The Impact of Genetics on AMD

Jeffry D. Gerson, O.D., F.A.A.O.

jgerson@Hotmail.com
Disclosure

I have been on advisory boards/a consultant to/received honoraria from/or been on speakers bureau list of the following:

- Allergan, Alcon, Arctic Dx, Bausch & Lomb, Carl Zeiss Meditec, Freedom Meditech, Optos, Optovue, Thrombogenix, VSP, ZeaVision

These affiliations will have no affect on the content of this lecture.
Can we sum it all up in 1 slide..

Offspring risk of advanced AMD

- Unaffected Mother
- Affected Father
- Unaffected Mother
- Unaffected Father

50% (Unaffected Mother X Affected Father)
12% (Unaffected Father X Affected Mother)

SURVEY SAYS??!
Genetics Trivia

• Who is this?
• More importantly...where did Watson get his PhD???
How do we find AMD?

• Must start with clinical exam
  
  – What exactly is the minimum findings for AMD?
What is “pre-AMD”

• Well defined “pre diabetes” that triggers interventions

• Do we have such a thing with AMD?
  – Should we?
  – Could we?
  – Why would we?
What’s up Doc?

• Most people think that __________ is the best food for their eyes and will help their vision.

• Carrots can be part of a healthy diet, and are high in beta carotene.

• Foods with L/Z likely better for health and vision
So What?? Why do we care??

QUALITY OF LIFE!!

THAT IS WHAT WE PRACTICE!!
A new opinion poll from the American Foundation for the Blind shows that 21 percent of Americans believe that losing their vision would have a more negative impact on their quality of life than many other health conditions.
What is AMD??

- AMD is a degenerative retinal disease that can cause central vision loss and blindness.
- The leading cause of severe vision loss in people over 50 years old in the western world... and is becoming more prevalent with aging of baby-boomers.
- The two forms of AMD:
  - Non-neovascular (Dry):
    - Affects 80-90% of patients
  - Neovascular (Wet):
    - Affects 10-20% of patients, responsible for 90% loss.
Age Related Macular Degeneration
Risk Factors

- Smoking
- Aging (33% over age 75)
- Family history (50% lifetime risk vs. 10-12% without)
- Hypertension / Cardiac Disease
- Race (Caucasian females)
- Obesity / high cholesterol
- Sun Exposure
Incidence of AMD is increasing

5 million new cases per year in Europe & US

Almost 30 million people in the US have some form of AMD

*More than 7 million have intermediate AMD

*1.75 million have advanced AMD with vision loss
AMD

• 80-90% of pts with AMD have Dry AMD
• Characterized by RPE disruption, RPE hyperplasia and drusen to varying degrees
• Typically bilateral and fairly symmetrical
• Variable degree of loss of central vision
AMD

• Wet AMD represents only 10-20% of those with AMD, yet accounts for 90% of patients who are legally blind from AMD

• Absolutely crucial to differentiate wet from dry!
Can’t “prevent” in everybody

• Some will develop wet AMD
• What next?
• How to monitor at home…

• PHP home
  – (Preferential Hyperacuuity Perimetry).
Artificial Distortion
Progressively make the elevation smaller

CNV Lesion

• When the elevation caused by CNV is larger than the artificial distortion, the patient will preferentially pick the spot of true distortion
I'll climb up this strand of DNA to see where life takes me.
Progression of AMD

When/where do we start to intervene?
Proactive vs Reactive approach

- Majority of articles and research regarding AMD pertains to Wet AMD
- Not enough attention paid to prevention and early detection
AMD Risk Factors

**Non – Modifiable**

- Age (chronological)
- Gender
- Hereditary: Genetics
  - Race / Pigmentation

3 gene groups involved w
- inflammation
- oxidation
- Mitochondria health

**Modifiable**

- Smoking
- CVDz
- ETOH
- Light exposure
- *Nutrition*
  - MPOD
Clinical Risk Factors: Per Blue Mountains Eye Study

• Large Drusen and Pigmentary change are most predictive for late AMD
• No large drusen or pigmenatry changes: <1% of advanced AMD in 5 yrs
• Large Drusen and pigmentary changes: >50% of advanced AMD
• Those in highest tertile of L/Z: approx 1mg/d had 65% reduced incident Neoasc. AMD
• You have to spend time talking!
• Before addressing modifyable risk factors, I try to discuss those that are not modifyable so that they understand
  — Genetic testing is an example
Proactive about risk factors: Smoking
SMOKING is 2\textsuperscript{nd} most IMPORTANT RISK FACTOR NEXT TO AGE

- Cigarette smoking increases risk of AMD 3X in men and women.
- Smokers develop AMD 6 to 10 years earlier than non-smokers.
- In MPS laser trials, risk for recurrent CNV was 50\% at 5 years but 85\% for current smokers!
- MPOD is lower in smokers.
Many people feel that / acknowledge UV is a risk factor....
Importance of “Protection”
Is UV the answer?

• Evidence pointing toward blue light damage and resultant oxidation as the “backbone” of oxidative stress and damage
• Multiple studies concur as to the damage
• Lenses available to block blue light (Not what you think…”Blue Blockers” infomercials)
What is More Harmful to the Eye, UV Light or Visible Light?

UV light causes:
• Cancers of ocular adnexa
• Pterygia
• Pinguecula
• Photokeratitis
• Cataract

In reality, rarely do any of these lead to blindness in the United States…

In fact, the cornea and lens block UV light, only visible light is incident on the retina.
MPOD and Blue Light damage

MPOD: Protecting the Eyes from Harmful Blue Light with Internal Sunglasses.
Zeaxanthin and Lutein increase Macular Pigment Optical Density.

VISION RISK from harmful blue light

VISION PROTECTION from harmful blue light

% Harmful Blue Light Reaching Photoreceptors

25% 18% 13% 9% 6% 3% 22% of population

100% 71% 50% 36% 31% 25% 18% 13% 9% 6% 3% 22% of population

MPOD score

300 - 400 UV RANGE
Protect Cornea/Lens with sun protection, sunglasses

400 - 520 BLUE LIGHT HAZARD
Protect Retina with Internal Sunglasses

Light Spectrum Wavelength

300
Blue Light SOURCES:
Computers
Sunlight
TVs
Lights
Cell Phones
Tablets

** Ciula, Ophthalmology 2001, 108: 730-737
Effect of Lutein + Zeaxanthin On risk of Advanced AMD

Adapted from Seddon JM et al. JAMA 1994; 272: 1413 -1420
MPOD

• Macular Pigment Optical Density
• The 2 macular pigments are from yellow and orange carotenoids (L&Z)
  – Unable to be synthesized by humans
  – Found in highest concentration in fovea
  – Accumulation can protect RPE and photoreceptors
• Lower MPOD associated with lower carotenoid intake/serum levels, females, smoking, diabetes, increased BMI....AMD
• Measurable
• May even help with light sensitivity

Reference: Macular pigments, update and measurement. Malinovsky V, Geirhart D.
Techniques for Measuring Macular Pigment Optical Density (MPOD)

- **HFP- Heterochromatic flicker photometry** – (gold standard)
  - Macuscope®
  - QuantifEye®
  - Densitometer
- SLO- based methods - HRA
- Reflectometry
- Raman Spectroscopy – (absorbance re-emission)
- Fluorescence attenuation

*1 degree 460nm/540nm flickering stimulus centrally & 7 degrees eccentrically*
The Science....Plenty of it!!!
MPOD and genetics

- Genetics play a role in MPOD
- Lowest tertile of l/z intake w certain genetics have higher MPOD than some in highest tertile
- No apparent link between CFH or ARMS2 and MPOD: other SNiPs
- Twin studies show that possibly 27% of MPOD response to l/z is heritable
  - Response rate in general to l/z is variable: 50-95%
“Enhancing Vision”
(with the carotenoids Lutein & Zeaxanthin)*

- Falsini Study – 2003
- LAST – April 2004
- TOZAL – Feb 2007
- LUXEA – April 2006 & Feb 2007
- LUNA – April 2007
- LAST II – May 2007
- CARMIS – Feb 2008
- Lutein in normal subjects July 09 British J. Nut
- ZVF study: Richer Nov 2011

*AREDS II is not formally evaluating Macular Pigment
Is 20/20 good enough?

• No...that is quantity not quality
• Adequate MPOD can improve contrast sensitivity: especially in dark conditions
  light sensitivity
  visual acuity
  shape discrimination
Visual Performance

• High MPOD levels enhance
  – Visual acuity
  – Glare tolerance
  – Glare recovery
  – Contrast sensitivity
  – Chromatic aberration
  – Photophobia

CS, photophobia & glare may be altered by Carotenoids: VISUAL ENHANCEMENT BY FEEDING OUR RETINA

LAST & ZVF study (Dr. Richer)
A comparison to visual fields

• In glaucoma, we talk about pre-perimetric glaucoma
• Is there such thing in AMD?
  – Pre-OCT or Pre-fundus or Pre-FAF AMD
• If there is, what does that mean?
• How do we act?
Dark Adaptation Curves: *A measure of RPE health
## Staging Test

- Impairment increases with AMD severity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Rod Intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5.7 ± 1.9 minutes</td>
</tr>
<tr>
<td>Early AMD</td>
<td>12.9 ± 6.1 minutes</td>
</tr>
<tr>
<td>High-Risk AMD</td>
<td>16.6 ± 5.2 minutes</td>
</tr>
<tr>
<td>Late AMD</td>
<td>19.0 ± 4.5 minutes</td>
</tr>
</tbody>
</table>

- Odds of having High-Risk AMD increase 11.9% per minute ($p = 0.0015$)
thickened Bruch’s membrane & drusen → impaired metabolic transport

Diagnostic Sensitivity

Imaging and AMD

Fundus Autofluorescence

Allows us to visualize metabolic changes at the level of the photoreceptors/RPE complex not visualized with standard photography or angiography.
Imaging and AMD

Normal Fundus Autofluorescence
Start to think about this....
Imaging and AMD

HYPER Fundus Autofluorescence
Imaging and AMD

HYPO Fundus Autofluorescence
Courtesy of Heidelberg Engineering
What does drusen formation “look like”?
AREDS: Demographic Data

• Category 1
  – No or few drusen (<63 microns), no pigment abnormalities, neither eye wet
  – 0% risk of wet at 5 yrs
• Category 2
  – Intermediate Drusen (<125 microns), mild pigment abnormalities, neither eye wet
  – <2% risk of wet at 5 yrs

• ***Note: Central retinal vein is approximately 125 microns***
AREDS Demographics cont.

- **Category 3: Intermediate**
  - combo of Extensive Int. or any Large drusen, or GA
  - 18% risk of wet in 5 yrs

- **Category 4: Advanced/High Risk**
  - One eye with Wet or BCVA worse than 20/32 from Dry
  - >42% risk of wet in 5 yrs
Quick AREDS Review

• Vitamins work....you should use them with AMD (At least AREDS category 3 and 4)
• AREDS showed we can decrease progression rates by 25% with “appropriate” formulation
• 19% decreased rate of vision loss of 3 or more lines of acuity
AREDS did not answer all...

- Does primary prevention work?
- Does prevention in early stages of AMD work?
- Might we benefit from Lutein / Zeaxanthin?
- Might we benefit from Fish oil?
- Can we reduce zinc?
- Can we take out Beta Carotene?
We’ll get to AREDS2 in a few minutes, but first what about Wet AMD Tx???
Wet AMD...what happens
The Catt is out of the bag...

- CATT: Comparison of Lucentis monthly vs Lucentis PRN vs Avastin monthly vs Avastin PRN
- Bottom line: Monthly either slightly better than PRN either
- Lucentis essentially equal to Avastin in outcome measures
- Lucentis essentially equal to Avastin in Adverse events: both relatively low
- Avastin has significant economic benefits!

Cost implications

Avastin per year
- Cost per injection: $50
- Monthly/yr: $600
- PRN: $350
- 250,000 Americans:
  - Monthly/yr: $150,000,000
  - PRN/yr: $87,500,000

Lucentis per year
- Cost per injection: $2000
- Monthly/yr: $24,000
- PRN: $14,000
- 250,000 Americans:
  - Monthly/yr: $6,000,000
  - PRN/yr: $3,500,000
Sibling Rivalry Continues: CATT 2 yrs out 5/2012

6 GROUPS (n = 1,107)
Continue q1M Avastin vs q1M Lucentis
Continue Avastin PRN vs Lucentis PRN
Pts switched from avastin q1M to PRN vs switch from lucentis q1M to PRN

Avastin (bevacizumab) vs. Lucentis (ranibizumab) Monthly vs. PRN

Lucentis q1M had DRYER retinas
14% avastin PRN vs 45% lucentis q1M
CATT

- Side effects
  - 40% Avastin vs 32% Lucentis
- Non-central GA was noted more often in LUCENTIS q1M grp vs Avastin prn grp, which interfere with reading
  - 26% lucentis q1M
  - 12% avastin PRN
Genetics and GA

• Klein et al. Progression of GA and genetics in AMD. Aug 2010.

• Some high risk genetic sub-types were related to presence of GA

• With regard to GA growth, no relationship between GA progression and variants in the CFH, C2, C3, APOE, and TLR3 genes. Only the rs10490924 (A69S) variant in the LOC387715/ARMS2/HTRA1 locus showed association with GA progression
Great news for our patients and economy, but....

• Does CATT change the way we practice?
• Does it change our primary focus???

• Ideally, nobody would need Avastin or Lucentis!

Avastin, Eylea and Lucentis sound great, so where do we fit in ......
Genetics of CATT

• Hagstrom et al. 3/13 Ophthalmology

• Genotypic frequencies were compared with VA, change in VA, 15-letter or more increase, retinal thickness, change in foveal thickness, presence of fluid, presence of leakage on FA, change in lesion size, and number of injections administered.

• No differences found in any variable with either drug for any time frame monthly or prn
• The best way to achieve a good treatment outcome is not to need that treatment! It is the only way to achieve 100% efficacy!
What about long-term Lucentis f/u
Not such a rosy bottom line..
What is the newest approved Anti-VEGF for AMD?
How do you know if a drug works?

When Wall Street likes the company that makes it!!
Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration

Objective: Two similarly designed, phase-3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) of neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye; Regeneron, Tarrytown, NY, and Bayer Healthcare, Berlin, Germany) with monthly ranibizumab.

Design: Double-masked, multicenter, parallel-group, active-controlled, randomized trials.

Participants: Patients (n = 2419) with active, subfoveal, choroidal neovascularization (CNV) lesions or juxtapfoveal lesions with leakage affecting the fovea) secondary to AMD.

Intervention: Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Pq4).

Main Outcome Measures: The primary end point was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart). Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.

Results: All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary end point (the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1%, respectively, for VIEW 1, and 95.6%, 96.3%, and 95.6%, respectively, for VIEW 2, whereas monthly ranibizumab was 94.4% in both studies). In a prespecified integrated analysis of the 2 studies, all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA; all aflibercept regimens also produced similar improvements in anatomic measures. Ocular and systemic adverse events were similar across treatment groups.

Conclusions: Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. These studies demonstrate that aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. Ophthalmology 2012;119:2537-2548 © 2012 by the American Academy of Ophthalmology.

*Group members listed online in Appendix 1 (http://aaojournal.org).
Eylea

- Eylea given for Wet AMD .5mg monthly, 2mg monthly, 2mg q2mos vs Lucentis monthly in >2400
- Primary outcome measure of stable vision – 95% vs 96% vs 91% vs 95%
What will be the next frontier

• In Anti-Vegf it will be topical and oral treatments
  – Both are in trials and showing promise
• Longer acting or sustained release delivery methods
• Newer drug classes
  – Complement factor inhibitors
  – Your imagination may fill in the blank...
Which is better (AREDS) 1 or 2....

A quick video for a break in the action
Some comic relief (This won’t be on the evaluation questions at the end)
AREDS2 Inclusion Criteria

Bilateral Large Drusen or Late AMD in One Eye

Large Drusen  GA  NV AMD

This is a different population than AREDS!!
Primary Outcome Analysis

Progression to Advanced AMD (AAMD)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Favors Treatment</th>
<th>Favors Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutein/Zeaxanthin</td>
<td></td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>DHA/EPA</td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Lutein/Zeaxanthin+DHA/EPA</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>Placebo (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio (98.7%CI)
Important Notes

• **Highly nourished cohort**
  
  – Baseline serum levels for L/Z were significantly higher than those in NHANES
  
  – Intake range for AREDS2 was 0.043 – 39.8 mg L+Z per day
  
  – 3% of subjects admitted to taking Lutein/Zeaxanthin supplements on their own

Effect of Dietary Intake of L/Z**

Progression to Advanced AMD by Quintiles

<table>
<thead>
<tr>
<th>L/Z Dietary Intake Quintile</th>
<th>Hazard Ratio (95%CI)</th>
<th>Favors L/Z</th>
<th>Favors No L/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest 1</td>
<td>HR=0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest 5</td>
<td></td>
<td></td>
<td>p=0.01</td>
</tr>
</tbody>
</table>

Quintile amounts: 0.7/1.1/1.6/2.2/3.9mg

AREDS 2 Research Group. (2013) JAMA
Lutein/Zeaxanthin
Conclusions

• The main effect of lutein/zeaxanthin demonstrated **10%** reduction of AAMD

• **26%** reduction in the risk of progression to AAMD for L/Z **beyond the effects of AREDS supplement** in persons with the lowest dietary intake of L/Z
  • Additionally, there was a significant reduction in risk of cataract surgery, any cataract or any severe cataract with L/Z supplementation in this lowest quintile

• **18%** reduction in the risk of progression to AAMD, particularly neovascular AMD, of L/Z in head-to-head comparison with beta-carotene

Conclusions

• How would you summarize the study?

• What about fish oil??
Fish Oil and Genetics


High risk CFH more likely to develop late AMD if <1/wk serving of fish
  - Similar but different affects seen for early AMD, especially if >70yo but not if <70yo
  - No synergy seen between CFH risk and C-reactive protein counts

Further: “We speculate that mechanisms for the development of early AMD (primary prevention) may not be the same as those involved in the progression from early to late AMD (secondary prevention).”
NEI Recommendation: Too simply put!

**ARED52 Formulation**

- Vitamin C (500 mg)
- Vitamin E (400 IU)
- **Beta Carotene** (15 mg)
- **Lutein** (10 mg)/Zeaxanthin (2 mg)
- Zinc (80 mg zinc oxide)
- Copper (2 mg cupric oxide)
- Omega 3 fatty acids (DHA/EPA)
Bridging the Gap

• Increase patient awareness
  – L/Z and appropriate antioxidants are essential nutrients needed to protect the eye
  – Getting the proven beneficial amounts daily through diet alone can be difficult
  – Most people only get 10-20% of the L/Z needed each day from dietary sources
  – Eye vitamins are an easy way to get the recommended amounts of L/Z …
  – This is where AREDS/AREDS2 and others comes in……..
So...Best Case Scenario

- You have a patient with Category 3 or 4 dry AMD
- They have low L/Z intake
- You use the “Proposed AREDS2” formula
- How much do you “help” them?
  - 25% from AREDS1 and additional 26% (not 25+26 but instead 25 + 26% of 25 = approx 33%)
  - So, about 33% prevention
That means 67% still convert!

• SO, the most practical advice for OD’s:
  • PREVENT AMD!
  • PROMOTE VISUAL PERFORMANCE
  • INDIVIDUALIZED CARE
  • EDUCATE PATIENTS
Pertinence...

- To what percentage of YOUR AMD patients does AREDS2 apply???
  - A) Some
  - B) Most
  - C) ALL
  - D) VERY FEW *****
How big should a study be?

$n$ of 1

Each person is an individual study of outcomes
Genetics Primer....It goes beyond this
Genetics 101
Introduction

• Information that will guide the development of an organism is contained in that organism’s DNA. Every species has a characteristic number of DNA molecules called chromosomes.
Genetic Concepts

• **Heredity** describes how some traits are passed from parents to their children.

• The traits are expressed by **genes**, which are small sections of DNA that are coded for specific traits.

• Genes are found on **chromosomes**.

• Humans have two sets of **23** chromosomes—one set from each parent.
Introduction

An individual receives one complete set of chromosomes from each parent, resulting in two complete sets. This is the **diploid** condition (2n).
Chromosomes occur in pairs called **homologous chromosomes**.

One from each parent.
Genes are the functional unit of heredity.

- Chromosomes are made up of genes that code for traits.
- A gene is found at a specific location or locus on a chromosome.
Heredity – Passing on Traits

- An individual can pass on genetic information to its offspring. In order to avoid doubling the number of chromosomes in each generation, cells must be created that carry only one set of chromosomes (haploid or 1n).

- An individual can pass along either of the two alleles it carries for a trait, but not both.

- A Pp individual can pass on either P or p.

- These haploid cells (eggs or sperm) are formed during meiosis.
Definitions

**Genotype**: the identify of a base at a single site (ie, G, A, T or C).

**Allele**: The particular form of a gene, sequence or even a base.

**Diplotype**: The form of a gene, sequence or base on the maternal and paternal DNA strands.

**Haplotype**: The form of a gene, sequence of base on a single strand of DNA.
Genetic Information

- **Gene** - basic unit of genetic information. Genes determine the inherited characters.

- **Genome** - the collection of genetic information.

- **Chromosomes** - storage units of genes.

- **DNA** - is a nucleic acid that contains the genetic instructions specifying the biological development of all cellular forms of life.
Word Match Activity

- base pair
- cell
- chromosome
- DNA (Deoxyribonucleic Acid)
- double helix*
- genes
- nucleus

Illustration Source: Talking Glossary of Genetic Terms
http://www.genome.gov/glossary.cfm?key=chromosome
"We think it has something to do with your genome."
Chromosome Logical Structure

- **Locus** - location of a *gene/marker* on the chromosome.

- **Allele** - one variant form of a *gene/marker* at a particular *locus*.
Human Genome

Most human cells contain 46 chromosomes:

- **2 sex chromosomes (X,Y):**
  - XY – in males.
  - XX – in females.

- **22 pairs of chromosomes named** autosomes.
Genotypes ↔ Phenotypes

- At each locus (except for sex chromosomes) there are 2 genes. These constitute the individual’s *genotype* at the locus.

- The expression of a genotype is termed a *phenotype*. For example, hair color, weight, or the presence or absence of a disease.
Genotypes ↔ Phenotypes (example)

- $E^b$ - dominant allele.
- $E^w$ - recessive allele.
When studying rare disorders, 6 general patterns of inheritance are observed:

- Autosomal recessive
- Autosomal dominant
- X-linked recessive
- X-linked dominant
- Codominant
- Mitochondrial
Autosomal recessive

• The disease appears in male and female children of unaffected parents.
• e.g., cystic fibrosis
Autosomal dominant

- Affected males and females appear in each generation of the pedigree.
- Affected mothers and fathers transmit the phenotype to both sons and daughters.
- e.g., Huntington disease.
X-linked recessive

- Many more males than females show the disorder.
- All the daughters of an affected male are "carriers".
- None of the sons of an affected male show the disorder or are carriers.
- e.g., hemophilia
Medical Genetics (cont.)

X-linked dominant

• Affected males pass the disorder to all daughters but to none of their sons.

• Affected heterozygous females married to unaffected males pass the condition to half their sons and daughters

• e.g. fragile X syndrome
Codominant inheritance

- Two different versions (alleles) of a gene can be expressed, and each version makes a slightly different protein.
- Both alleles influence the genetic trait or determine the characteristics of the genetic condition.
- E.g. ABO locus
Mitochondrial inheritance

- This type of inheritance applies to genes in mitochondrial DNA
- Mitochondrial disorders can appear in every generation of a family and can affect both males and females, but fathers do not pass mitochondrial traits to their children.
- E.g. Leber's hereditary optic neuropathy (LHON)
Computer code digitizes the world
DNA is the physical basis of inheritance. It has 4 variables.
DNA building blocks
DNA duplicates by “splitting”

Mutation: 1 / 250,000,000
Elaborate proof reading and repair mechanisms exist. If too much DNA mismatch occurs the cell will auto destruct.
Single Nucleotide Polymorphisms

A SNiP is a known mutation
What is a “SNiP”
The Evolution of Single Nucleotide Polymorphisms

100 Generations

Gene Pool

“Adam and Eve”

2010
DNA variation determines who we are

There are about 10 million variations
Although many SNPs do not produce physical changes in people, scientists believe that other SNPs may predispose people to disease and even influence their response to drug regimens.

It will only be a matter of time before physicians can screen patients for susceptibility to a disease by analyzing their DNA for specific SNP profiles.

NCBI dbSNP

Using SNPs to study the genetics of drug response will help in the creation of "personalized" medicine.
"Your DNA test shows you're predisposed to sue doctors."
Better living through science

Multi genetic testing
Risk stratification

1° Prevention
Natural environment △ Drug prophylaxis Family planning

2° Prevention
Customized early detection
Customized treatment
Early Detection and Early treatment = Improved Outcomes

Early Detection

- 1052 participants at 22 centers
- Examinations at 6 mo. Then annually for 5 – 6 yrs.

“monitoring of a population with bilateral large drusen, using annual fluorescein angiography, allowed neovascular lesions to be detected early, when most lesions were occult, small and outside the fovea.”

Early Treatment

Lucentis (ranibizumab):

“a sub group analysis of the MARINA trial showed that treatment benefit was greater with higher baseline visual acuity and smaller lesions”
Mainstreaming of genetics

June 2000: Code cracked: Dr. Francis Collins and Dr. Craig Venter
AMA statement to FDA in 2011

• “We urge the Panel...that genetic testing, except under the most limited circumstances, should be carried out under the personal supervision of a qualified health professional”

• Counter point: Hugh Rienhoff, MD, entrepreneur and founder of mydaughtersdna.org
  “Doctors are not going to drive genetics into clinical practice. It’s going to be consumers....Cardiologists do not know dog shit about genetics”
AAO (The other one..)

- In general, opposed to genetic testing for complex disease processes without definitive actionable results. Opposed to any direct to consumer models, especially with physician interaction and explanation.
A Nice summary

• The NEI point of view from Dr. Emily Chew
Show me the data
What if you knew.... Genetics can help us see into the future!

"You say you're having trouble seeing into the future?"
Angelina Jolie obviously understands the importance of genetic testing…

But, does the average patient?
Is AMD in your DNA?
AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk

In other words: AMD is >70% due to genetics!

J.M. Seddon, B Rosner et al; IOVS May 2009
Not all genetics confers increased risk

• Some genes are actually protective
• Some genes show a higher likelihood of only mild AMD and not progression to GA or CNVM\(^1\)
• There may be some association of other systemic factors/genetics and AMD
  – Cholesterol and LIPC gene, also tendency for obesity and overall poor health and vasculopathy

Genetic of AMD...co-dominant

- Not as simple as a punnett square
- "allele dosage" effect: That is, two risk alleles are twice as bad as one risk allele, which is worse than no risk alleles.
- Moreover, the genes all seem to work independently of one another. So if one ARMS2 risk allele increased a person's risk by 3, two would increase the risk by 6.
- The technical description of this is "co dominant". The classic description of dominant genetics says that one risk allele is just bad as having 2. Recessive says that one risk allele is just as good as having none. If the disease displays co dominant genetics then there is a "gene dosage" effect.
## AMD Progression – Four Biologic Pathways

<table>
<thead>
<tr>
<th>Complement Genes</th>
<th>Cholesterol Genes</th>
<th>Energy Mediators</th>
<th>Matrix Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>LIPC</td>
<td>ARMS2</td>
<td>TIMP 3</td>
</tr>
<tr>
<td>Component 3</td>
<td>CEPT</td>
<td>ND2</td>
<td></td>
</tr>
<tr>
<td>Component 2</td>
<td>LPL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor H</td>
<td>ABCA1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor I</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Genetic Risk for Progression of AMD (vision loss)

36 different combinations studied w highest risk representing 400x that of lowest

J Maller / J Seddon: Nature Genetics;Vol 38, No 9, Sept 2006
Main players

- **CFH (Complement Factor H)**
  - The complement cascade is responsible for primitive inflammation
- **ARMS2 (Age Related Maculopathy Susceptability 2)**
  - Plays a role in the excretion of oxygen free radicals
- **ND2**
  - A gene that controls mitochondrial oxidative stress through their role in oxidative phosphorylation
- **C3 (Complement Cascade Component 3)**
  - Mediates inflammation and cell health: Increases sensitivity of CFH risk
- Additionally, Cholesterol metabolism plays a role, and there are 4 gene variants
- **TIMP3**: Tissue Inhibitor of Metalproteinase
Great Science - Key AMD genes

Not as simple as “yes” or “no”, but degrees of risk/polyorphism

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>rs3766405</td>
<td>TT</td>
</tr>
<tr>
<td>CFH</td>
<td>rs412852</td>
<td>TT</td>
</tr>
<tr>
<td>CFH</td>
<td>rs1048663</td>
<td>GG</td>
</tr>
<tr>
<td>CFI</td>
<td>rs10033900</td>
<td>CC</td>
</tr>
<tr>
<td>C3</td>
<td>rs2230199</td>
<td>CC</td>
</tr>
<tr>
<td>C2</td>
<td>rs9332739</td>
<td>CC</td>
</tr>
<tr>
<td>CFB</td>
<td>rs541862</td>
<td>AA</td>
</tr>
<tr>
<td>LIPC</td>
<td>rs10468017</td>
<td>CC</td>
</tr>
<tr>
<td>ABCA1</td>
<td>rs1883025</td>
<td>TT</td>
</tr>
<tr>
<td>CETP</td>
<td>rs3764261</td>
<td>CC</td>
</tr>
<tr>
<td>Col8A1</td>
<td>rs13095226</td>
<td>TT</td>
</tr>
<tr>
<td>APOE4</td>
<td>rs429358/rs7412</td>
<td>TT/TT</td>
</tr>
<tr>
<td>TIMP3</td>
<td>rs9621532</td>
<td>CC</td>
</tr>
<tr>
<td>ARMS2*</td>
<td>372_815del443ins54</td>
<td>NN</td>
</tr>
</tbody>
</table>
Why bother with genetics

• May tell who is more or less likely to respond to vitamin therapy\(^1\)

• Trials to see if genetics “controls” response to Anti-VEGF medications

• This all helps make the case for genetic testing for more individualized medicine\(^2\)

2. Personalized medicine in AMD. Souied, E and Leveziel N. AJO 9/12.
How it can “flow”
Macula Risk Score

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

Macula Risk 3, 4 & 5 = 20% of the Caucasian population
**Highest Risk** (Include other factors)

**Patient profile:**
- Age greater than 65;
- Present with Drusen;
- Macula Risk Score 3, 4 or 5.

<table>
<thead>
<tr>
<th>Macula Risk Score</th>
<th>Risk of GA or CNV (%)</th>
<th>Prevalence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Low)</td>
<td>0-5</td>
<td>49.6</td>
</tr>
<tr>
<td>2 (Average)</td>
<td>6-15</td>
<td>30.6</td>
</tr>
<tr>
<td>3 (Increased)</td>
<td>16-40</td>
<td>16.6</td>
</tr>
<tr>
<td>4 (High)</td>
<td>40-55</td>
<td>2.2</td>
</tr>
<tr>
<td>5 (Very High)</td>
<td>55 – 96.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Should be monitored more than once / year
### Macula Risk NXG Lab Report

#### Risk of Conversion to GA or CNV (%) based on genetic and non genetic features

<table>
<thead>
<tr>
<th>Category</th>
<th>2 Years</th>
<th>5 Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient, Sample</td>
<td>16</td>
<td>39</td>
<td>67</td>
</tr>
<tr>
<td>10 Year Macula Risk Score</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
</tbody>
</table>

#### 2-10 Year Conversion Risk

- **Calculated Risk %** vs Age

#### 10 Year Macula Risk (MR) Score

- **Calculated Risk %** vs Macula Risk Score

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Result</th>
<th>Gene</th>
<th>SNP</th>
<th>Result</th>
<th>Gene</th>
<th>SNP</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>rs2765405</td>
<td>CC</td>
<td>C2</td>
<td>rs932739</td>
<td>CC</td>
<td>GO</td>
<td>COL4A1</td>
<td>TT</td>
</tr>
<tr>
<td>CFH</td>
<td>rs142952</td>
<td>CC</td>
<td>CFB</td>
<td>rs641862</td>
<td>AA</td>
<td>APOE</td>
<td>rs42938</td>
<td>--</td>
</tr>
<tr>
<td>CFH</td>
<td>rs1206603</td>
<td>CC</td>
<td>LPC</td>
<td>rs1468017</td>
<td>CT</td>
<td>APOE</td>
<td>rs42938</td>
<td>--</td>
</tr>
<tr>
<td>CFH</td>
<td>rs10303190</td>
<td>CC</td>
<td>ABOA1</td>
<td>rs183925</td>
<td>CC</td>
<td>TIMP3</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>rs2235199</td>
<td>CC</td>
<td>CETP</td>
<td>rs3764261</td>
<td>AC</td>
<td>ARMS2</td>
<td>372</td>
<td>NN</td>
</tr>
</tbody>
</table>

**Genetic Risk Subscore: 68% (range: 0 – 100, average = 50)**

---

**AMD Status, BMI and Smoking**

- 2, 5 and 10 Year Risk of Progression

---

**Patient Report**

- **Accession Number**: AMLNXG-xxxxx
- **Patient Name**: Patient, Sample

---

**Macula Risk Score**

- **Receiving Facilities**: Receiving Physician's

---

**Genetic Risk Subscore**
# Primary Eye Care Protocol

## Macula Risk® Advisory Panel® Recommendations

**Risk Stratification by Macula Risk (MR) Score and Disease Stage**

<table>
<thead>
<tr>
<th>MACULA RISK SCORE</th>
<th>AMD DISEASE STAGE</th>
<th>EXAM FREQUENCY (INTERVALS IN MONTHS)</th>
<th>FUNDUS PHOTOGRAPHY (IF AVAILABLE)</th>
<th>OCT</th>
<th>NUTRITIONAL SUPPLEMENTS</th>
<th>AMSLER GRID</th>
<th>REFERRAL TO RETINA SPECIALIST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MR 1-2</strong></td>
<td>Early AMD</td>
<td>12</td>
<td>1/YR</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intermediate AMD</td>
<td>6-12</td>
<td>1/YR</td>
<td>1-2/YR</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Advanced Dry AMD</td>
<td>3-6</td>
<td>1-3/YR</td>
<td>2-4/YR</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>CNV Suspected/Confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>MR 3</strong></td>
<td>Early AMD</td>
<td>6</td>
<td>1/YR</td>
<td>1-2/YR</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intermediate AMD</td>
<td>6</td>
<td>1/YR</td>
<td>2-3/YR</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Advanced Dry AMD</td>
<td>3-4</td>
<td>1-3/YR</td>
<td>3-4/YR</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>CNV Suspected/Confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>MR 4</strong></td>
<td>Early AMD</td>
<td>4-6</td>
<td>1/YR</td>
<td>2-3/YR</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intermediate AMD</td>
<td>4</td>
<td>1-2/YR</td>
<td>3-4/YR</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>Advanced Dry AMD</td>
<td>3-4</td>
<td>2-3/YR</td>
<td>3-4/YR</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>CNV Suspected/Confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>MR 5</strong></td>
<td>Early AMD</td>
<td>4-6</td>
<td>1/YR</td>
<td>2-3/YR</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intermediate AMD</td>
<td>4</td>
<td>1-2/YR</td>
<td>3-4/YR</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>Advanced Dry AMD</td>
<td>3-4</td>
<td>2-3/YR</td>
<td>3-4/YR</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>CNV Suspected/Confirmed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

Other tests

- RetnaGene by Sequenom
  - Also cheek swab done in office
  - 12 SNiP’s along with age, smoking and phenotype

Contribution of Risk Factors to Risk of CNV in AREDS Subjects
Baseline Disease, Genetics, Age, and Smoking

Reported risk scores for developing CNV are based on four risk factors:

1. Phenotype: Baseline disease stage defined by the AREDS simplified severity scale grade (as defined in the Age-Related Eye Disease Study)
2. Genotype: The genetic profile of 12 disease-associated single nucleotide polymorphisms (SNPs)
3. Age
4. Environment: Smoking status
23 and me

• 23andme
  – Direct to consumer
  – No longer health related: ancestry related
    • Where you are from, who are relatives and how neanderthal...

**Not all tests will be the same due to patents and other proprietary markers/information (pending Supreme Court decision)**
By the way...

- How much does the test cost and who pays (Based on Macula Risk by ArcticDx)
  - Manufacturer accepts insurance/Medicare assignment without balance bill and without co-pay due to lab-test
  - If cash pay, then charge is aprox $450
  - Insurance covers any “brand” as long as Dx of drusen or dry AMD (test is validated on this population)
    - Is it valid on “normals”? 
So, now that we discussed genetics....

• Is it a worthwhile thing to test?

• Does it have the potential to change your treatment and/or follow-up schedule?

Anybody in the room with Drusen? Or a Family h/o AMD?? DO YOU WANT TO KNOW???
DR. GRAY SUDDENLY ABANDONS HIS DNA TESTING TO FOCUS ON JEAN-SPlicing.
Genetics of AMD and supplementation

CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration

Carl C. Awh, MD\textsuperscript{1}, Anne-Marie Lane, MPH\textsuperscript{2}, Steven Hawken, MSc\textsuperscript{3}, Brent Zanke, MD, PhD\textsuperscript{4,5}, \textsuperscript{1}\textsuperscript{2}\textsuperscript{3}\textsuperscript{4}\textsuperscript{5}\textsuperscript{6}, Ivana K. Kim, MD\textsuperscript{2}
First do no harm....

- Zinc can cause harm/prevent benefit to some....potentially determined by genetics
  - Although for approx 12% Zinc alone was best, approx 64% should NOT get zinc!!!!!! (about 29% do as well with NOTHING as with anything)

Individualize care based on genotype (not just phenotype)

- The dawn of pharmacogenetics in eyecare!
Implication of Study **

• CFH polymorphisms do NOT benefit from Zinc, and in fact, may be harmful
• ARMS2 polymorphisms do NOT benefit from antioxidants, and may be harmed with antioxidants
• No mention of L/Z: neither positive or negative
What???
n=1
Vs
n=MANY
Dawn of Pharmacogenetics

- **Pharmacogenomics** is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict response to treatment.

**Bottom line:** Genetics determines response to drugs!

- Is there a difference between pharmacogenomics and pharmacogenetics?
- **Pharmacogenetics** refers to the study of inherited differences (variation) in drug metabolism and response.
Examples of pharmacogenomics

• Plavix: over $9Billion a year
  – Genetics can predict ability of body to metabolize and use drug

• Warfarin: over 20 Million Rx’s per year
  – Genetics can predict dosage needed to prevent overdose related bleeding

• Statins: Most commonly Rx’d drug class in world
  – Genetics can predict muscle inflammation: some people are at 20x risk
Pharmacogenetics cont..

- Flucloxacillin (Floxapen) can cause liver toxicity
  - Gene variant carries 80x risk of liver injury
- Cox-2 inhibitors: risk of liver toxicity
  - Genetic variant has 5x risk
- BRAF mutation-directed drugs
  - In appropriate pts, over 80% have success for treatment of malignant melanoma...those without appropriate genes, get worse!
Epigenetics

• We will not discuss in depth today
• Definition: Heritability not related to DNA sequence
• This is why “identical” twins are different!
Example:

What would you recommend for this patient?

Not so fast, don’t you want to know genetics?
How do you calculate vitamin risk?
So, for this patient

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>rs3766405</td>
<td>CC</td>
</tr>
<tr>
<td>CFH</td>
<td>rs412852</td>
<td>CC</td>
</tr>
<tr>
<td>ARMS2</td>
<td>372_815del443ins54</td>
<td>Wildtype (NN)</td>
</tr>
</tbody>
</table>

Vitamin Recommendation: Antioxidants without Zinc
But could have been

- Have to use both phenotype and genotype in judgement of appropriate treatments

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>rs3766405</td>
<td>CC</td>
</tr>
<tr>
<td>CFH</td>
<td>rs412852</td>
<td>CC</td>
</tr>
<tr>
<td>ARMS2</td>
<td>372_815del443insS4</td>
<td>Heterozygous (ND)</td>
</tr>
</tbody>
</table>

**Vitamin Recommendation:**  Antioxidants without Zinc

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>rs3766405</td>
<td>CC</td>
</tr>
<tr>
<td>CFH</td>
<td>rs412852</td>
<td>CT</td>
</tr>
<tr>
<td>ARMS2</td>
<td>372_815del443insS4</td>
<td>Heterozygous (ND)</td>
</tr>
</tbody>
</table>

**Vitamin Recommendation:**  Antioxidants and Zinc

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>rs3766405</td>
<td>CC</td>
</tr>
<tr>
<td>CFH</td>
<td>rs412852</td>
<td>CT</td>
</tr>
<tr>
<td>ARMS2</td>
<td>372_815del443insS4</td>
<td>Indel (DD)</td>
</tr>
</tbody>
</table>

**Vitamin Recommendation:**  Zinc alone

Individualized analysis and treatment is what each patient deserves.
Does this study apply to you?

- ABSOLUTELY....Genetics Matters!!
- Analysis of BMES shows association of genetics and response to nutrition\(^1\)
  - Those with highest risk alleles
    - responded most favorably to L/Z in preventing incident AMD by >20%
    - And weekly fish consumption reduced late AMD 40%
  - Genetic factors (CFH and ARMS2) help predict GA\(^2\)

2. Joachim et al. GA: observations from population based. Ophth 10/13
Awh was neither the first or only..

CFH and LOC387715/ARMS2 Genotypes and Treatment with Antioxidants and Zinc for Age-Related Macular Degeneration

Michael L. Klein, MD,1 Peter J. Francis, MD, PhD,1 Bernard Rosner, PhD,2 Robyn Reynolds, MPH,3 Sara C. Hamon, PhD,4 Dennis W. Schultz, PhD,1 Jurg Ott, PhD,4,5 Johanna M. Seddon, MD, ScM3

Objective: To determine if CFH and LOC387715/ARMS2 genotypes influence treatment response to AREDS-type nutritional supplementation with antioxidants and zinc.

Design: Retrospective analysis of participants in a randomized, controlled clinical trial, the Age-Related Eye Disease Study (AREDS).

Participants and/or Controls: Eight hundred seventy-six AREDS study participants who were considered at high risk for developing advanced age-related macular degeneration (AMD).

Methods: Using DNA extracted from venous blood of 876 white participants in AREDS categories 3 and 4, that is, those considered to be at high risk for progression to advanced AMD, the authors genotyped for the single nucleotide polymorphisms in the CFH (Y402H, rs1061170) and LOC387715/ARMS2 (A69S, rs10490924) genes. The authors performed adjusted unconditional logistic regression analysis and assessed interactions of these genotypes to determine the relationship between CFH and LOC387715/ARMS2 genotype and treatment with antioxidants plus zinc.

Main Outcome Measures: Interaction between genetic variants and treatment response as determined by progression from high-risk to advanced AMD.

Results: Progression occurred in 264 of 876 patients from AREDS category 3 (intermediate AMD) to category 4 or 5 (unilateral or bilateral advanced AMD, respectively), or from category 4 to category 5. A treatment interaction was observed between the CFH Y402H genotype and supplementation with antioxidants plus zinc (CC; \(P = 0.03\)). An interaction (\(P = 0.004\)) was observed in the AREDS treatment groups taking zinc when compared with the groups taking no zinc, but not in groups taking antioxidants compared with those taking no antioxidants (\(P = 0.59\)). There were no significant treatment interactions observed with LOC387715/ARMS2.

Conclusions: The findings of this study indicate that an individual’s response to AREDS supplements may be related to CFH genotype. This could have clinical relevance by predicting treatment outcome and potentially preventing unwanted side effects in those who may not benefit. Corroboration of these analyses is needed before considering modification of current management. This is among the first pharmacogenetic studies to suggest interaction between genotype and treatment. Ophthalmology 2008;115:1019–1025 © 2008 by the American Academy of Ophthalmology.
Bottom line

- Klein et al. Ophth. 6/08. Genotypes and Tx for AMD

Conclusions: The findings of this study indicate that an individual's response to AREDS supplements may be related to CFH genotype. This could have clinical relevance by predicting treatment outcome and potentially preventing unwanted side effects in those who may not benefit. Corroboration of these analyses is needed before considering modification of current management. This is among the first pharmacogenetic studies to suggest an interaction between genotype and treatment. Ophthalmology 2008;115:1019–1025 © 2008 by the American Academy of Ophthalmology.
In fact...

Editorial

Progress Toward Personalized Medicine for Age-related Macular Degeneration
Sayoko E. Moroi, MD, PhD - Ann Arbor, Michigan
John R. Heckenlively, MD - Ann Arbor, Michigan
Each of your patients is an individual with their own potential needs

“This is the beginning of the end of worshiping at the altar of the large randomized placebo-controlled clinical trial. It introduces the era of personalized medicine based on, among other findings, genetic profile.”

Leo Semes, O.D., F.A.A.O.
Did my genetic tests come back?

Yeah, sit down. Is it bad news? What are my risk factors?

We can't be sure about this, but we've analyzed genes on several of your chromosomes, and it's hard to avoid the conclusion:

At some point, your parents had sex.

Oh god! Stay calm! It's possible. It was just once!

I... I need to be alone.
Genetics of supplements

- Wang et al. Ophthalmol 3/14: Effect of genetics on Antiox
- Those with highest genetic risk showed significant decrease (20%) in incident AMD
- Fish oil in same group showed 40% decreased late AMD
- No affect with Beta Carotene or Vit C
- Previous studies have shown less late AMD with L/Z
  - Ma et al. BJ Nut. 2012
This is why you MUST “PRESCRIBE” a specific supplement!!
Which supplement

• Will each patient benefit the same from a specific supplement?
• Is there any 1 answer, or easy cook-book approach?
• Can 1 supplement fit all?
My Challenge to YOU!!

- Don’t “Blindly” recommend supplements to your patients
- Treat each patient as you would yourself or your family!
  - Individualized medicine practiced to the fullest extent possible!

**DIVERSIFY YOUR PORTFOLIO!**

- Tests you use to make a decision, treatment options and f/u
Questions?
Thank You!

Jeffry D. Gerson, O.D., F.A.A.O.
jgerson@Hotmail.com