The Impact of Genetics on AMD
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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

Offspring risk of AMD: 50%
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 ________ 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!!
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% of severe vision 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 Hyperacuity Perimetry)
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.

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 pigmentary 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 2nd most IMPORTANT RISK FACTOR NEXT TO AGE

Beaver Blue N Rotterdam

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” from infomercials)

What is More Harmful to the Eye, UV Light or Visible Light?

UV light causes:
- Cancer 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.
Zeissenthin and Lutien increase Macular Pigment Optical Density.
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

Color Photomicrographs – courtesy of Max Snodderly, PhD
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)
**AMD Pathogenesis**

- Thickened Bruch's membrane & drusen
- Impaired metabolic transport


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**Diagnostic Sensitivity**

- Dark Adaptation
- Contrast Sensitivity
- Photopic Visual Field
- Scotopic Visual Field
- Visual Acuity

*Owsley et al. (2001) Ophthalmology 108:1196*

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**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…. 
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: $24000
- PRN: $14000
- 250,000 Americans:
  - Monthly/yr: 6,000,000,000
  - PRN/yr: 3,500,000,000

Sibling Rivalry Continues: CATT 2 yrs out 5/2012

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

<table>
<thead>
<tr>
<th>Avastin (monthly) vs. Lucentis (monthly) Monthly vs. PRN</th>
<th>Lucentis q1M had DRYER retinas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Monthly</td>
<td>Bevacizumab Monthly</td>
</tr>
<tr>
<td><strong>14% avastin PRN</strong> vs <strong>45% lucentis q1M</strong></td>
<td><strong>6.8</strong></td>
</tr>
<tr>
<td><strong>5.0</strong></td>
<td><strong>6.7</strong></td>
</tr>
</tbody>
</table>
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

- 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!!
VIEW1 and VIEW2: approval of 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>Hazard Ratio (98.7%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutein/Zeaxanthin</td>
<td>0.8</td>
<td>0.12</td>
</tr>
<tr>
<td>DHA/EPA</td>
<td>0.7</td>
<td>0.70</td>
</tr>
<tr>
<td>Lutein/Zeaxanthin+DHA/EPA</td>
<td>1.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Placebo (reference)</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

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>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>HR=0.74 p=0.01</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td></td>
</tr>
</tbody>
</table>

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

References:
Lutein/Zeaxanthin

Conclusions

• The main effect of lutein/zeaxanthin demonstrated 10% reduction of AAMD
• 30% 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

• Wang et al. Fish oil and CFH in AMD. AJ Epidemiol. 3/2009.
  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!

**AREDS2 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 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
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

- 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.

Illustration Source: Talking Glossary of Genetic Terms
http://www.genome.gov/glossary.cfm?key=chromosome

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=genes

"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.

Locus 1
Possible Alleles: A₁, A₂

Locus 2
Possible Alleles: B₁, B₂, B₃

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.
Medical Genetics

When studying rare disorders, 6 general patterns of inheritance are observed:

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

Medical Genetics (cont.)

Autosomal recessive

- The disease appears in male and female children of unaffected parents.
- e.g., cystic fibrosis
Medical Genetics (cont.)

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.

Medical Genetics (cont.)

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
Medical Genetics (cont.)

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

Medical Genetics (cont.)

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 SNP is a known mutation.

**What is a “SNiP”**
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.

Using SNPs to study the genetics of drug response will help in the creation of "personalized" medicine.
Better living through science

- Multi genetic testing
- Risk stratification
- Natural environment
- Drug prophylaxis
- Family planning
- 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):
- 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?

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
• 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.
• More over, 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.

<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 &amp; Component 3</td>
<td>LIPC &amp; CEPT</td>
<td>ARMS2 &amp; ND2</td>
<td>TIMP 3</td>
</tr>
<tr>
<td>Component 2 &amp; Factor H</td>
<td>LPL &amp; ABCA1</td>
<td>Factor B &amp; Factor I</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


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/polymorphism

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
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<td>YC</td>
<td>GC</td>
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<td>NA</td>
<td>NB</td>
<td>BB</td>
</tr>
</tbody>
</table>
Why bother with genetics

- May tell who is more or less likely to respond to vitamin therapy
- Trials to see if genetics “controls” response to Anti-VEGF medications
- This all helps make the case for genetic testing for more individualized medicine


How it can “flow”

Macula Risk Score

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>
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</tbody>
</table>

Macula Risk Score

Macular Risk Score

2-5 and 10-year Risk of Progression

Primary Eye Care Protocol

Macula Risk Advisory Panel Recommendations
Risk Stratification by Macula Risk (MR) Score and Disease Stage

Other tests

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

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

Bottom line: Genetics determines response to drugs!

Examples of pharmacogenomics

- Plavix: over $9Billion a year
  - Genetics can predict ability of body to metabolize and use drug
- Warfarin: over 20Million 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..

- Flucloraxillin (Floxa) 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

But could have been
• Have to use both phenotype and genotype in judgement of appropriate treatments

Does this study apply to you?
• ABSOLUTELY....Genetics Matters!!
• Analysis of BMES shows association of genetics and response to nutrition
  – 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. 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

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

**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 Aritis supplements may depend on **CFH** genotype. This could have clinical relevance by predicting treatment outcome and potentially forestalling adverse 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.

There is good biological plausibility to support a possible role for **CFH** in determining response to treatment with antioxidants and zinc. The gene encodes a protein involved in the complement pathway. An argument may be made for genetic screening of those individuals at high risk for developing advanced AMD to identify those likely to achieve the greatest benefit and for increasing motivation to take the supplements. Those less...
Personalized Medicine

- 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.

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
- Prev. studies have shown less late AMD w L/Z
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!

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jgerson@Hotmail.com