GENETIC TESTING IN AMD: CRITICAL.......USEFUL.......OR INAPPROPRIATE?

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GENETIC TESTING IN AMD

• DETERMINES RISK OF PROGRESSION TO ADVANCED AMD (GEOGRAPHIC ATROPHY OR CNV) BASED UPON GENETICS AND OTHER DEMOGRAPHIC / LIFESTYLE FACTORS

• 5 LEVELS OF RISK PROJECTED OUT OVER 2-10 YEARS WITH ARCTIC DX TEST
THE GENETIC PLAYERS

- A VERY LARGE NUMBER, BUT TWO MAIN PLAYERS
  - CFH (COMPLEMENT FACTOR H)
  - ARMS II (AGE RELATED MACULOPATHY SENSITIVITY II)

- CFH BINDS TO ZINC
- ARMS II LOCALIZES TO MITOCHONDRIA
- PATIENTS CAN CARRY 0, 1, OR 2 ALLELES FOR BOTH CFH AND ARMS II
• UTILIZES BUCCAL SWAB FROM EACH CHEEK AND DEMOGRAPHIC FACTORS

• TEST KITS KEPT IN DOCTOR'S OFFICE, NO CHARGE TO DOCTOR TO OBTAIN

• NO BILLING BY COLLECTING DOCTOR, BILLING BY THE LAB (OUT OF POCKET COST HAS VARIED OVER TIME, $0.00-$50.00)

• RESULTS IN ABOUT TWO WEEKS

• HIGH RISK PATIENTS CAN BE FOLLOWED MORE CLOSELY, UTILIZE FORSEE AT HOME, ETC. (MUST HAVE INTERMEDIATE DRY AMD TO USE FORSEE HOME DEVICE)

• ALSO MAKES RECOMMENDATIONS ON ZINC BASED UPON GENETICS .....................THIS IS VERY CONTROVERSIAL
SECOND AVAILABLE GENETIC TEST FOR AMD: VISIBLE GENOMICS

- **AMDIGUARD DNA PROGRESSION TEST**
  - Must have early or intermediate dry AMD
  - For over 55
  - Gives a lifetime risk score of progression to advanced AMD
  - No insurance filing, so no doctor order needed
  - Patient can order directly and handle sample collection themselves, $199
  - Telehealth review of results with an OD
  - No zinc recommendation provided (but raw data is there)

- **AMDIGUARD DNA RISK TEST**
  - For people with a family history of AMD
  - For under 55
  - Gives a lifetime risk of developing advanced AMD
  - Same sample collection and cost are the same ($199)
  - Telehealth review of results with an OD
  - No zinc recommendation provided (but raw data is there)
ZINC

• ZINC IS AN ESSENTIAL MINERAL, SO WE NEED IT (IMMUNE SYSTEM, CELL GROWTH, ETC.)

• RDA OF ABOUT 10MG FOR ADULTS, UPPER TOLERABLE LIMIT OF 40MG (80 MG IN AREDS / AREDS II FORMULA)

• IN EXCESS.............CAN LEAD TO NAUSEA, DIARRHEA, HEADACHES, GENITOURINARY TRACT PROBLEMS AND PERHAPS EVEN ALZHEIMER’S (CONTROVERSIAL)
THE CAMPS

• DR. CARL AWH, ET AL

• GENETICS PLAY A MAJOR ROLE IN THE BENEFIT…….. OR DETRIMENT…….. OF ZINC SUPPLEMENTATION IN PATIENTS WITH AMD

• DR. EMILY CHEW, ET AL

• GENETICS PLAY NO ROLE IN THE BENEFIT OF ZINC IN AMD: ZINC IS HELPFUL FOR ALL
Refresher: Original AREDS

- Both groups analyzed data from AREDS I (2001) patients who had available DNA.
- In AREDS, AMD classified into 4 categories, with Category 4 being advanced.
- Basic finding was that the AREDS formula decreased the 5-year progression rate of Category 3 intermediate disease to Category 4 advanced disease by 25%.
- No benefit in slowing progression of early disease to intermediate disease.

- 15 mg beta carotene
- 500 mg vitamin C
- 400 IU vitamin E
- 80 mg zinc
- 2 mg copper

- AREDS II removed beta carotene (possible increased risk of lung cancer in smokers), but added 10 mg of lutein and 2 mg of zeaxanthin.
AREDS REFRESHER

• FOUR GROUPS

• PLACEBO
• ANTIOXIDANTS
• ZINC
• ANTIOXIDANTS PLUS ZINC (FULL ORIGINAL AREDS FORMULA)

• COULD ALSO TAKE CENTRUM (66% CHOSE TO), SO THESE PATIENTS HAD MORE ZINC, WITH 15 EXTRA MILLIGRAMS, AND VERY FEW TRUE “PLACEBO’ PATIENTS
AWH STUDY #1 IN 2013
(OPHTHALMOLOGY 120;11; NOV. 2013)

- PURCHASED APPLICABLE DNA FROM PATIENTS IN AREDS I
- USED WHITE PATIENTS WITH CATEGORY 3 (INTERMEDIATE) DISEASE IN AT LEAST ONE EYE, BUT COULD BE CATEGORY 3 OR LESS IN THE FELLOW EYE (COULD NOT HAVE CATEGORY 4 IN EITHER EYE)
- 4757 IN STUDY..........2258 CAUCASIANS WITH CATEGORY 3 IN AT LEAST ONE EYE AND NOT CATEGORY 4 IN EITHER......995 WITH DNA. SO 995 EVALUATED
• The 995 were compared to the 2258 and were not statistically different in sex, smoking, BMI, education, treatment category, or progression percentage.

• .6 year difference in average age.

• CFH 1, CFH 2 had no benefit from any zinc containing formula.

• CFH 2, ARMS II 0 showed 43% greater progression rate with any zinc than with placebo.

• With antioxidant therapy alone, more ARMS II alleles = greater progression.

• CFH 2, ARMS II 2 = 75% progression rate no matter what they took, with no benefit from anything.
AWH STUDY #1

- Authors’ Conclusion: Zinc potentially harmful in CFH patients, but Zinc potentially helpful in ARMS II patients

- Projected estimated 10-year progression rate……..
  - Placebo 47%
  - AREDS 40.5%
  - If targeted 31.5%

- This study started the controversy
CHEW RESPONSE ANALYSIS
(OPHTHALMOLOGY 2014)

• Used the AREDS patients with the same criteria as AWH, but also included patients with category 4 in one eye and less than category 3 in the fellow eye.

• Used sex, age, smoking, etc. as variables along with CFH and ARMS II, so 27 separate categories studied.

• Concluded that genetics had no role in the protective value of zinc or antioxidants, and that all groups showed a benefit from the AREDS formula.
AWH STUDY #2
(OPHTHALMOLOGY 2014)

• LOOKED AT SAME CATEGORY GROUPS AS BEFORE, BUT ALSO INCLUDED THOSE PATIENTS WITH CATEGORY 4 IN ONE EYE
• NO STATISTICAL DIFFERENCE FROM AREDS WHITE, DNA AVAILABLE POPULATION REGARDING AGE, SEX, SMOKING, BMI, ETC.
• HAD 9 TOTAL GROUPS, BASED UPON CFH 0-2 AND ARMS II 0-2
• LOOKED AT ACTUAL 7-YEAR PROGRESSION RATE (NOT PROJECTED) IN EACH GROUP

• SAMPLES:
  • CFH 2, ARMS II 0: PLACEBO 17% PROGRESSION, ANY ZINC 43% PROGRESSION
  • CFH 0 OR 1 ARMS II 1 OR 2: PLACEBO 43% PROGRESSION, ANY ZINC 25% PROGRESSION
  • CFH 2, ARMS II 1 OR 2: PLACEBO 48% PROGRESSION, NOTHING ELSE ANY BETTER
AWH STUDY # 2

- SO THINK IN TERMS OF 4 GROUPS
- ZINC **INCREASES** THE DELETERIOUS EFFECTS OF CFH AND ZINC **DIMINISHES** THE DELETERIOUS EFFECTS OF ARMS II
- **LOW CFH, LOW ARMS II** (28% OF STUDY GROUP): ZINC DOES NOT HELP OR HURT
- **HIGH CFH, LOW ARMS II** (13%): ZINC IS HARMFUL AND AT LEAST DOUBLES THE RISK OF PROGRESSION
- **LOW CFH, HIGH ARMS II** (35%): ZINC HELPS
- **HIGH CFH, HIGH ARMS II** (23%): NOTHING HELPS
INDEPENDENT STATISTICAL ANALYSIS

- 2015
- RAFAL KAFSTRA, PHD
- BIOSTATISTICS, UNIVERSITY OF TORONTO
- BERNARD ROSNER, PHD
- BIOSTATISTICS, HARVARD MEDICAL SCHOOL

- BOTH ANALYZED THE DATA USED BY AWH AND CHEW, AS WELL AS THEIR CONCLUSIONS
- DETERMINED THAT GENETICS PLAY A ROLE IN THE RESPONSE TO ZINC, AND THAT ZINC IS HARMFUL TO SOME
INDEPENDENT STATISTICAL ANALYSIS

• SEDDON, SILVER, AND ROSNER
• JULY, 2016 IN BRITISH JOURNAL OF OPHTHALMOLOGY
• USE THE INDIVIDUAL EYE, NOT THE PATIENT, AS THE ENDPOINT. THIS INCREASED THE STATISTICAL POWER
• LOOKED AT 2317 PEOPLE, 4124 EYES
• ASSESSED CFH AND ARMS 2 (0=LOW, 1 OR 2 = HIGH)
• LOW/LOW, LOW/HIGH, HIGH/LOW, HIGH/HIGH
• AVERAGE FOLLOW-UP OF 6.6 YEARS
• 882 PROGRESSION TO ADVANCED DISEASE (GA OR NV)
• CONCLUSION: THE EFFECTIVENESS OF ANTIOXIDANTS AND ZINC DO DIFFER BY GENOTYPES
TWO MORE IN LATE 2017

• ASSEL, ET. AL IN OPHTHALMOLOGY
• THREE INDEPENDENT GROUPS OF STATISTICIANS WORKING SEPARATELY
• DETERMINED ZINC PLAYS NO ROLE

• VAVVAS, AWH, ET. AL
• ONLY LOOKED AT PROGRESSION TO NV, AS AREDS FORMULA NOT SHOWN TO PROTECT AGAINST GEOGRAPHIC ATROPHY
• USED “BOOTSTRAPPING” TECHNIQUE
• FOUND AN EVEN STRONGER ASSOCIATION BETWEEN GENETIC TYPES AND HARM FROM ZINC OR BENEFIT FROM AREDS FORMULA
• USED A NEVER BEFORE STUDIED GROUP OF 299 AREDS STUDY PATIENTS
Gain Study: Genetics & AREDS Formula Interaction in Neovascular AMD

- Conducted at multiple retinal practices around the country (Ohio, Pennsylvania, California)
- Stephen Kaufman, MD & Pradeepa Yoganathan, MD with others

- Started with a group of 1000 patients who had recently converted to neovascular AMD (important: not speculative)
- Inclusion: Reliable history of greater than 5 years of AREDS formula use (either one or two pills per day) or no history of AREDS formula use (less than 30 days total use ever)
- Exclusion: Any genetic testing prior to wet AMD diagnosis, macular laser, vitrectomy, history of non-AMD induced CNV
GAIN STUDY

- MASKED GENOTYPING: GENOTYPE GROUPS 1, 2, 3, 4, BASED UPON HIGH OR LOW CFH AND ARMS II
- 266 PATIENTS MET THE CRITERIA: 46 AREDS USERS (5 OR MORE YEARS) AND 219 NON-USERS
- OF THESE, 27 AREDS USERS WITH GENOTYPE 2 (HIGH CFH, LOW ARMS II) OR GENOTYPE 3 (LOW CFH, HIGH ARMS II), AND 140 NON-USERS WITH GENOTYPES 2 OR 3
- ALSO COLLECTED AGE, SEX, SMOKING STATUS, AND BMI. (ALL PATIENTS WERE CAUCASIAN)
GAIN STUDY

• IF THERE IS NO INTERACTION WITH GENETICS, THEN THE RATIO OF AREDS USERS TO NON-USERS WILL BE THE SAME IN GENOTYPE GROUP 2 AND GENOTYPE GROUP 3

• IF THERE IS AN INTERACTION WITH GENETICS, THEN THERE WILL BE AN INCREASED PROPORTION OF AREDS USERS IN GENOTYPE GROUP 2 (BECAUSE ZINC HARMs THEM), AND AN INCREASED PROPORTION OF NON-AREDS USERS IN GENOTYPE GROUP 3 (BECAUSE ZINC HELPS THEM)
GAIN STUDY RESULTS

• ODDS RATIO FOR AREDS USE IN GENOTYPE GROUP 2 VS GENOTYPE GROUP 3…………..
  4.18 (4.81 WHEN ADJUSTED FOR CONFOUNDERS)

• HIGH DOSE ZINC APPEARED TO HARM GENOTYPE GROUP 2, AND HELP GENOTYPE GROUP 3 (REMEMBER THAT PATIENTS WERE INCLUDED IF THEY TOOK ONE OR TWO PILLS PER DAY, SO EITHER 40 MG OR 80 MG OF ZINC)

• THINGS TO CONSIDER…..
  • REAL WORLD PATIENTS, NOT FROM THE AREDS STUDY POPULATION
  • ONLY INCLUDED PATIENTS WHO HAD ALREADY CONVERTED TO WET AMD
  • SHOWED “HARM” AND “HELP” AS PREDICTED IF THERE IS AN INTERACTION
  • RELATIVELY SMALL TOTAL PATIENT NUMBERS IN GROUP 2 (47) AND GROUP 3 (120)
  • AREDS FORMULA USE HISTORY COLLECTED BY AN INDEPENDENT DATA COORDINATING CENTER (RELIED ON PATIENT REPORTING), THAT ALSO COLLATED GENETIC TESTING RESULTS
PREDICTORS OF PROGRESSION TO ADVANCED DISEASE IN AMD
“DEVELOPING PROGNOSTIC BIOMARKERS IN INTERMEDIATE AGE RELATED MACULAR DEGENERATION: THEIR CLINICAL USE IN PREDICTING PROGRESSION”

CLINICAL AND EXPERIMENTAL OPTOMETRY 2018;101:172-181

FROM AUSTRALIA: INTENSIVE LITERATURE SEARCH

LOOKED AT CONVERSION OF INTERMEDIATE AMD TO GEOGRAPHIC OR EXUDATIVE DISEASE
PREDICTORS OF PROGRESSION

- USED SD-OCT FINDINGS
- LOOKED AT EYES WITH INTERMEDIATE AMD PROGRESSING TO ADVANCED DISEASE
- MANY, IF NOT MOST, OD’S HAVE OCT CAPABILITY, SO VERY VALUABLE AND PRACTICAL INFORMATION.
- MANY DIFFERENT PREDICTORS IDENTIFIED

- HYPER-REFLECTIVE FOCI
- RETICULAR PSEUDODRUSEN / SUBRETINAL DRUSENOID DEPOSITS
- NASCENT GEOGRAPHIC ATROPHY / IRORA
- SUB-RPE HYPER-REFLECTIVE COLUMNS / HYPERTRANSMISSION DEFECTS
- DRUSEN WITH SUBRETINAL FLUID
- DRUSEN SUBSTRUCTURES
- DRUSEN LOAD
- DRUSEN REGRESSION
1) HYPER-REFLECTIVE FOCI

- DOT SHAPED INTRARETINAL LESIONS AT THE APEX OF DRUSEN
- OFTEN CORRESPOND TO FOCAL HYPERPIGMENTATION
- START IN THE OUTER RETINA AND MIGRATE INWARD
- LIKELY REPRESENT PIGMENT GRANULES
- ANCILLARY AREDS II OCT STUDY SHOWED THEM TO BE ASSOCIATED WITH A 5X RISK OF GEOGRAPHIC AMD IN TWO YEARS. NO EXTRA RISK OF CNV
HYPER-REFLECTIVE FOCI
HYPER-REFLECTIVE FOCI
2) RETICULAR PSEUDODRUSEN / SUBRETINAL DRUSENOID DEPOSITS

- **SUBRETINAL DRUSENOID DEPOSITS** on OCT (below the retina but above the RPE)
- Show up well on FAF also
- Yellowish interconnected deposits
- Most frequent in the superior macula and superotemporal arcade
- Show up poorly in photographs
- 2-6 X increased risk of progression to advanced disease; more GA than CNV

FAF better than photo
TRADITIONAL DRUSEN: PHOTO SHOWS MUCH BETTER THAN FAF
3) NASCENT GEOGRAPHIC ATROPHY / IRORA (INCOMPLETE RPE AND OUTER RETINAL ATROPHY)

- THINNING OF THE OPL AND INL WITH A HYPOREFLECTIVE WEDGE AND CHOROIDAL HYPERTRANSMISSION DEFECT
- NO COMPLETE PHOTORECEPTOR OR RPE LOSS
- 90% OF THE TIME WITHIN CENTRAL 1500 MICRONS OF THE MACULA
- STRONGLY ASSOCIATED WITH IMPENDING GA
- NO EXTRA RISK OF CNV
- CRORA; COMPLETE RPE AND OUTER RETINAL ATROPHY ON OCT: GEOGRAPHIC ATROPHY, BUT MAY NOT YET SHOW UP ON PHOTOS. SHOWS UP ON FAF
4) SUB-RPE HYPER-REFLECTIVE COLUMNS / HYPERTRANSMISSION DEFECTS

- INCREASED TRANSMISSION OF SIGNAL COLUMNS BENEATH THE RPE (HYPER-REFLECTIVE)
- OVERLYING RPE APPEARS INTACT
- MAY REPRESENT FINE CRACKS IN THE RPE
- OPPOSITE APPEARANCE OF SHADOWS CAST BY RETINAL BLOOD VESSELS
- EXTRA RISK OF GEOGRAPHIC DISEASE AND CNV
5) DRUSEN WITH SUBRETINAL FLUID WITHOUT EVIDENT CNV

- SUBRETINAL FLUID POCKETS ABOVE DRUSEN
- FLUID DOES NOT EXTEND HIGHER THAN THE PEAKS OF THE DRUSEN
- NO CNV ON ADVANCED TESTING (IVFA, ICG)
- MAY BE SUBCLINICAL CNV OR MECHANICAL STRAIN
- INCREASED RISK OF CNV
6) DRUSEN SUBSTRUCTURES

- Non-homogeneous internal reflectivity of soft drusen
- All look the same on examination/photos, but have differing OCT reflectivity
- May precede drusen regression
- Increased risk of GA but not CNV
THREE IN ONE!

2019

ERM too

2016
7) DRUSEN LOAD AND DRUSEN REGRESSION

- CENTRAL DRUSEN VOLUME IMPORTANT

- DRUSEN VOLUME GREATER THAN .03 CUBIC MM IN THE CENTRAL 3 MM MACULAR DIAMETER = 4 X RISK OF PROGRESSION TO ADVANCED DISEASE: CAN CALCULATE IN SOME IMAGE MANAGEMENT SOFTWARE

- REGRESSION OF DRUSEN CAN OCCUR IN UP TO 50% OF INTERMEDIATE AMD EYES OVER 2 YEARS

- INCREASED RISK OF GEOGRAPHIC ATROPHY OR CNV. OFTEN A DIRECT PRECURSOR EVENT
DRUSEN REGRESSION OD 2015-2019 WITH GA
DRUSEN REGRESSION OS 2015-2019 WITH GA
DRUSEN REGRESSION GA OU FAF
8) OTHER RISKS SPECIFICALLY FOR CNV

- 2019 JAMA OPHTHALMOLOGY ARTICLE PUBLISHED 4-25 ON-LINE
- SECONDARY ANALYSIS OF THE FELLOW EYES IN THE HARBOR TRIAL (A STUDY OF RANIBIZUMAB ADMINISTERED MONTHLY OR ON AN AS-NEEDED BASIS IN PATIENTS WITH SUBFOVEAL NEOVASCULAR AGE-RELATED MACULAR DEGENERATION)
- INCREASED CNV RISK WITH...........................
- INCREASED CENTRAL DRUSEN VOLUME, CONFIRMING PREVIOUS FINDINGS
- INCREASED REFLECTIVITY OF DRUSEN ON OCT
- FEMALE
- AGE (OF COURSE!)
- PRESENCE OF THE GENE VARIANT RS61941274 @ THE ACAD10 LOCUS