer absorption of nutrients
- Red downward arrow: Iron deficiency in children and young adults
- Green upward arrow: Iron overload causes insulin resistance
- Red downward arrow: Iodine deficiency - need Synthroid
- Red downward arrow: Vitamin D - dark skin requires sunshine
- Red downward arrow: Vitamin B12 with Metformin
- Orange downward arrow: Calcium Deficiency
- Orange downward arrow: Magnesium Deficiency
Biological Interactions are affected by Genetics

Single nucleotide polymorphisms, frequently called SNPs (pronounced “snips”), are the most common type of genetic variation among people.

SNPs associated with AMD are located on genes that affect biological pathways of the disease.
Anti aging and Caloric Restriction

The Hunger Gains: Extreme Calorie-Restriction Diet Shows Anti-Aging Results

A new study shows five days of hunger a month may reduce risk factors for aging and age-related diseases

By Richard Conniff on February 16, 2017
Caloric Restriction and aging

The monkey on the standard diet left (A & B), looks older than the Calorie Restricted monkey on the right (C & D) - http://www.crvitality.com/2014/04/calorie-restriction-in-rhesus-monkeys/
Getting Hooked on Carbs

Eating carbohydrates locks you into a glucose-dependent metabolism

![Graph showing blood sugar levels and the effects of sugar spike and sugar crash.]
Insulin Response over time sorted by macronutrient → Minimizing Chronic Disease (AMD included) with ↓ Insulin Production
Sources of Added Sugar in the Typical American Diet

- Soft Drinks: 33%
- Sugars & Candy: 16%
- Cakes, Cookies, Pies: 13%
- Other Grains: 6%
- Dairy Desserts & Milk Products: 9%
- Fruit Drinks: 10%
- All Other: 13%

Canned Fruit is not even mentioned as one of the foods contributing more than 5% of added sugars.

Source: ADA's Complete Food & Nutrition Guide
Failure of Low Fat Guidelines
### Ratio of Macronutrients (%)

<table>
<thead>
<tr>
<th>Diet Name</th>
<th>Carbohydrates</th>
<th>Fats</th>
<th>Protein</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atkins</td>
<td>32</td>
<td>46</td>
<td>22</td>
<td>Best retention diet</td>
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<tr>
<td>Zone</td>
<td>40</td>
<td>30</td>
<td>30</td>
<td>Reduces inflammation</td>
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<td>Learn</td>
<td>55</td>
<td>10</td>
<td>30</td>
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<tr>
<td>Low Fat</td>
<td>46</td>
<td>34</td>
<td>20</td>
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<tr>
<td>Dean Ornish</td>
<td>52</td>
<td>29</td>
<td>19</td>
<td>Eat more, weigh less</td>
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<tr>
<td>Low carb, ketogenic</td>
<td>20</td>
<td>65</td>
<td>15</td>
<td>Good for healthy people</td>
</tr>
<tr>
<td>Human Breast Milk</td>
<td>39</td>
<td>54</td>
<td>7</td>
<td>Infant brain needs glucose to produce energy</td>
</tr>
<tr>
<td>Mediterranean</td>
<td>50</td>
<td>25</td>
<td>25</td>
<td>8% saturated fat. Reduces risk of AMD by 33%</td>
</tr>
</tbody>
</table>
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D.,

CONCLUSIONS
Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. (Funded by the Spanish government’s Instituto de Salud Carlos III and others; Controlled-Trials.com number, ISRCTN35739639.)
Higher adherence to the Mediterranean Diet was associated with a 41% reduced risk of incident AMD.

Incident AMD is defined as any progression from early to advanced AMD (INCLUDES GA and CNV).
Gut Microbiota

- Gut microbiota plays an important role in our lives and in the way our bodies function.
- The composition of gut microbiota is unique to each individual, just like our fingerprints.
- Our gut microbiota contains tens of trillions of bacteria—ten times more cells than in our body.
- There are more than 3 million microbial genes in our gut microbiota—150 times more genes than in the human genome.
The Gut-Brain Axis

Neuroinflammation

Blood Brain Barrier

Vagus Nerve

Quinolinic Acid
- Kynurenine
- Tryptophan

HPA axis
- CRF
- ACTH
- Cortisol

Proinflammatory Cytokines

Stress Infection Antibiotic Poor Diet

Immune Cells

SCFA Prebiotic Probiotic Good Diet

Intact Barrier

Gut Microbiota

Epithelium

Ocludin

Claudin

Disrupted Barrier

Lumen
Gut Microbiota influences angiogenesis in obesity-driven choroidal neovascularization

Elisabeth MMA Andriessen\textsuperscript{1}, Ariel M Wilson\textsuperscript{2}, Gaelle Mawambo\textsuperscript{3}, Agnieszka Dejda\textsuperscript{3,4}, Khalil Miloudi\textsuperscript{5}, Florian Sennlaub\textsuperscript{6} & Przemyslaw Sapieha\textsuperscript{1,3,4,5,*}
Gut microbiota influences pathological angiogenesis in obesity-driven choroidal neovascularization.
Role of diet and food intake in age-related macular degeneration: a systematic review

Clinical and Experimental Ophthalmology 2019; 47: 106–127

- Study quality level sorted using the Oxford Centre of Evidence Base Medicine 2011.
- Studied Level Quality 1, 2 and 3 only, discarded level quality 4-5
<table>
<thead>
<tr>
<th>PR</th>
<th>Author</th>
<th>Study design</th>
<th>AMD stage</th>
<th>Comments and Interpretation</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td>Merle et al. (2015)</td>
<td>Cohort 13 yrs</td>
<td>Advanced AMD</td>
<td>A high adherence to the Mediterranean diet (MI) associated with a <strong>26% lower risk of progression to advanced AMD</strong> compared with a low adherence to the MI.</td>
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<td>2</td>
<td>Cougnard-Gregoire et al. (2016)</td>
<td>Cohort Study 6 yrs</td>
<td>Late AMD</td>
<td>Regular use of olive oil was associated with a <strong>56% reduction in the odds of progressing to late AMD</strong> compared with no use of olive oil.</td>
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<tr>
<td>2</td>
<td>Amirul et al. (2014)</td>
<td>Cohort Study 13 yrs</td>
<td>Advanced AMD</td>
<td>A high quartile intake of grains, fish, steam/broiled chicken, vegetables and nuts compared with a low quintile intake was associated with a <strong>51% decreased odds of developing advanced AMD.</strong></td>
</tr>
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<td>3</td>
<td>Chiu et al. (2014)</td>
<td>Cross-sectional</td>
<td>Early and advanced AMD</td>
<td>A high quintile Oriental pattern score compared with a low quintile score had a <strong>26% reduction in early AMD odds and 62% reduction of the advanced AMD odds</strong></td>
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<tr>
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<td>A high Western diet pattern score compared with a low score had a <strong>56% increase in early AMD odds and 270% increase in advanced AMD odds</strong></td>
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<td>Both diet pattern scores were more strongly associated with advanced AMD</td>
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<tr>
<td>3</td>
<td>Hogg et al. (2017)</td>
<td>Cross Sectional</td>
<td>Neovascular AMD</td>
<td>A high quartile for Mediterranean diet score (MDS) was associated with a <strong>47% reduction in the odds of developing neovascular AMD</strong> compared with a low MDS diet score quartile one.</td>
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<td>2</td>
<td>Wu et al. (2017) Nurses Health Study (NHS) + Health Professions Follow Up Study (HP)</td>
<td>Cohort Study 28 and 24 years</td>
<td>Intermediate AMD – NHS Advanced AMD - HP</td>
<td>High intake of EPA/DHA was associated with a reduced risk of progression to advanced AMD by 32% compared with low intake for the health professions mail cohort. Omega-3 fatty acids intake did not show an association with advanced AMD in this study.</td>
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<td>2</td>
<td>Joachim et al. (2015)</td>
<td>Cohort Study 15 years</td>
<td>Late AMD</td>
<td>Fish consumption of more than one serving per week was associated with a 52% reduction in the odds of developing a late AMD compared with less than one serving per week.</td>
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<td>2</td>
<td>Christen et al. (2015)</td>
<td>Cohort Study 10 years</td>
<td>AMD VA &lt; 6/9 attributed to AMD</td>
<td>A high three ratio of Omega six fatty acids to omega-3 fatty acids in the diet compared with a low ratio was associated with a 55 to 77% increased risk of AMD. The lower risk of AMD with fish consumption appeared to be attributed to the high consumption of dark meat fish and canned tuna fish, with both associated with a 44% lower risk of AMD.</td>
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<td>3</td>
<td>SanGiovanni et al. (2007)</td>
<td>Case-Control</td>
<td>Neovascular AMD</td>
<td>Consumption of more than two servings of fish per week, compared with less than one serving per month, was associated with a 39% reduction in the odds of developing neovascular AMD.</td>
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<td>3</td>
<td>Seddon et al. (2006)</td>
<td>Case-Control</td>
<td>Intermediate and late AMD</td>
<td>Consumption of more than two servings of fish per week, compared with less than one serving per week, was...</td>
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<td>Chong et al. (2009)</td>
<td>Cohort Study 10 Years</td>
<td>Early AMD</td>
<td>High quartile for trans fat consumption compared with low quartile trans fat consumption had a 76% increase in late AMD odds. There were no statistically significant associations between most dietary fats fish intake, total fat, other fats, butter or margarine) and AMD (early, intermediate or late) odds.</td>
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<td>2</td>
<td>Kaushik et al. (2008)</td>
<td>Cohort Study 8 years</td>
<td>Early AMD</td>
<td>A high dietary G.I. diet quartile four compared with a low G.I. diet quartile one was associated with a 77% increased risk of incident early AMD.</td>
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<td>2</td>
<td>Chiu et al. (2007)</td>
<td>Cohort Study 8 years</td>
<td>No AMD to early AMD</td>
<td>The high G.I. diet compared with a low G.I. diet was associated with a 10% increased risk of AMD progression in the combined group (no, early and intermediate AMD).</td>
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<td>Early AMD to progression to AMD (EAPA)</td>
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<td>Intermediate AMD to EAPA</td>
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<td>All AMD groups to (EAPA)</td>
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<td>Late AMD</td>
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</table>

High intake of food sourced carotenoids was associated with a 35 to 36% reduced risk of developing advanced AMD compared with low intake of carotenoids.

High intake of carotenoids was not significantly associated with the risk with the risk of developing intermediate AMD.

<table>
<thead>
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<tr>
<td>2</td>
<td>Wu et al. (2015)</td>
<td>Cohort Study</td>
<td>Advanced AMD</td>
<td>High intake of food sourced carotenoids was associated with a <strong>35 to 36% reduced risk of developing advanced AMD</strong> compared with low intake of carotenoids. High intake of carotenoids was not significantly associated with the risk of developing intermediate AMD.</td>
</tr>
<tr>
<td>3</td>
<td>Aoki et al. (2016)</td>
<td>Case Control</td>
<td>Neovascular AMD</td>
<td>A high intake of zinc, vitamin D, also wrote, vitamin C, omega-3 fatty acids and beta-carotene was associated with a reduction in the odds of developing neovascular AMD by <strong>60 to 90% compared with low intakes of these</strong> a <strong>199% increase in the odds of developing late AMD micronutrients.</strong></td>
</tr>
<tr>
<td>2</td>
<td>Chong et al.</td>
<td>Cohort Study</td>
<td>Early AMD</td>
<td>Salami or continental sausage consumption of more than one time per week was associated with a <strong>137% increase in the odds of developing late AMD</strong> compared with less than one time per month.</td>
</tr>
<tr>
<td>2</td>
<td>Gopinath et al. (2014)</td>
<td>Cohort Study</td>
<td>Late AMD</td>
<td>A low dietary calcium intake was associated with a <strong>199% increase in the odds of developing late AMD</strong> compared with a high dietary calcium intake. There were no statistically significant associations between dairy products in early AMD odds.</td>
</tr>
</tbody>
</table>
| 2  | Adams et al. (2012) | Cohort Study | Early AMD | Alcohol intake of more than 20 g per day was associated with a **21% increase in the odds of developing early AMD**.
Hippocrates quote: “Let food be thy medicine and medicine be thy food.”

For the first time in history lifestyle diseases are killing more people than communicable diseases.

These lifestyle diseases include diabetes, heart disease, some cancers, and ocular diseases – AMD, Dry Eye & Diabetic Retinopathy.

More than 75% of these diseases are preventable.

Food has the power to be medicine or poison.
AREDS Primer

- AREDS is indicated for patients who may be at risk to nvAMD
- AREDS is not advised nor should it be used for patients who have geographic atrophy (GA)
- AREDS does not delay or prevent GA.
- The AREDS story runs a span of ~ 20 years
- Conflicting conclusions occurred due to incorrect methodologies and incorrect determination of clinical endpoint.
Why was Age Related Eye Disease (AREDS) RCT undertaken?

To separate fact from fiction
RDI of Nutrients used in AREDS 1

Vitamin C – 500 mg (5X RDI)
Vitamin E – 400 IU (13X RDI)
Zinc – 80 mg (Zinc Oxide (11X RDI)
Multivitamin – Centrum Silver
Beta-carotene – 15 mg (25,000 IU) (8X RDI).
Synthetic nutrients used in AREDS 1.
RDI = Recommended Daily Intake
AREDS 1 Conclusions and Insights for AREDS 2

- AREDS 1 ➔ 25% modest reduction in progression of AMD for categories 3 and 4

- For AREDS 2 - **Goal was for a 50% reduction progression of AMD** (an additional 25% reduction from AREDS 1 conclusions)

- Secondary randomization to assess L and Z without Betacarotene.

- Lutein (L) and Zeaxanthin (Z) and Omega 3 were to be determined
AREDS 2 – Hope For A 50% Reduction In The Progression of AMD

- ~ 4,000 patients consumed original AREDS1 or modified AREDS1 supplements
- Study duration for 5 years with:
  - 10 mg/day Lutein and 2 mg/day Zeaxanthin
  - 1 gram/day Omega fatty acids (DHA, EPA)
  - High zinc 80 mg, low zinc 25 mg.
- Conclusions released May 2013
Conclusions and Relevance  Addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD. However, because of potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.

Trial Registration  clinicaltrials.gov Identifier: NCT00345176


Goal for a 50% reduction in the progression of AMD (an additional 25% reduction from AREDS1 conclusions) failed
Omega 3 and AREDS 2

The preponderance of evidence suggests the omega-6/omega-3 ratio to be of paramount importance at any stage of AMD, despite it being disregarded in the AREDS II intervention study.

Although conclusions with respect to fish oil supplementation were null with AREDS 2, in contrast with AREDS I post-hoc data and the preponderance of biological and epidemiologic evidence showing a benefit of fish and fish oil supplementation in AMD.

This anomaly likely resulted from:
- Higher intake
- Insufficient DHA
- Older age of the subject population
Recommending Calcium?

Ca supplements are generally used as a means to reduce bone fracture risk.

Calcium supplementation accelerates vascular calcification, increases cardiovascular events in healthy postmenopausal women, and increases mortality in patients with renal failure.

Prolonged Ca supplementation is associated with increased risk for heart attack.

Clinical Pearl ➔ Calcium-rich diet may be protective for the heart.

➔ Calcium supplements may damage the heart.
Calcium Intake From Diet and Supplements and the Risk of Coronary Artery Calcification and its Progression Among Older Adults: 10-Year Follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA)

John J.B. Anderson, PhD; Bridget Kruszka, MPH; Joseph A.C. Delaney, PhD; Ka He, MD, ScD; Gregory L. Burke, MD, MSc; Alvaro Alonso, MD, PhD; Diane E. Bild, MD, MPH; Matthew Budoff, MD; Erin D. Michos, MD, MHS, FACC, FAHA

Background—Recent randomized data suggest that calcium supplements may be associated with increased risk of cardiovascular disease (CVD) events. Using a longitudinal cohort study, we assessed the association between calcium intake, from both foods and supplements, and atherosclerosis, as measured by coronary artery calcification (CAC).

Methods and Results—We studied 5448 adults free of clinically diagnosed CVD (52% female; aged 45–84 years) from the Multi-Ethnic Study of Atherosclerosis. Baseline total calcium intake was assessed from diet (using a food frequency questionnaire) and calcium supplements (by a medication inventory) and categorized into quintiles. Baseline CAC was measured by computed tomography, and CAC measurements were repeated in 2742 participants ≈10 years later. At baseline, mean calcium intakes across quintiles were 313.3, 540.3, 783.0, 1168.9, and 2157.4 mg/day. Women had higher calcium intakes than men. After adjustment for potential confounders, among 1567 participants without baseline CAC, the relative risk (RR) of developing incident CAC over 10 years, by quintile 1 to 5 of calcium intake, were 1 (reference), 0.95 (0.79–1.14), 1.02 (0.85–1.23), 0.86 (0.69–1.05), and 0.73 (0.57–0.93). After accounting for total calcium intake, calcium supplement use was associated with increased risk for incident CAC (RR=1.22 [1.07–1.39]). No relation was found between baseline calcium intake and 10-year changes in log-transformed CAC among those participants with baseline CAC >0.

Conclusions—High total calcium intake was associated with a decreased risk of incident atherosclerosis over long-term follow-up, particularly if achieved without supplement use. However, calcium supplement use may increase the risk for incident CAC. (J Am Heart Assoc. 2016;5:e003815 doi: 10.1161/JAHA.116.003815)

Key Words: calcium • cardiovascular imaging • coronary artery calcium • diet • epidemiology
AMD Treatment - Standard of Care

Dry AMD

AREDS 2 Ocular Vitamins
Vitamin E (400 IU), Vitamin C (500mg),
Lutein (10 mg), Zeaxanthin (2 mg),
Copper (2 mg), Zinc (80mg/25mg)
Not FDA approved and no other supporting study exits

Wet AMD

Standard of Care

VEGF INHIBITOR INJECTIONS
• AVASTIN (bevacizumab)
• LUCENTIS (ranibizumab)
• EYLEA (aflibercept)
• Steroids, Visudyne, Macugen...

A scientific controversy can directly impact what the standard of care is
Confounding data surrounding AREDS Controversy

Emily Chew and Carl Awh are in complete disagreement with each other's interpretation of the AREDS data.

Is there any other scientific evidence to support either position?
The primary clinical question surrounding AREDS research

- Is there validated scientific evidence to show that the response to treatment using AREDS in cases of wet AMD, is determined by genetics?
Personalized Nutrition using genetics

→ A different way to view AREDS1 data

Varied Response to Treatment
Genetics and disease – risk alleles “the luck of the draw”

Allele Definition. - Any of the alternative forms of a gene

- AMD has the strongest genetic contribution of all human multigenetic diseases
Genes affect the pathogenesis of AMD

- 2 major Genes: CFH and ARMS2 involved in AMD
- 52 independently associated common and rare variants
- Complement cascade – part of the immune system, CFH, C2, CFB, C3, and CFI
- ARMS2 gene has been associated with AMD is important and is involved with energy metabolism within the mitochondria
n=337 developed AMD, n=91 early AMD
n=2 CFH genetic alleles, smoked a pack 7+-yrs.,
and were in the highest-risk diet and exercise
categories were more than 4x more likely to
have AMD compared to n=0 CFH, healthy diet
and 10 hrs. / week of light exercise or at least 8
hrs. of moderate activity (brisk walking).
CFH AND CFI risk alleles

Blood levels indicating vitamin D deficiency (less than 12 ng/mL of 25 hydroxyvitamin D) were associated with a 1.8-fold increase in the odds of having AMD among women with no risk alleles, but a 6.7-fold increase in the odds of having AMD among women with two risk alleles, compared with women who had no genetic risk alleles and adequate levels of vitamin D.

JAMA Ophthalmol, August 2015
High risk alleles shortens the timeline to develop serious vision loss with AMD.

Patients carrying 4 risk alleles in CFH and ARMS2 developed Exudative AMD 12.2 (95% CI, 6.2-18.3) years earlier than patients with zero risk alleles (P < .001).
For 23% of patients, the AREDS formulation was the best treatment.

49% of patients derive more benefit from a formulation other than AREDS.

For 13% of the patients, the AREDS combination was harmful and accelerated vision loss significantly faster than placebo.

As of this date Emily Chew did not release any study data about possible relationships with AREDS formulations and genetic samples.
Projected Results

**CFH RISK GENES**

- Zinc increases progression risk

<table>
<thead>
<tr>
<th>Genotype 4</th>
<th>Genotype 5</th>
<th>Genotype 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIME (Years)</strong></td>
<td><strong>TIME (Years)</strong></td>
<td><strong>TIME (Years)</strong></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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<td>48.8</td>
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<td>56.3</td>
<td>61.9</td>
<td>9.7</td>
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<td>19.2</td>
<td>26.7</td>
<td>5.2</td>
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<td>38.0</td>
<td>46.9</td>
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<td>62.1</td>
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<td>76.64</td>
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<td>3.3</td>
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</tr>
<tr>
<td>8.8</td>
<td>18.1</td>
<td>7.1</td>
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<td>22.1</td>
<td>42.0</td>
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<td>25.82</td>
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<td>29.0</td>
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<tr>
<td>12.4</td>
<td>35.69</td>
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</tr>
<tr>
<td>29.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>48.8</td>
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<td>0.0</td>
</tr>
<tr>
<td>55.49</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo and AREDS</th>
</tr>
</thead>
</table>

**ARMS2 RISK GENES**

- Antioxidants increase progression risk

- Zinc
- Zinc + AO
- Placebo
- AO (Vit C & E)
1. AREDS2 – No report on genetic findings
2. 1237 AREDS Category 3 Patients
3. Patients were analyzed from 27 subgroups – 11 of the 27 subgroups had fewer than 30 patients.
4. Statistical design made it impossible to demonstrate a significant effect
5. Endpoint = Progression to AREDS Category 4 – Advanced AMD
AREDS #38 refers to data in AREDS #8

Fig. 1A: “the AREDS supplements...reduced the risk of development of late AMD...by 25%”
AREDS #38 Chew - AREDS no better than Placebo – Does AREDS actually work?

| CFH | ARMS2 | AREDS F | | Placebo | |
|-----|-------|---------|----------------|----------|
|     |       | Total   | Events | Non Events | Total   | Events | Non Events |
| 0   | 0     | 24      | 1      | 23         | 25      | 3      | 22         |
| 0   | 1     | 24      | 2      | 22         | 25      | 7      | 18         |
| 0   | 2     | 11      | 5      | 6          | 3       | 0      | 3          |
| 1   | 0     | 40      | 8      | 32         | 31      | 4      | 27         |
| 1   | 1     | 42      | 5      | 37         | 29      | 14     | 15         |
| 1   | 2     | 15      | 4      | 11         | 19      | 3      | 16         |
| 2   | 0     | 61      | 19     | 42         | 63      | 11     | 52         |
| 2   | 1     | 76      | 30     | 46         | 59      | 20     | 39         |
| 2   | 2     | 30      | 14     | 16         | 24      | 14     | 10         |
| Total |       | 323     | 88     | 235        | 278     | 76     | 202        |

This value differs from AREDS#8 = 0.66
AREDS #38 used a sub sample of original AREDS data.

Odds Ratio = \( \frac{88/235}{76/202} \) = 0.995
According to the results AREDS #38 paper AREDS not superior to placebo from any sub group - 1237 patients analyzed as 27 independent sub groups

No statistically significant interaction between treatment effect and genotype

- Too few numbers of patients in subgroups to observe a statistically significant effect.
The data presented in AREDS 38 does not show a beneficial effect in the prevention or delay of AMD for subjects who consumed the AREDS formulation of antioxidants and zinc.

Reports 8 and 38 use very different statistical techniques to analyze progression events, making them not directly comparable.

AREDS Report 38 also has many internal data inconsistencies making it impossible to know what data was actually analyzed by the authors.

When the primary data is lifted from the manuscript and basic modeling statistics are performed, a strong interaction between CFH, ARMS2 and response to zinc use is observed.
Rosner agrees with the report by Rafal Kustra, although he summarized the data in a different manner.

There definitely is an interaction between the number of risk alleles for the CFH gene and the efficacy of the combination treatment currently recommended (antioxidants and zinc).
Awh et al refutes Chew’s AREDS #38 presented at the American Society of Retinal Specialists (ASRS) annual meeting 2015

Treatment Response to Antioxidants and Zinc Based on CFH and ARMS2 Genetic Risk Allele Number in the Age-Related Eye Disease Study

Carl C. Awh, MD,1 Steven Hawken, MSc,2 Brent W. Zanke, MD, PhD2,3,4

Objective: To evaluate the impact of complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) risk alleles on the observed response to components of the Age-Related Eye Disease Study (AREDS) formulation.

Conclusions: The benefit of the AREDS formulation seems the result of a favorable response by patients in only 1 genotype group, balanced by neutral or unfavorable responses in 3 genotype groups. Ophthalmology 2014;8:1–8 © 2014 by the American Academy of Ophthalmology.
How did Awh come up with:
GTG1, GTG2, GTG3, and GTG4?

- Mendellian genetics: there are 3 copies of a gene:
  
  AA- Homozygous – most potent gene  
  A,a – Heterozygous- less potent gene  
  a,a – Homozygous recessive – least potent gene

- With 2 major polymorphism of CFH and ARMS 2 you have 3 possibilities for each risk allele or a total of $3 \times 3 = 9$ genetic combinations to test for.

- Dr. Awh had the same problem as with Dr. Chew with AREDS #38 – i.e. Too few numbers of patients in subgroups to observe a statistically significant effect.
Defined 4 genotype groups to allow sufficient numbers per group to satisfy statistical significance

Resulted in 4 distinct Genotype Groups with Higher or Lower CFH and ARMS2 risk
Awh et al. 2014 – Actual Outcomes

Actual outcomes in this group are not rare 13% of study patients

131/989

7-year progression rates to advanced AMD within each genotype group (GTG) as a function of treatment. -- AREDS F = AREDS Formulation -- http://x.doi.org./10.1026/j.ophtha.2014.07.049
Personalized Nutrition verses RCT
→ A different way to view AREDS1 data

AREDS for all AMD patients

Varied Response to Treatment
Macular Degeneration: 10 Common and Rare Genetic Variants, Demographic, Environmental, and Macular Covariates


Purpose

An online risk calculator was developed and is available in the public domain at seddonamdriskscore.org

Results

Attributable risk calculations revealed that 60% of incident AMD is attributable to genetic factors, adjusting for demographic covariates and baseline macular phenotypes...

Conclusions

Rare variant C3 K155Q was independently associated with AMD progression. The comprehensive model may be useful for identifying and monitoring high-risk patients, selecting appropriate therapies, and designing clinical trials.
Algorithm Development of Genetic Testing


- This information can be combined into an age-adjusted risk profile for individuals having various forms of the genes.
Assessing risk of progression to nvAMD

<table>
<thead>
<tr>
<th>Test Components</th>
<th>Clinical Exam</th>
<th>Genetics</th>
<th>Non-Genetic Risk Factors</th>
</tr>
</thead>
</table>
| Clinical Exam            | • AMD Status  | • 15 Genetic Markers Across 12 AMD-Associated Genes | • Age
• BMI
• Smoking History
• Education |
| Non-Genetic Risk Factors |               |          |                          |
Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis

Johanna M Seddon, Rachel E Silver, Bernard Rosner

Conclusions The effectiveness of antioxidant and zinc supplementation appears to differ by genotype. Further study is needed to determine the biological basis for this interaction.

Please note! She also observed that the inclusion of Geographic Atrophy combined with nvAMD patients will dilute the dataset under analysis.
Conclusions: Patients who meet criteria for supplements to prevent AMD progression should be offered zinc and antioxidants without consideration of genotype - Assel 2018
Assel's investigators did not consider Seddon’s December, 2016 research prior to their investigation. They analyzed the incorrect clinical endpoint.

1. ASSELS et al. looked at advanced AMD which is composed of Geographic Atrophy + Choroidal Neovascularization.

2. 55% of patients progressed to **Geographic Atrophy** which diluted the study population and watered down the results.

**FIG. 2.** Chew, Awh and Assel included subjects who progressed to both GA and CNV. Seddon and Vavvas restricted their analysis to subjects who progressed to CNV—the correct clinical endpoint.
GTG2 group (CFH risk alleles) compare: Assel’s data: GA+CNV vs. only CNV

Assel’s data with GA in sample

Assel’s data without GA in sample

GA or CNV-free status in GTG 2

CNV-free status in GTG 2

Probability of progression free status

Category groups observed and clinical endpoints analyzed sorted by Researcher

<table>
<thead>
<tr>
<th>Study</th>
<th>AREDS Category patients</th>
<th>Clinical Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Chew (2014)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Awh (2015)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Seddon (2016)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Assel (2017)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vavvas (2018)</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
New study shows strong interaction between genetics and nutritional supplement treatment on progression to neovascular age-related macular degeneration (AMD)

In a study published on January 8, 2018 in the Proceedings of the National Academy of Sciences (PNAS), Demetrios G. Vavvas, MD, PhD, Associate Professor of Ophthalmology at Harvard Medical School and Incumbent of the Monte J. Wallace Ophthalmology Chair in Retina at Mass. Eye and Ear, as well as investigators from University of Toronto and Stanford University, addressed a controversial topic in the field of ophthalmology -- whether treatment with the Age-Related Eye Disease Study (AREDS) formulation, a combination of high-dose antioxidants and zinc, is helpful or harmful to patients based on their underlying genetics.
**CFH** and **ARMS2** genetic risk determines progression to neovascular age-related macular degeneration after antioxidant and zinc supplementation

Demetrios G. Vavvas (Δημήτριος Γ. Βάββας), Kent W. Small, Carl C. Awh, Brent W. Zanke, Robert J. Tibshirani, and Rafał Kustra

*Department of Ophthalmology Retina Service, Massachusetts Eye and Ear Institute, Harvard Medical School, Boston, MA 02114*; *Macula and Retina Institute, Los Angeles, CA 90048*; *Tennessee Retina, Nashville, TN 37203*; *Department of Medical Affairs, Arctic Medical Laboratories, Grand Rapids, MI 49504*; *Department of Biomedical Data Science, Stanford University, Stanford, CA 94305*; *Department of Statistics, Stanford University, Stanford, CA 94305*; and *Dalla Lana School of Public Health, University of Toronto, Toronto, ON M5T 3M7, Canada*

Contributed by Robert J. Tibshirani, December 12, 2017 (sent for review October 18, 2017; reviewed by Tom Friberg and J. Sunil Rao)

We evaluated the influence of an antioxidant and zinc nutritional supplement [the Age-Related Eye Disease Study (AREDS) formulation] on delaying or preventing progression to neovascular AMD (NV) in persons with age-related macular degeneration (AMD). In the complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) genes have the greatest impact on the progression to advanced AMD (5–7). The Age-Related Eye Disease Study (AREDS) concluded that

**ARMS2** risk had decreased progression risk. Analysis of **CFH** and **ARMS2** genotype groups from a validation dataset reinforces this conclusion. Bootstrapping analysis confirms the presence of a genetics–treatment interaction and suggests that individual treatment response to the AREDS formulation is largely determined by genetics. The AREDS formulation modifies the risk of progression to NV based on individual genetics. Its use should be based on patient-specific genotype.
Vavvas used the largest Dataset of all AREDS Researchers investigating progression to nvAMD
Risk of harm increased ~ 3 times patients with GTG2
Beneficial to patients with GTG3

### Progression to nvAMD or Central GA (n = 802)
AREDS vs. Placebo

<table>
<thead>
<tr>
<th>Genotype group</th>
<th>AREDS-NV</th>
<th></th>
<th>AREDS-GA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P value</td>
<td>HR</td>
<td>P value</td>
</tr>
<tr>
<td>GTG1</td>
<td>1.41</td>
<td>0.43</td>
<td>0.70</td>
<td>0.40</td>
</tr>
<tr>
<td>GTG2 (high CFH, low ARMS2 risk)</td>
<td>2.92</td>
<td>0.018</td>
<td>1.04</td>
<td>0.93</td>
</tr>
<tr>
<td>GTG3 (low CFH, high ARMS2 risk)</td>
<td>0.50</td>
<td>0.008</td>
<td>0.60</td>
<td>0.09</td>
</tr>
<tr>
<td>GTG4</td>
<td>1.03</td>
<td>0.91</td>
<td>0.88</td>
<td>0.74</td>
</tr>
<tr>
<td>Interaction (χ², 2 df)</td>
<td>—</td>
<td>0.01</td>
<td>—</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Validation Sample independent from Dr. Awh’s Dataset Confirms Primary Effect

Validation Analysis:
Progression to nvAMD in the Unique dataset* (n = 299)

<table>
<thead>
<tr>
<th>Genotype group</th>
<th>HR AREDS vs. placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTG2 (high CFH, low ARMS2 risk)</td>
<td>4.9</td>
<td>0.021</td>
</tr>
<tr>
<td>GTG3 (low CFH, high ARMS2 risk)</td>
<td>0.36</td>
<td>0.003</td>
</tr>
</tbody>
</table>

- AREDS is harmful for patients who are GTG2
- AREDS is beneficial for patients who are GTG3
This is an analysis of patients with exudative AMD and a history of AREDS use. Subjects were recruited from community-based retina practices. None of the investigators were aware of the genotype and of AREDS use or not. Blinding was important. NV AMD was determined by fellowship trained retinologists based upon clinical exam and OCT findings. The odds ratio was computed as the proportion of patients who use AREDS use in GTG2 individuals compared to GTG3 individuals. Their analysis indicated that GTG2 patients were far more likely to have taken the AREDS prior to the development of NV AMD than those with any other genotype. This finding validates the work of Vavvas 2018.
Inclusion criteria:
1. Aged $\geq 65$ years at the time of diagnosis of wet AMD
2. Newly diagnosed wet AMD, or new wet AMD diagnosed within 12 months of the start of the study in one or both eyes. (Patients with longstanding wet AMD are less likely to reliably recall AREDS supplement use.) Diagnosis of wet AMD will be determined by the examining physician to be due to AMD based on clinical examination, OCT, and, if necessary, any additional testing needed to confirm the diagnosis.
3. History of either AREDS use 5 or more times a week for the past five years or no AREDS Formula supplement use (defined as use of AREDS Formula supplement use of less than one month in the last three years).
   - The 2 study groups are ‘5 years AREDS’ vs ‘never’
4. Patients may have used a daily multivitamin with 15 mg or less of zinc

Study process
- Questionnaire
- Genetic testing (ignore all results that are GTG1 or GTG4 [i.e. only seeking GTG2 or GTG3])
- Statistical analysis
Genes influence a response with AREDS


2. Measuring Progression to Advanced AMD (GA plus CNV). - Two Gene investigations –

1. Summary: The Science of Gene – AREDS

Early Discovery: The Biology of Drusen & Single gene investigations


2./ Summary: The Science of Gene – AREDS

Discovery: Two Gene investigations – Measuring Progression to Advanced AMD (GA plus CNV)


3. Awh C., Hawkin, S., Zanke B.; Treatment Response to Antioxidants and Zinc Based on CFH and ARMS2 Genetic Risk Allele Number in the Age-Related Eye Disease Study; Ophthalmology, September 2014.

Summary: The Science of Gene – AREDS

Validation: Two Gene Investigations – Measuring Progression to CNV (Wet AMD) Only

1. Seddon J.M., Silver R E., Rosner B. Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis; *BJO Online First*, published on July 28, 2016 as 10.1136/bjophthalmol-2016-308624

2. Vavvas D., Small K., Awh C., Zanke B., Tibshirani R., Kustra R.; *CFH* and *ARMS2* genetic risk influences the safety and efficacy of AREDS against progression to Wet AMD (NV); *PNAS*, January 2018

New evidence about the AREDS Controversy

- Recent research by Seddon and Vavvas demonstrates validated scientific evidence to show that the response to treatment using AREDS in cases of wet AMD, is determined by genetics.

- Vavvas confirmed his finding using a unique dataset (299) independent from Awh (Vavvas, 2018).

- There exists a different AREDS treatment response based upon CFH and ARMS2 risk alleles.

- Chew, Awh, and Assels’s analyzed the inappropriate clinical end point which diluted their patient samples.

- Kauffman et al. 2019 paper validates Vavvas work.

- Based upon recent research, AREDS is beneficial for many and harmful for some.

- More research is recommended to confirm findings.
Time is of the essence to manage AMD


Time is your enemy – especially if your patient has one eye converted to WET AMD. Recommending AREDS could ↑ AMD progression.
Options for Nutritional Recommendation pertaining to AREDS and AMD

- Continue to give AREDS to all patients regardless of genotype
- Do not prescribe AREDS for all patients
- Determine whether your patient genetic profile contains CFH and ARMS2 has risk alleles.
Is Self Recommendation of AREDS vitamins safe?

- The NIH does not recommend patients to take AREDS vitamins who have either no clinical signs or stage I of the disease.

- Individuals taking antioxidants (AREDS) that have no genetic risk are subjected to an increase in risk of progression to AMD. (Based upon Vavass et al. 2018).

- Self recommendations by the public to consume AREDS in the absence of an eye examination increase the odds of potential visual risk of harm.
Multifactorial processes indicating risk to Exudative AMD
### Table 3. Diet and food intake recommendations based on results from studies evaluating the role of diet and food intake in AMD

<table>
<thead>
<tr>
<th>Dietary factor</th>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oriental diet</td>
<td>Recommend higher intake of vegetables, legumes, fruit, whole grains, tomatoes and seafood.</td>
</tr>
<tr>
<td>Western diet</td>
<td>Avoid higher intake of red meat, processed meat, high-fat dairy products, fried potatoes, refined grains and eggs.</td>
</tr>
<tr>
<td>Food group</td>
<td>Consumption of food group containing grains, fish, non-fried chicken, vegetables and nuts preferable to red meat.</td>
</tr>
<tr>
<td>Carotenoids (L/Z)</td>
<td>Recommend higher intake of L/Z-containing green leafy vegetables, vegetables and food. For example, kale, spinach, watercress, basil, peas, lettuce, zucchini, broccoli, tomatoes, corn, Brussels sprouts, spring onions, egg yolk, pumpkin and leeks.</td>
</tr>
<tr>
<td>Omega-3 fatty acids and fish</td>
<td>Omega-3 fatty acids required in proportion to omega-6 fatty acids. Reduce omega-6 fatty acid consumption (vegetable oils and animal fats) as required and/or increase consumption of omega-3 fatty acid containing oily fish. For example, salmon, anchovy mackerel, tuna, sardines, and swordfish.</td>
</tr>
<tr>
<td>Fats</td>
<td>Avoid trans-fats. Regular use of olive oil has benefits.</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Low GI foods (slow-release carbohydrates) preferable to high GI foods (highly refined carbohydrates).</td>
</tr>
<tr>
<td>Micronutrients (vitamins and minerals)</td>
<td>Vitamins and minerals are found abundantly in fruits and vegetables. Consume fruits and vegetables to increase micronutrient intake for its antioxidant properties.</td>
</tr>
<tr>
<td>Red meat</td>
<td>Reduce fresh or processed red meat consumption.</td>
</tr>
<tr>
<td>Salami or continental sausage</td>
<td>High association with AMD risk. Limit to once a month.</td>
</tr>
<tr>
<td>Calcium</td>
<td>High calcium dietary intake preferable to low calcium dietary intake. Caution required with increasing dairy intake. Other sources of dietary calcium: kale, bok choy, collard green, broccoli, okra, sesame and chia seeds, fresh and canned fish, beans and soya bean products.</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Limit daily alcohol consumption to less than two standard drinks.</td>
</tr>
</tbody>
</table>

AMD, age-related macular degeneration; GI, glycaemic index; L/Z, lutein and zeaxanthin.
The Three Stages of Truth

All truth passes through three stages.

First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident.

*Arthur Schopenhauer, German philosopher (1788 – 1860)*
Thank you for your participation today

Dennis Ruskin  OD, FAAO

druskinod@gmail.com