GENETIC TESTING IN AMD: CRITICAL…….USEFUL…….OR INNAPROPRIATE?

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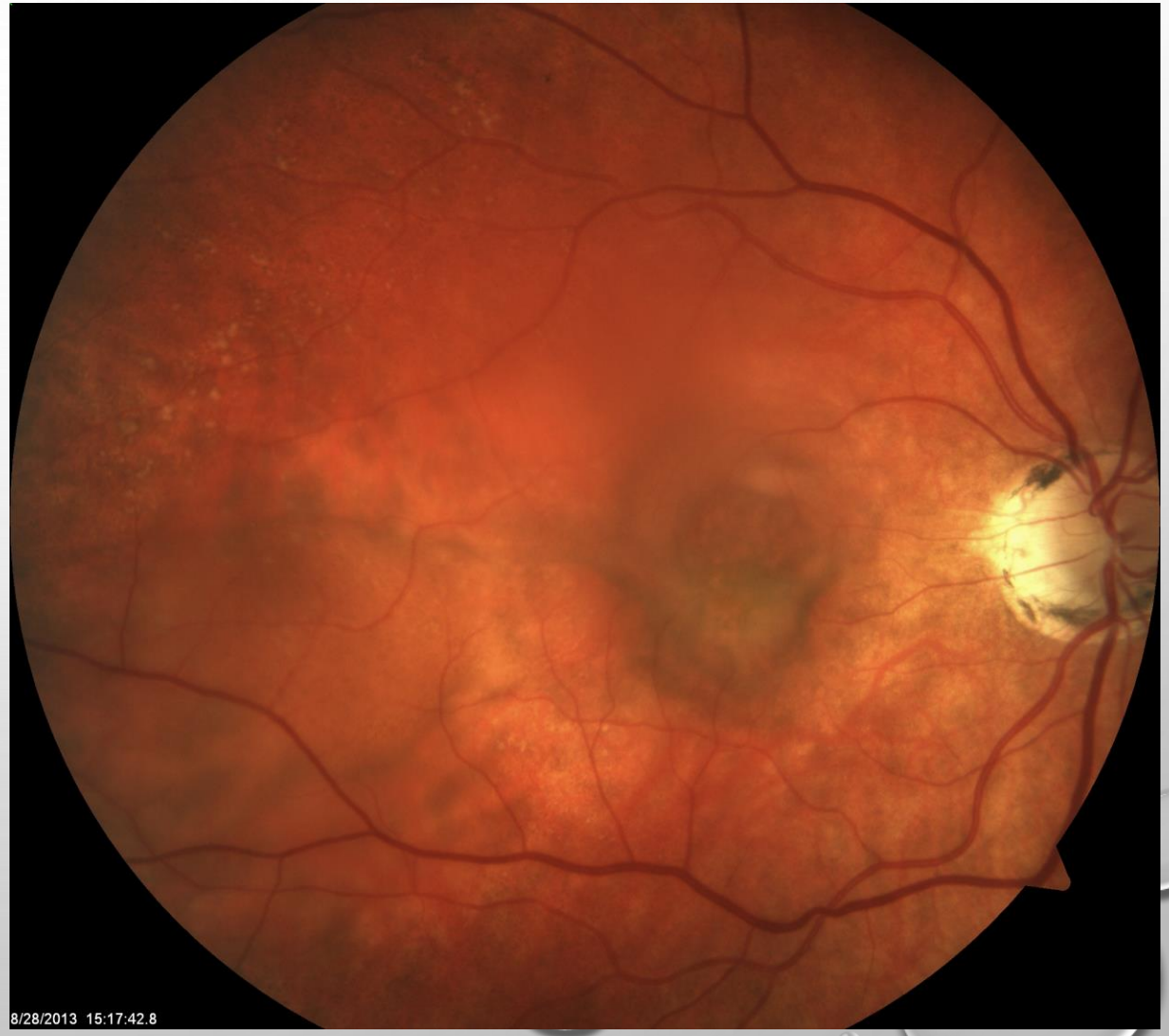
GENETIC TESTING IN AMD

- DETERMINES RISK OF PROGRESSION TO ADVANCED AMD (GEOGRAPHIC ATROPHY OR CNV) BASED UPON GENETICS AND OTHER FACTORS
- 5 LEVELS OF RISK PROJECTED OUT OVER 2-10 YEARS



THE GENETIC PLAYERS

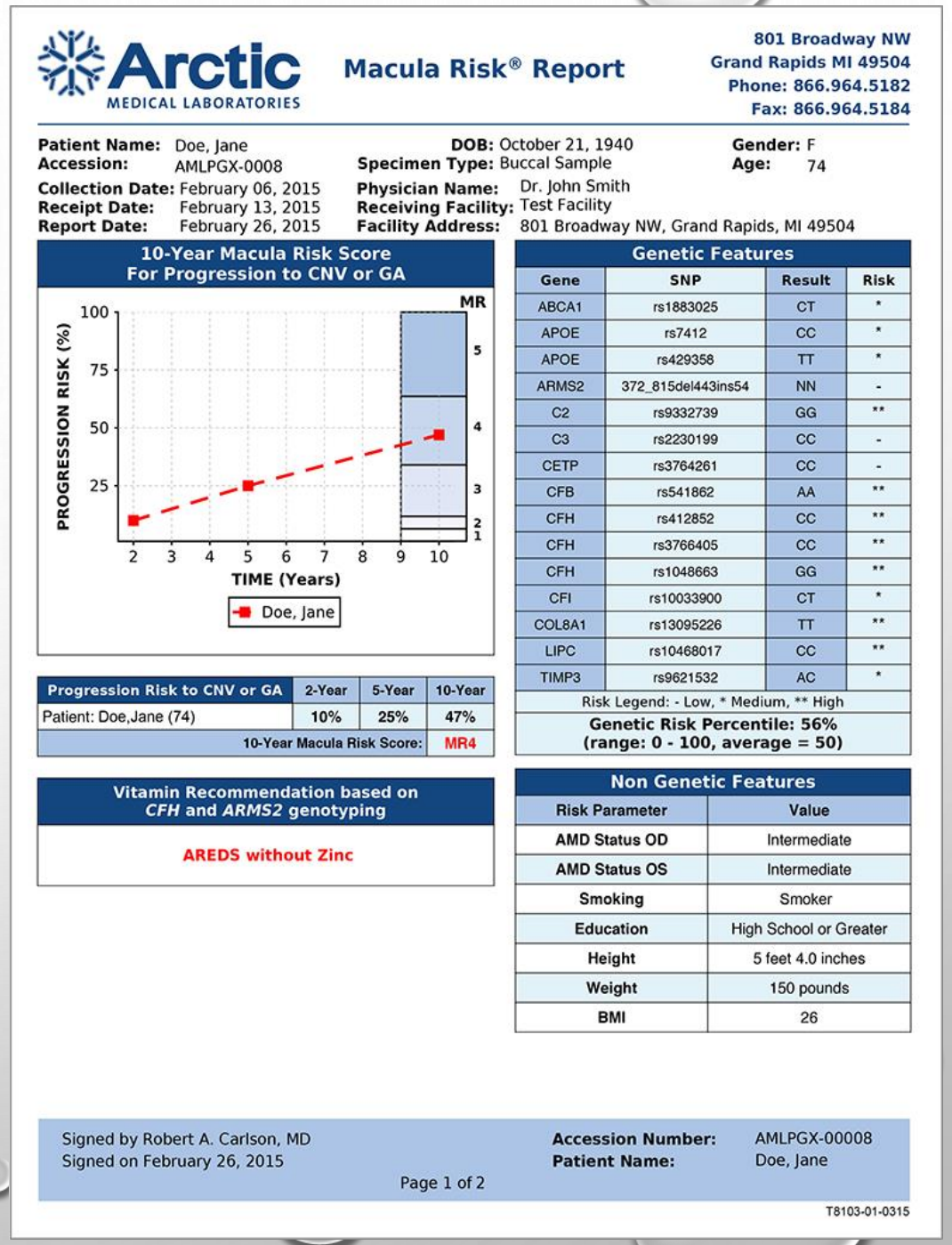
- A VERY LARGE NUMBER, BUT TWO MAIN PLAYERS
- CFH (COMPLEMENT FACTOR H)
- ARMS II (AGE RELATED MACULOPATHY SENSITIVITY II)

- CFH BINDS TO ZINC
- ARMS II LOCALIZES TO MITOCHONDRIA
- PATIENTS CAN CARRY 0,1,OR 2 ALLELLES FOR BOTH CFH AND ARMS II

PRINTOUT

- UTILIZES BUCCAL SWAB FROM EACH CHEEK AND DEMOGRAPHIC FACTORS
- TEST KITS KEPT IN OFFICE
- NO BILLING BY COLLECTING DOCTOR, BILLING BY THE LAB (OUT OF POCKET COST HAS VARIED OVER TIME, OFTEN $0.00-$50.00)
- RESULTS IN ABOUT TWO WEEKS
- HIGH RISK PATIENTS CAN BE FOLLOWED MORE CLOSELY, UTILIZE FORSEE AT HOME, ETC.

- NEWLY APPROVED TEST FROM VISIBLE GENOMICS. JUST BECAME COMMERCIALLY AVAILABLE, SOME DIFFERENCES COMPARED TO ARTIC DX TESTING



Arctic MEDICAL LABORATORIES

Macula Risk® Report

801 Broadway NW
Grand Rapids MI 49504
Phone: 866.964.5182
Fax: 866.964.5184

Patient Name: Doe, Jane
Accession: AMLPGX-0008
DOB: October 21, 1940
Specimen Type: Buccal Sample
Gender: F
Age: 74
Collection Date: February 06, 2015
Receipt Date: February 13, 2015
Report Date: February 26, 2015
Physician Name: Dr. John Smith
Receiving Facility: Test Facility
Facility Address: 801 Broadway NW, Grand Rapids, MI 49504

10-Year Macula Risk Score For Progression to CNV or GA

Progression Risk to CNV or GA	2-Year	5-Year	10-Year
Patient: Doe,Jane (74)	10%	25%	47%
10-Year Macula Risk Score:			MR4

Genetic Features

Gene	SNP	Result	Risk
ABCA1	rs1883025	CT	*
APOE	rs7412	CC	*
APOE	rs429358	TT	*
ARMS2	372_815del443ins54	NN	-
C2	rs9332739	GG	**
C3	rs2230199	CC	-
CETP	rs3764261	CC	-
CFB	rs541862	AA	**
CFH	rs412852	CC	**
CFH	rs3766405	CC	**
CFH	rs1048663	GG	**
CFI	rs10033900	CT	*
COL8A1	rs13095226	TT	**
LIPC	rs10468017	CC	**
TIMP3	rs9621532	AC	*

Risk Legend: - Low, * Medium, ** High

Genetic Risk Percentile: 56%
(range: 0 - 100, average = 50)

Vitamin Recommendation based on *CFH* and *ARMS2* genotyping

AREDS without Zinc

Non Genetic Features

Risk Parameter	Value
AMD Status OD	Intermediate
AMD Status OS	Intermediate
Smoking	Smoker
Education	High School or Greater
Height	5 feet 4.0 inches
Weight	150 pounds
BMI	26

Signed by Robert A. Carlson, MD
Signed on February 26, 2015

Accession Number: AMLPGX-00008
Patient Name: Doe, Jane

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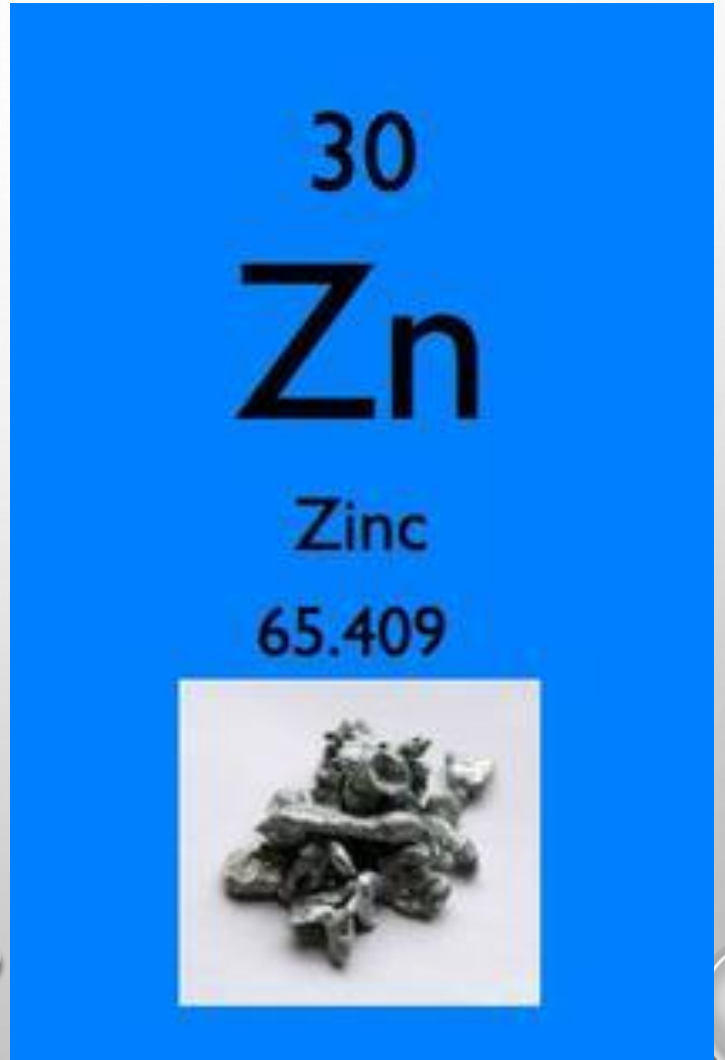
T8103-01-0315

BUT WHAT ABOUT GENETIC TESTING IN AMD AS IT RELATES TO ZINC? CONTROVERSIAL!

- 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

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

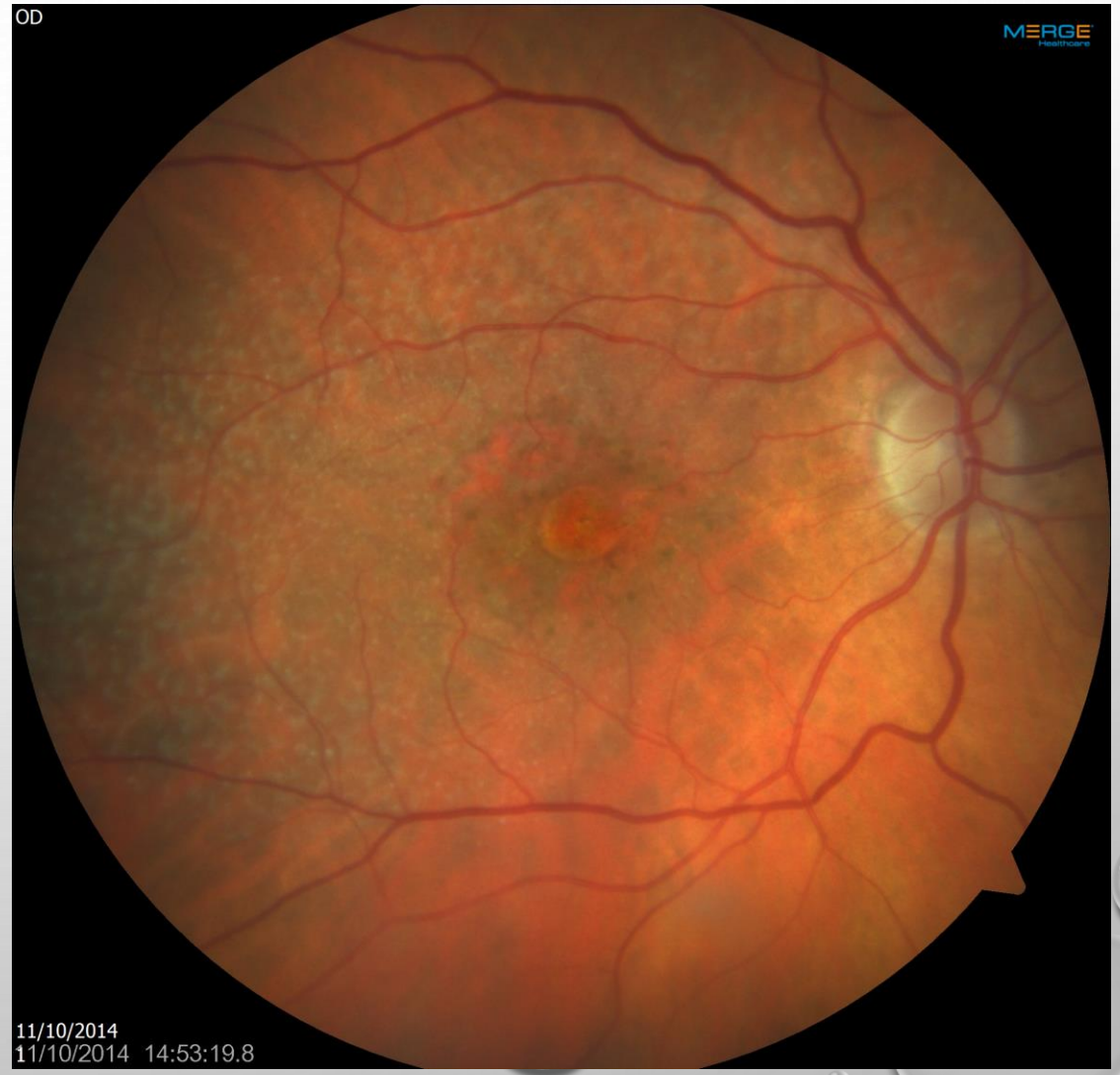
- AREDS II REMOVED BETA CAROTENE (POSSIBLE INCREASED RISK OF LUNG CANCER IN SMOKERS), BUT ADDED 10MG OF LUTEIN AND 2MG OF ZEAXANTHIN

AREDS REFRESHER

- FOUR GROUPS

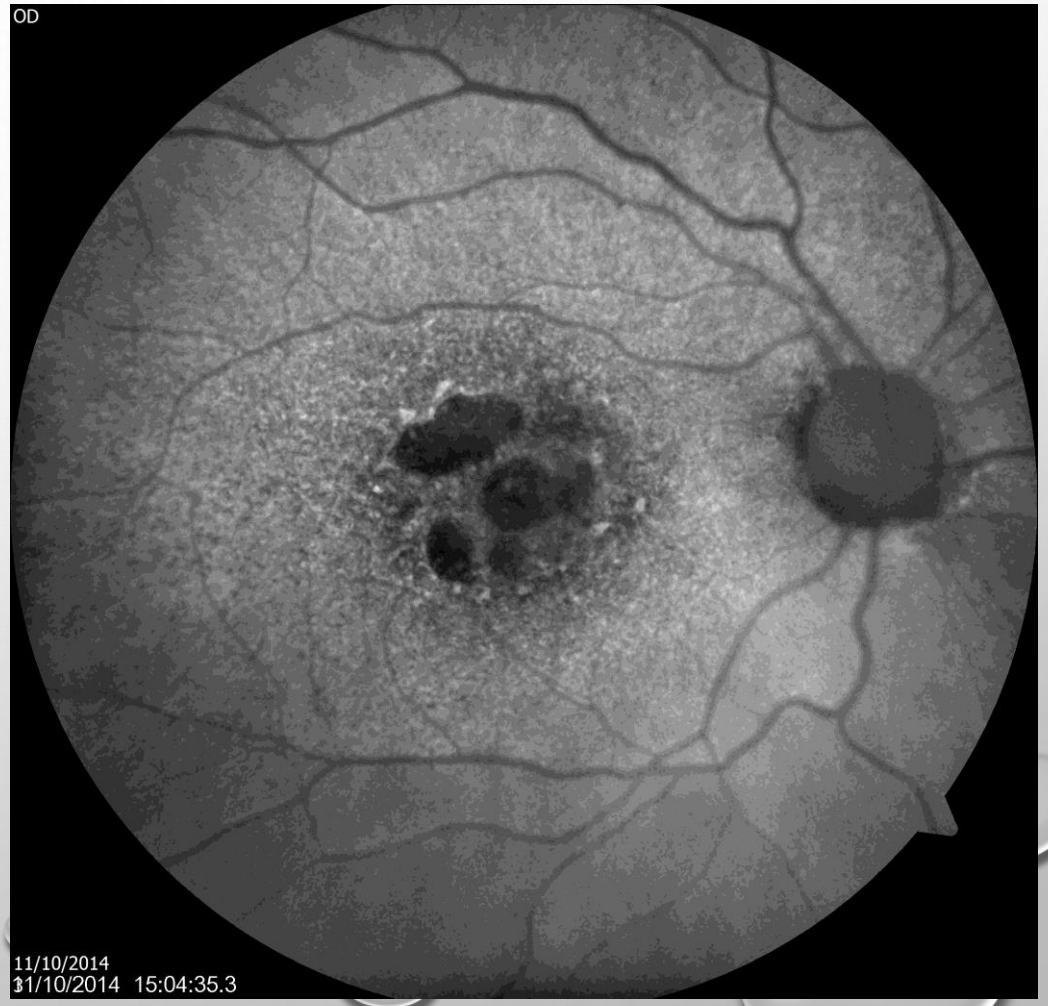
- PLACEBO
- ANTIOXIDANTS
- ZINC
- ANTIOXIDANTS PLUS ZINC (FULL ORIGINAL AREDS FORMULA)

- 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



AWH STUDY # 1

- 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
- THIS STUDY STARTED THE CONTROVERSY

- PROJECTED ESTIMATED 10 YEAR PROGRESSION RATE……..
- PLACEBO 47%
- AREDS 40.5%
- IF TARGETED 31.5%

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 (OPTHALMOLOGY 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 O : 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 0R 2: PLACEBO 48% PROGRESSION, NOTHING ELSE ANY BETTER

AWH STUDY # 2

- SO THINK IN TERMS OF 4 GROUPS
- ZINC ***INCREASES*** THE DELETERIOUS EFECTS 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 PROGRESSED 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

- PRESENTED AT THE 2019 A.S.R.S. MEETING, PUBLISHED IN JOURNAL OF VITREORETINAL DISEASES 8-19-2020
- 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

ARTICLE

- *"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

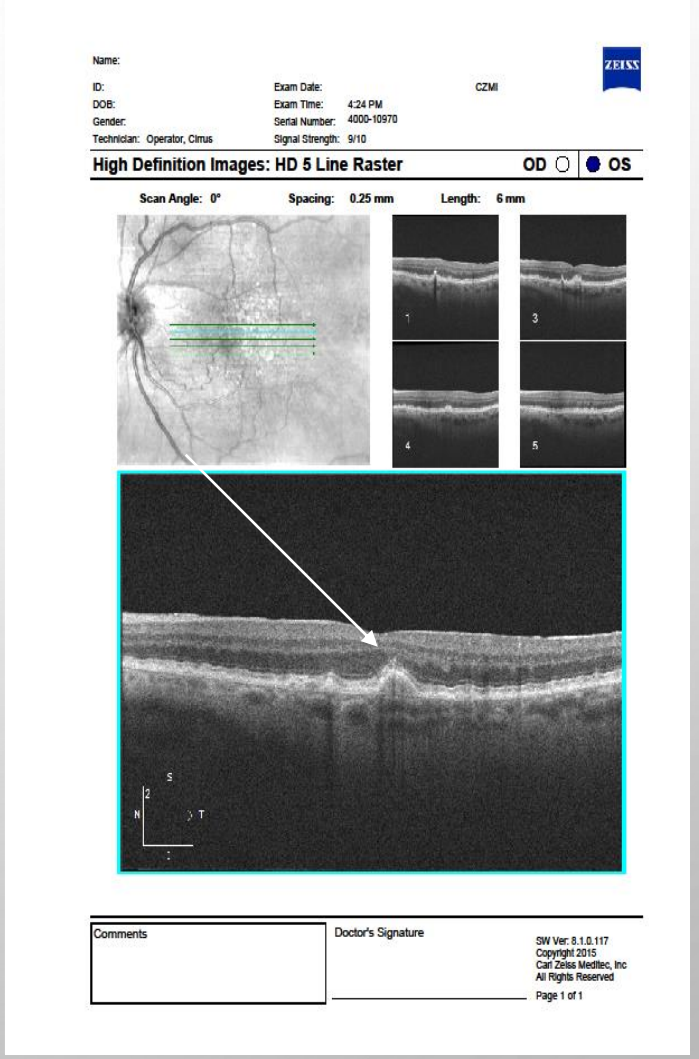
PREDICTORS OF PROGRESSION

- 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**
- **NASCENT GEOGRAPHIC ATROPHY**
- **SUB-RPE HYPER-REFLECTIVE COLUMNS**
- **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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Gender:
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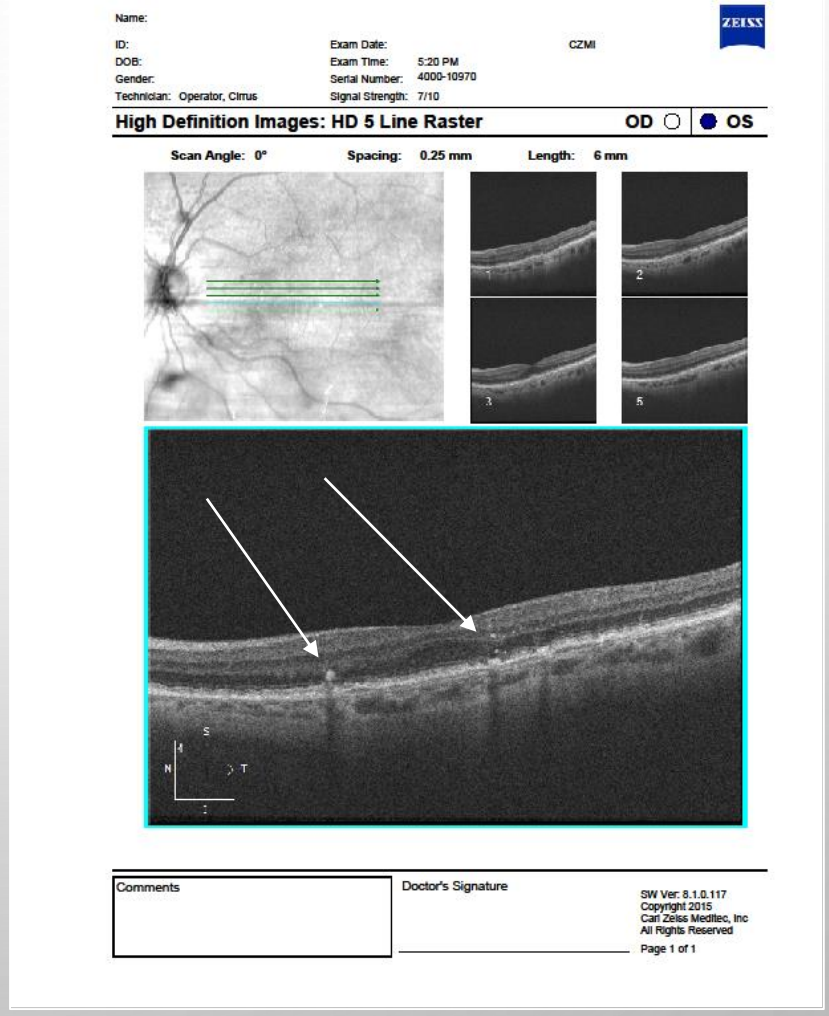
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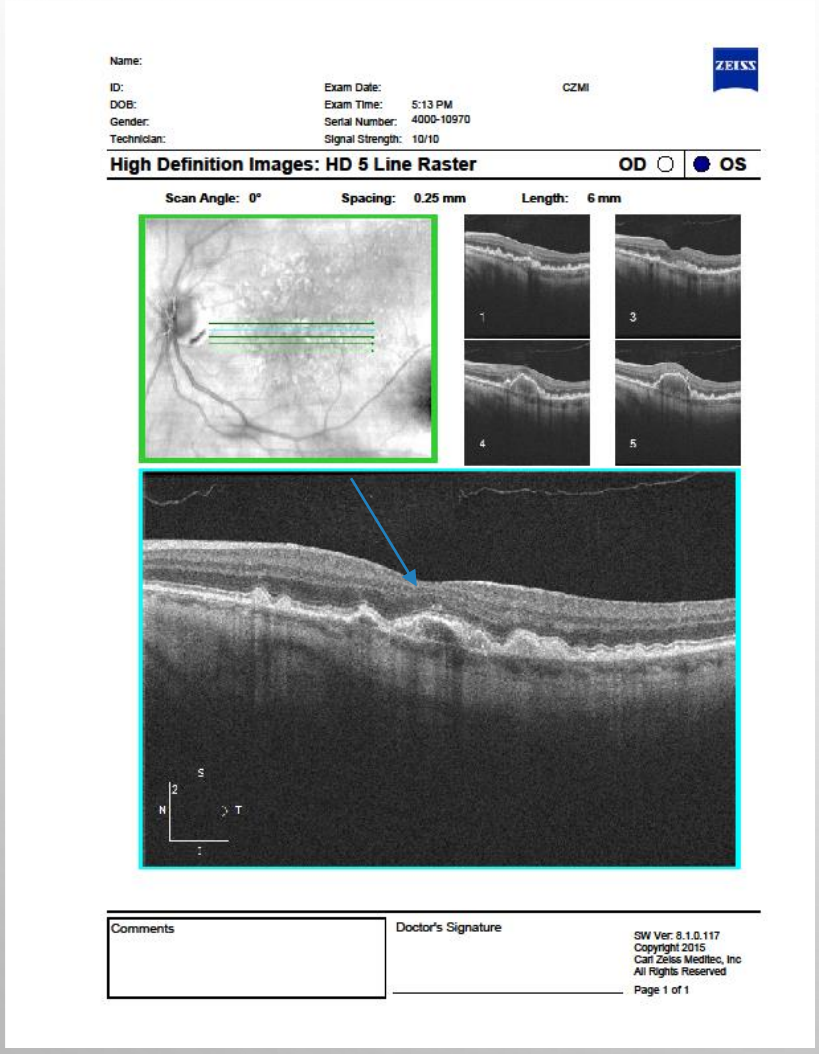
HYPER-REFLECTIVE FOCI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ID:
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CZMI

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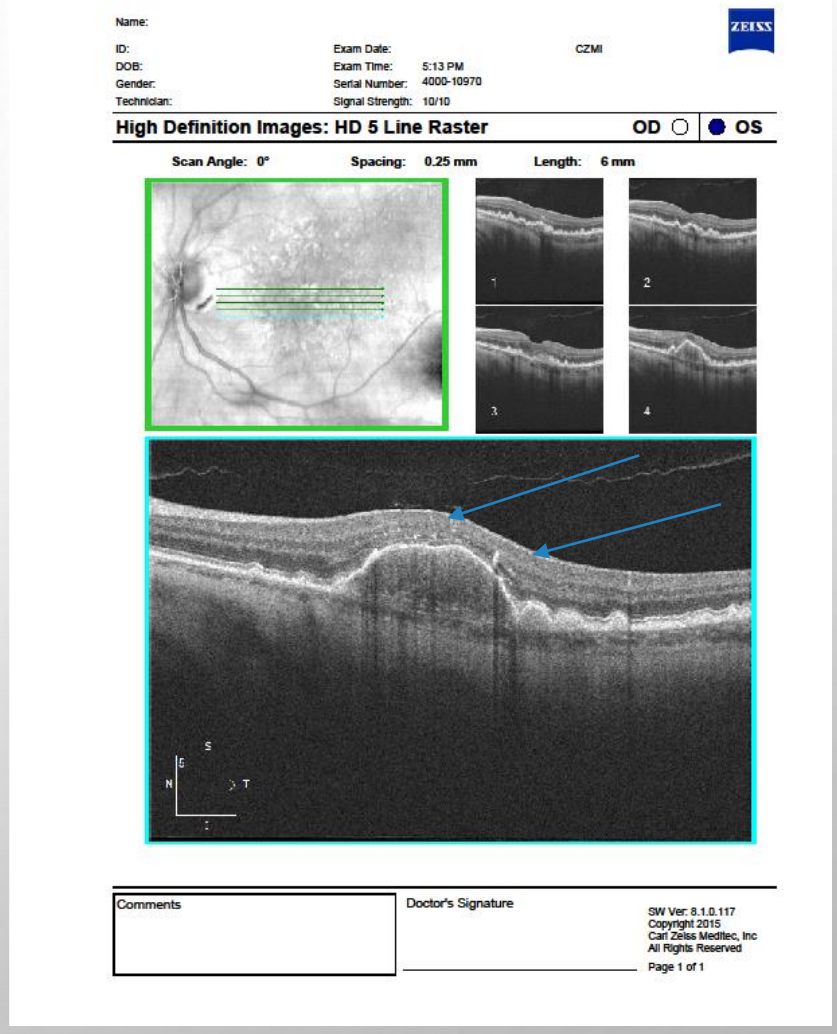
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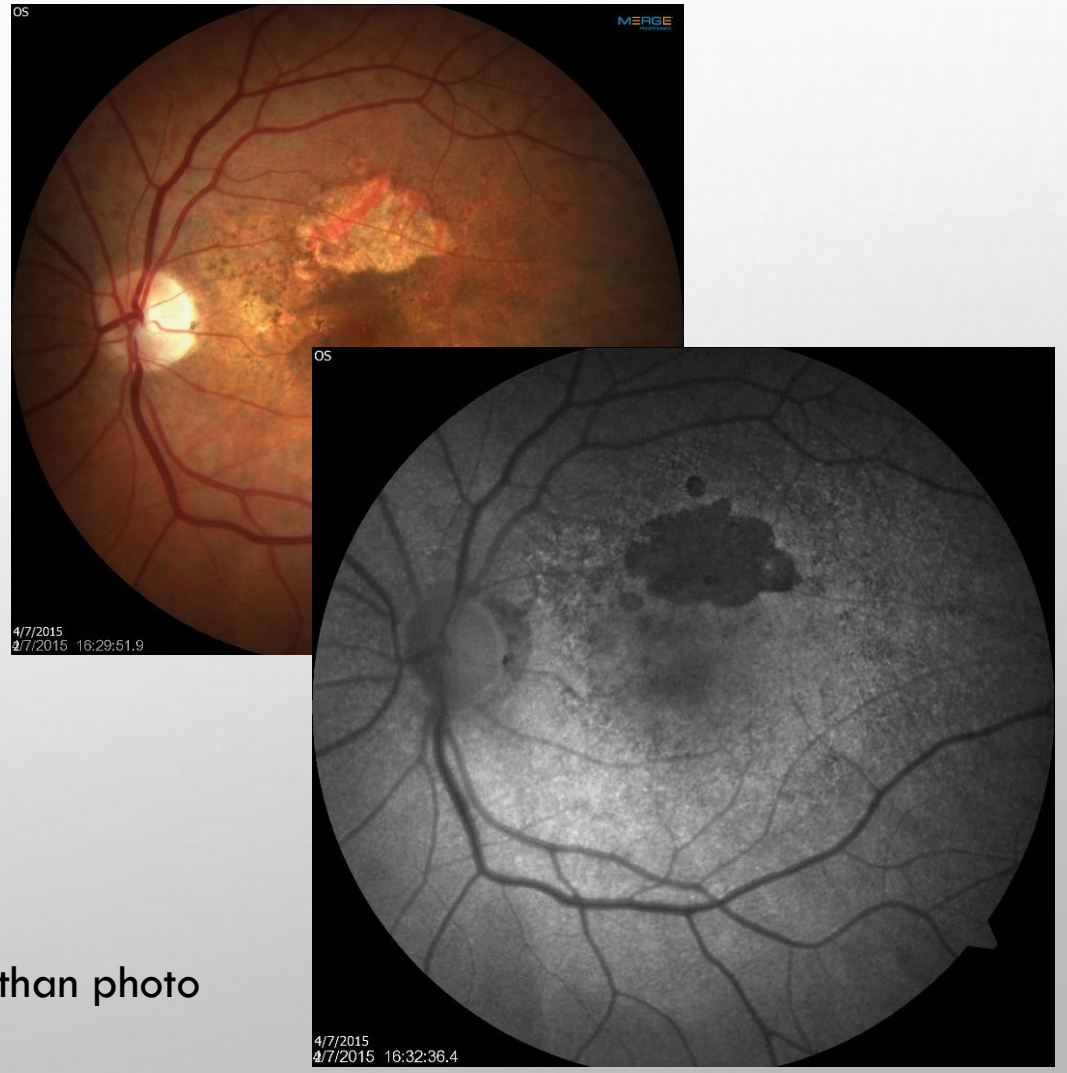
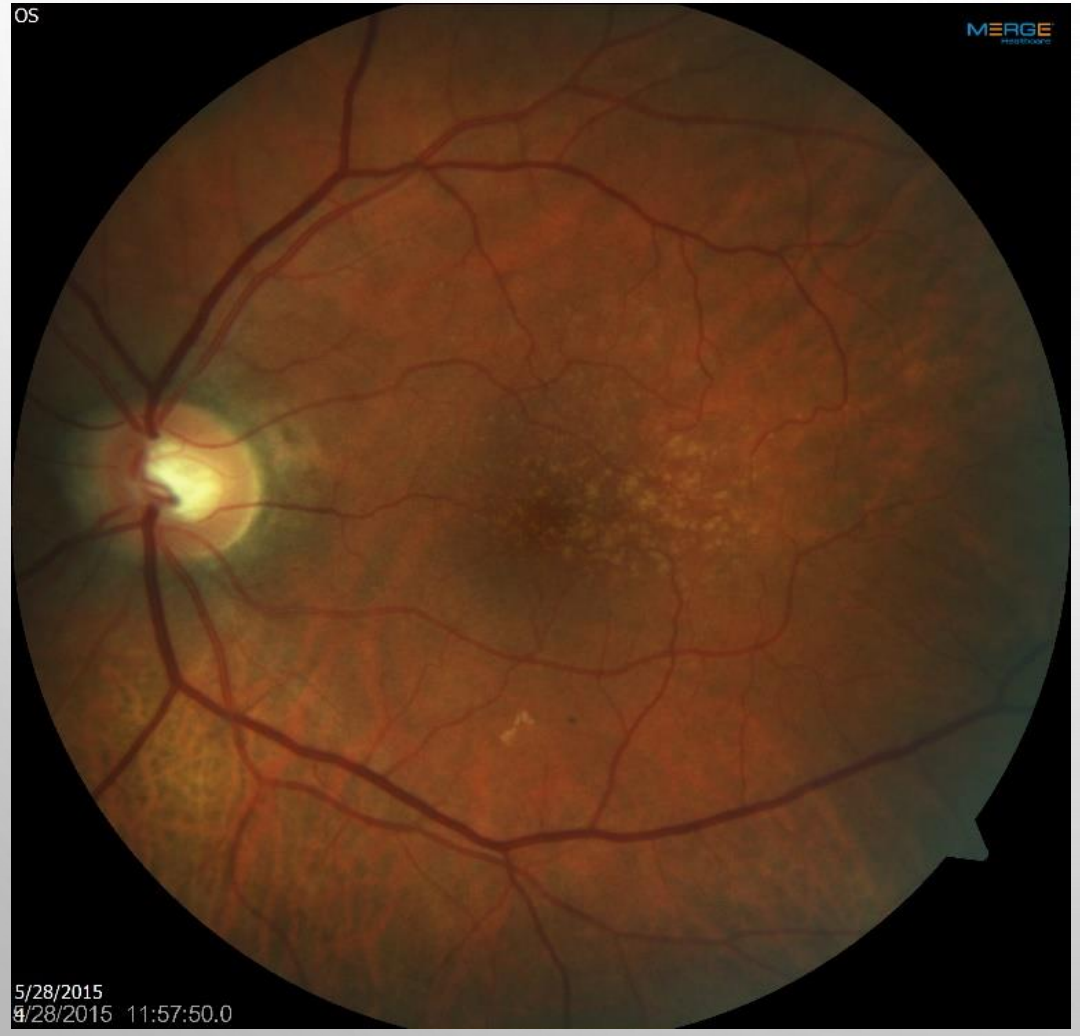
2) RETICULAR PSEUDODRUSEN

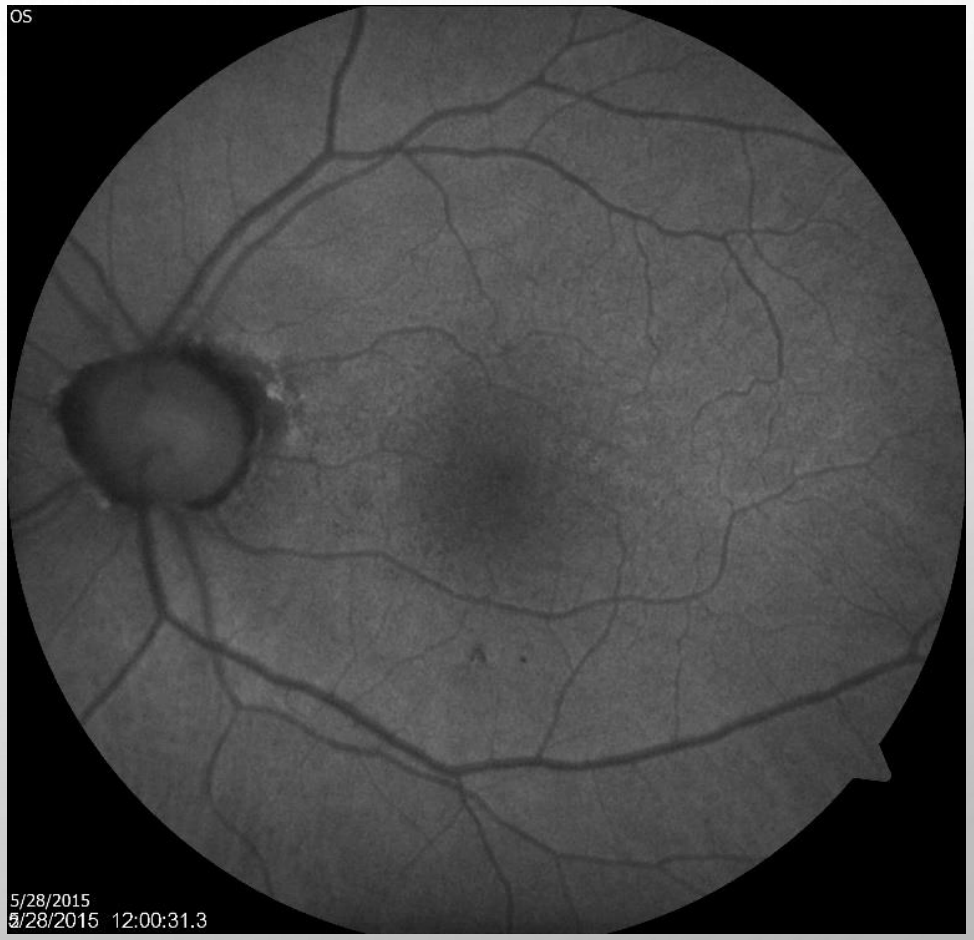
- SUBRETINAL DRUSENOID DEPOSITS ON OCT (BELOW THE RETINA BUT ABOVE THE RPE)
- SHOW UP WELL ON FAF ALSO
- YELLOWISH INTERCONNECTED DEPOSITS
- MOST FREQUENT IN THE SUPERIOR MACULA AND SUPEROTEMPORAL ARCADE (ODDLY,BIGGER RISK)
- SHOW UP POORLY IN PHOTOGRAPHS
- 2-6 X INCREASED RISK OF PROGRESSION TO ADVANCED DISEASE; MORE GA THAN CNV



FAF better than photo

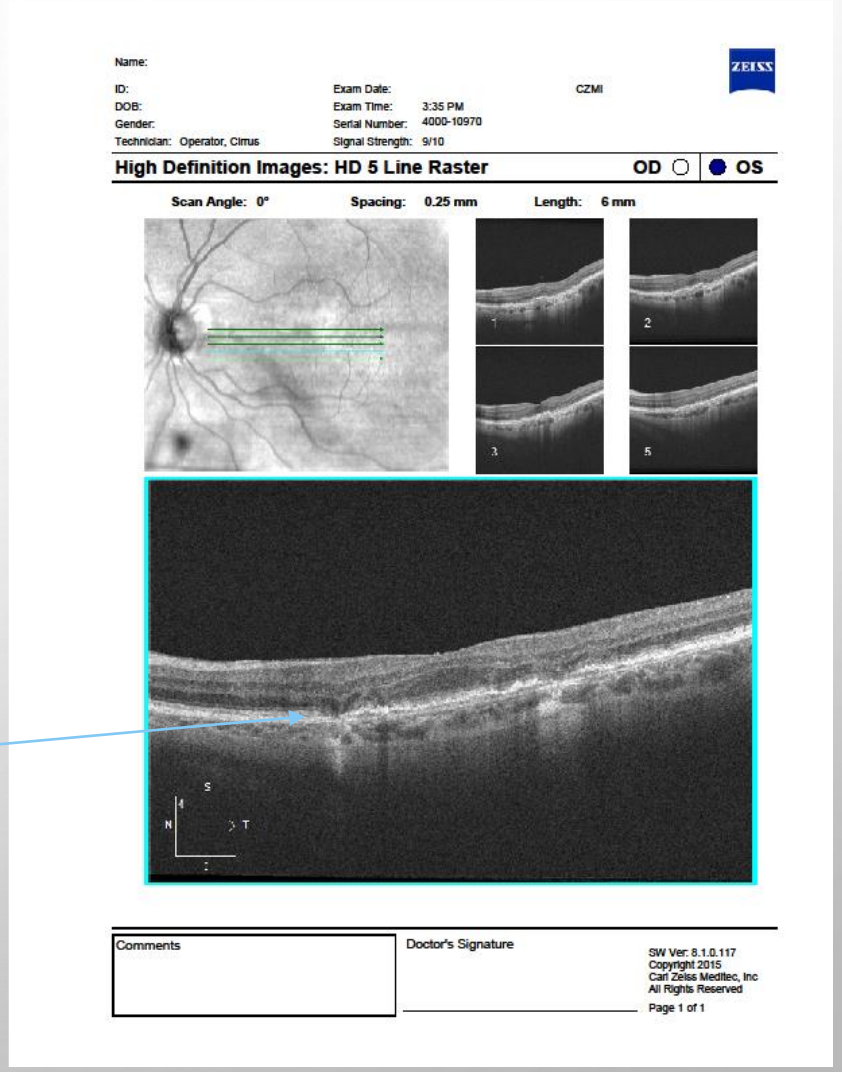
TRADITIONAL DRUSEN: PHOTO SHOWS MUCH BETTER THAN FAF





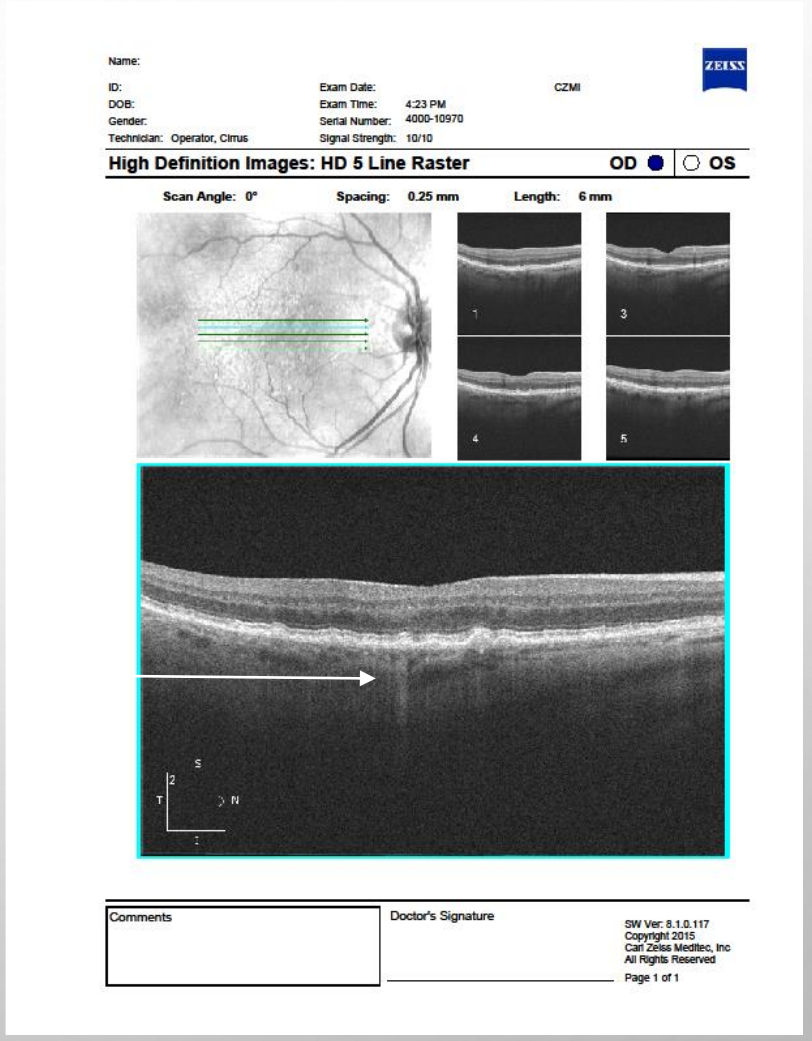
3)NASCENT GEOGRAPHIC ATROPHY

- THINNING OF THE OPL AND INL WITH A HYPOREFLECTIVE WEDGE
- NO 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



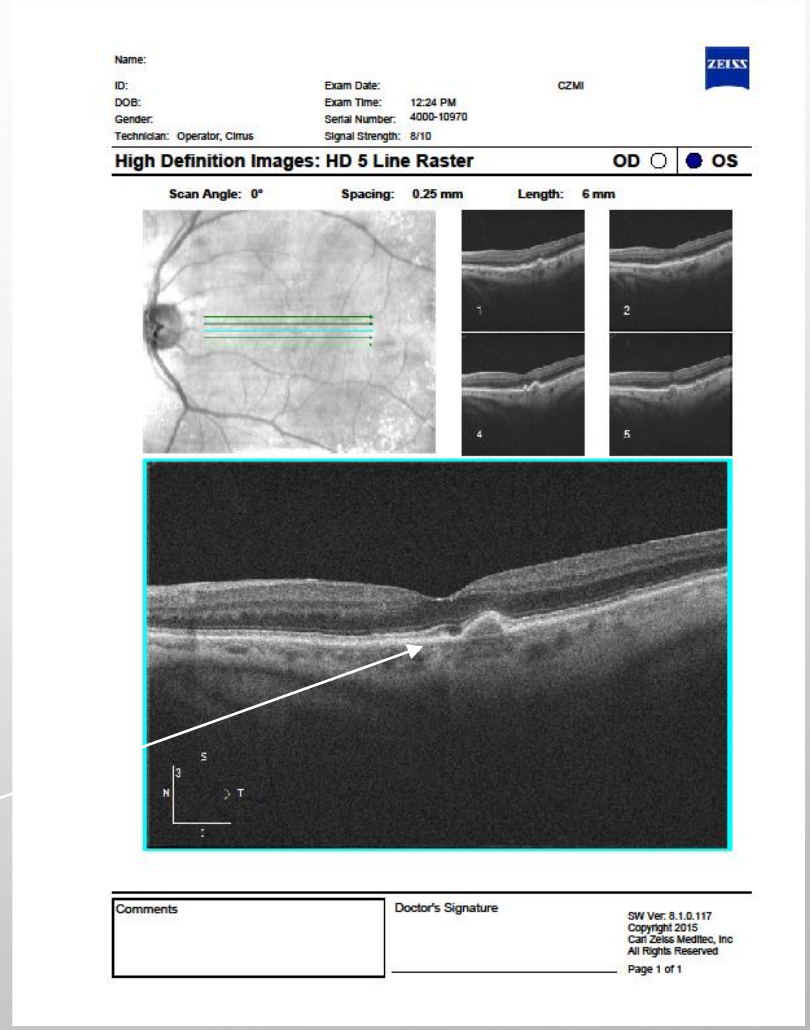
4) SUB-RPE HYPER-REFLECTIVE COLUMNS

- INCREASED TRANSMISSION OF SIGNAL COLUMNS BENEATH THE RPE (HYPER-REFLECTIVE)
- OVERLYING RPE APPEARS INTACT
- MAY REPRESENT FINE CRACKS IN IN THE RPE
- OPPOSITE APPEARANCE OF SHADOWS CAST BY RETINAL BLOOD VESSELS
- EXTRA RISK OF GEOGRAPHIC DISEASE AND CNV



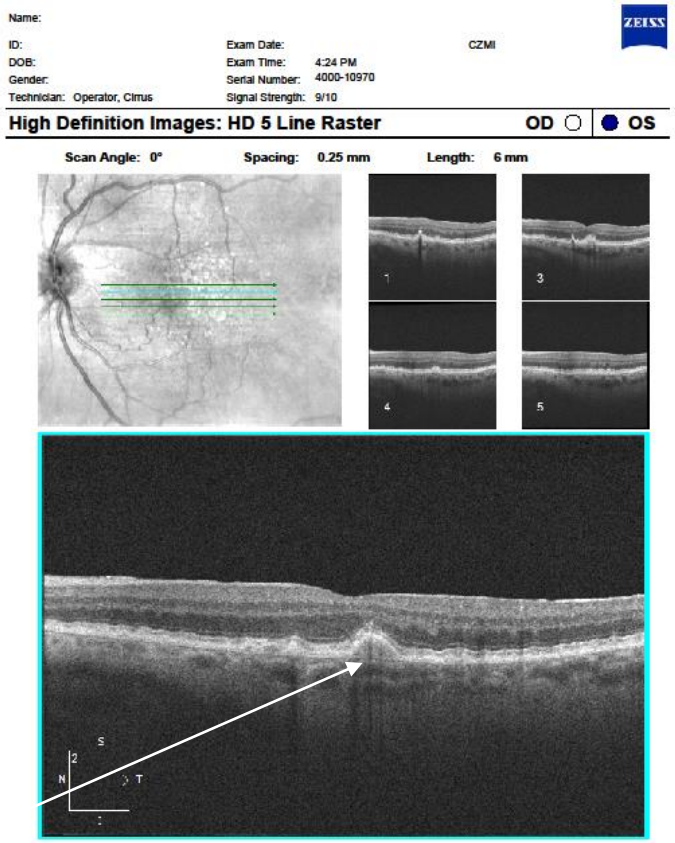
5) DRUSEN WITH SUBRETINAL FLUID WITHOUT EVIDENT CNV

- 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

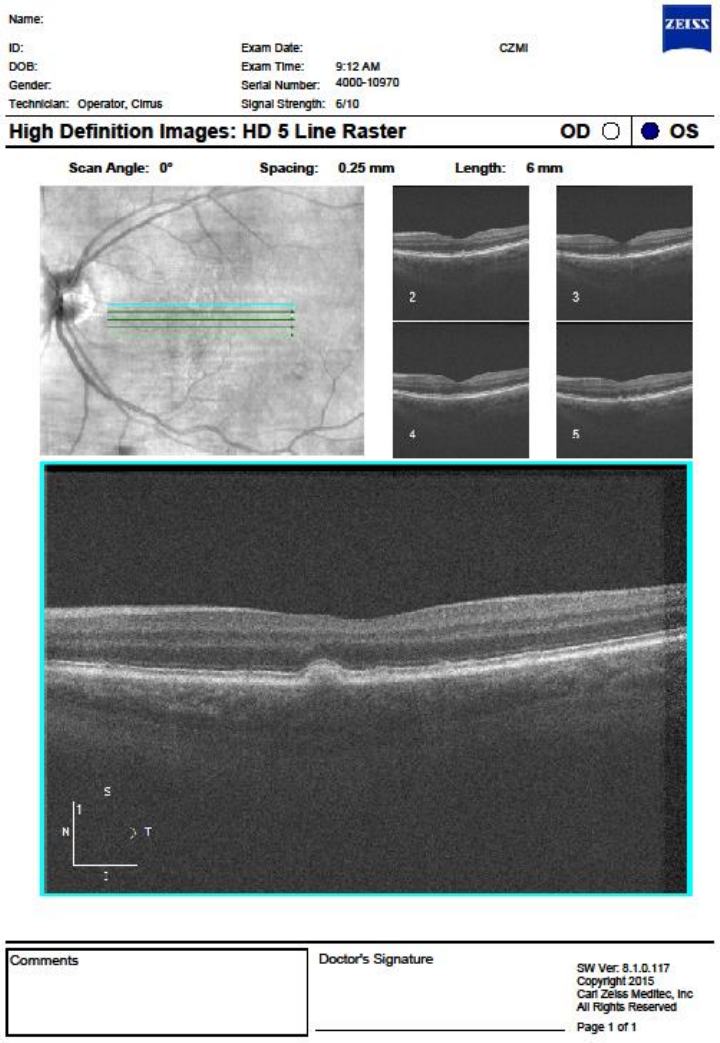


6) DRUSEN SUBSTRUCTURES

- 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



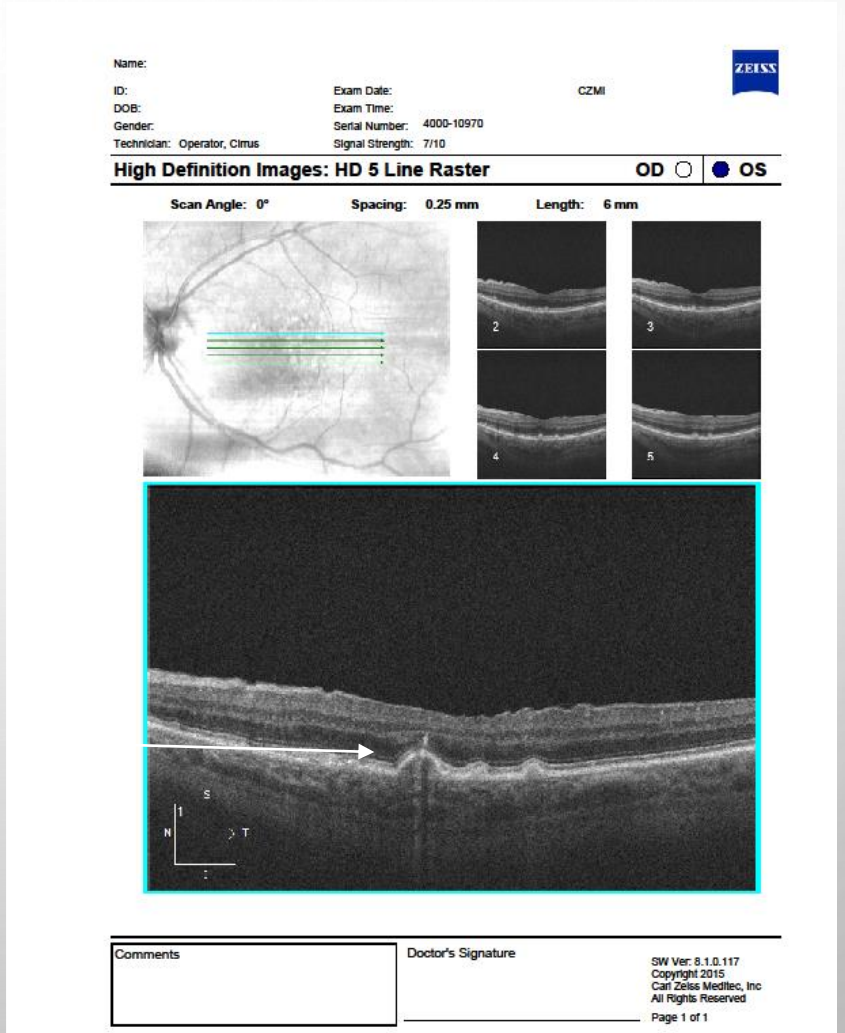
THREE IN ONE!



2019

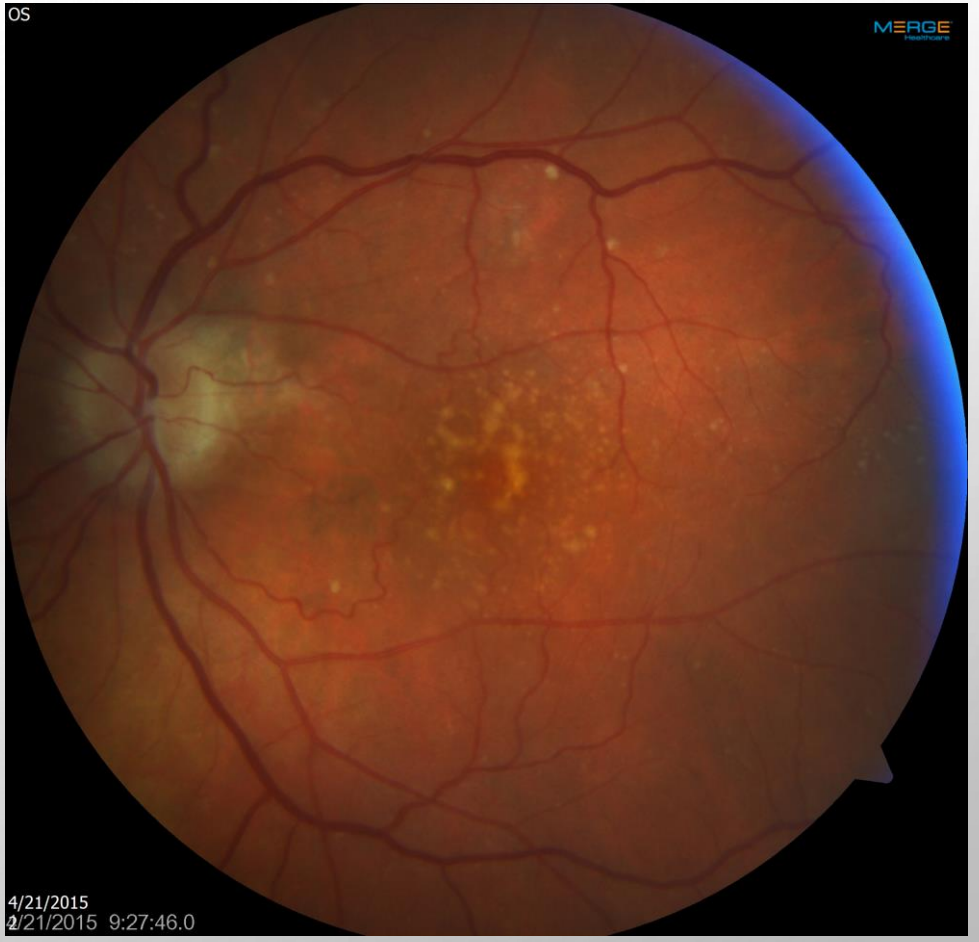
ERM too

2016

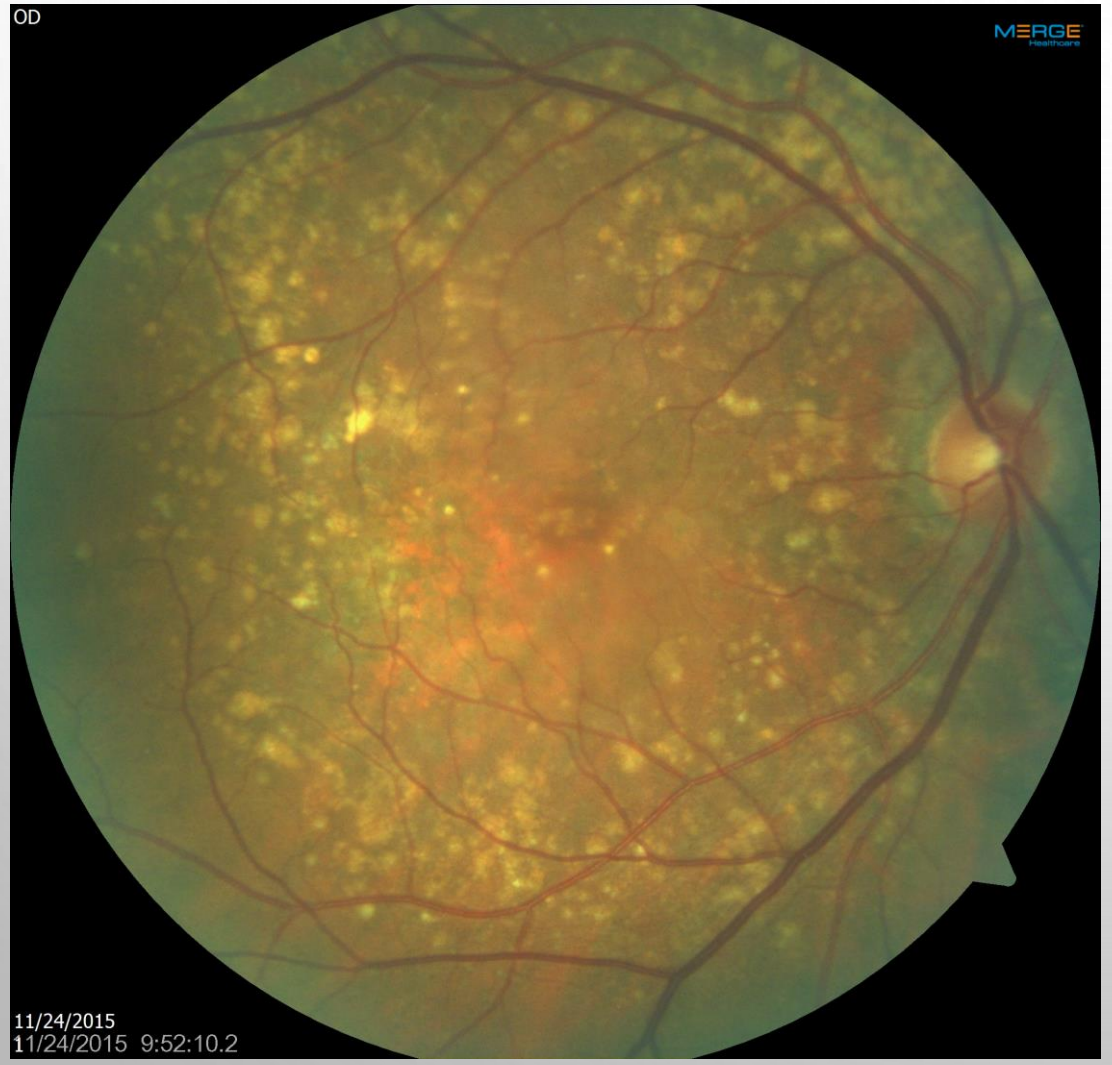


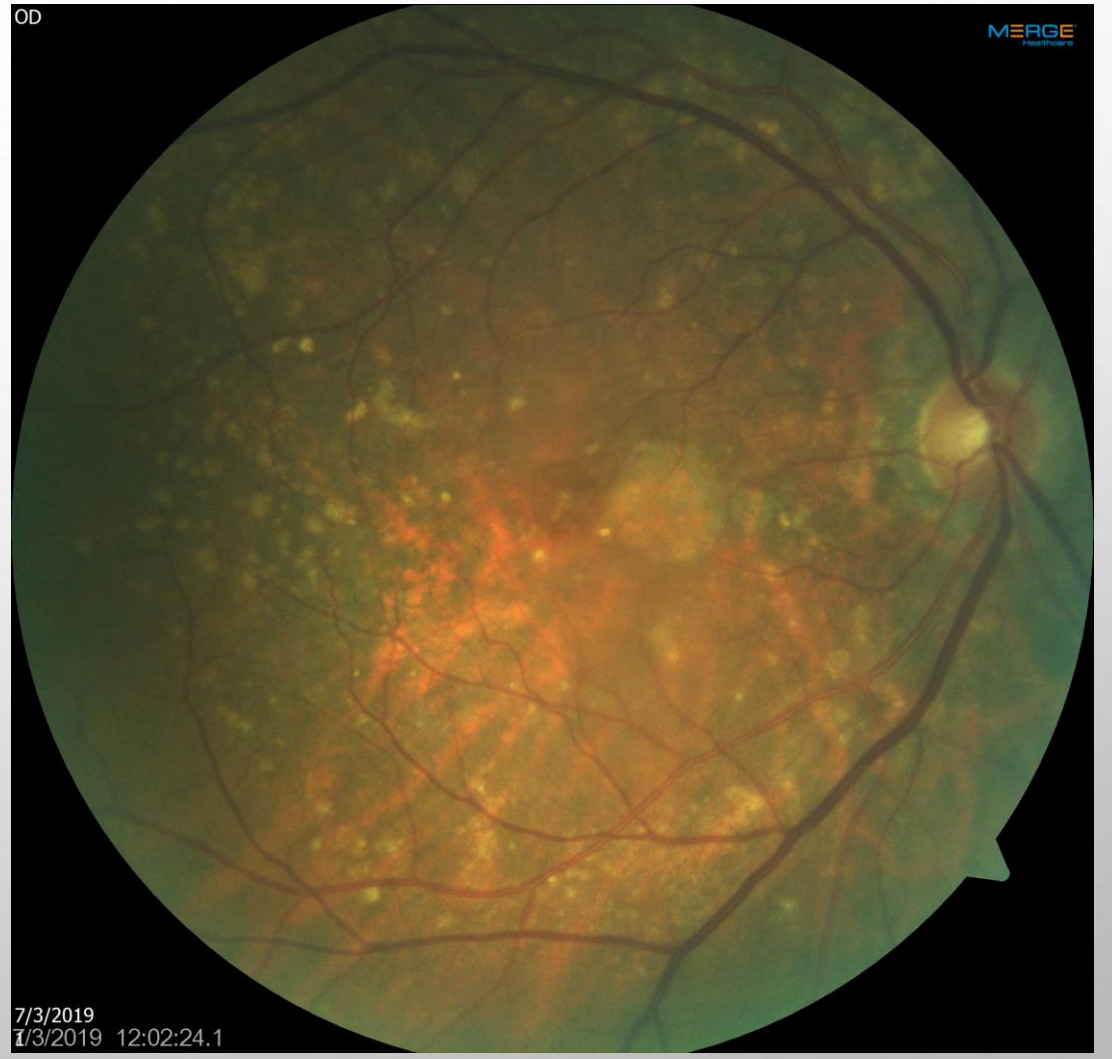
7) DRUSEN LOAD AND DRUSEN REGRESSION

- 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
- 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

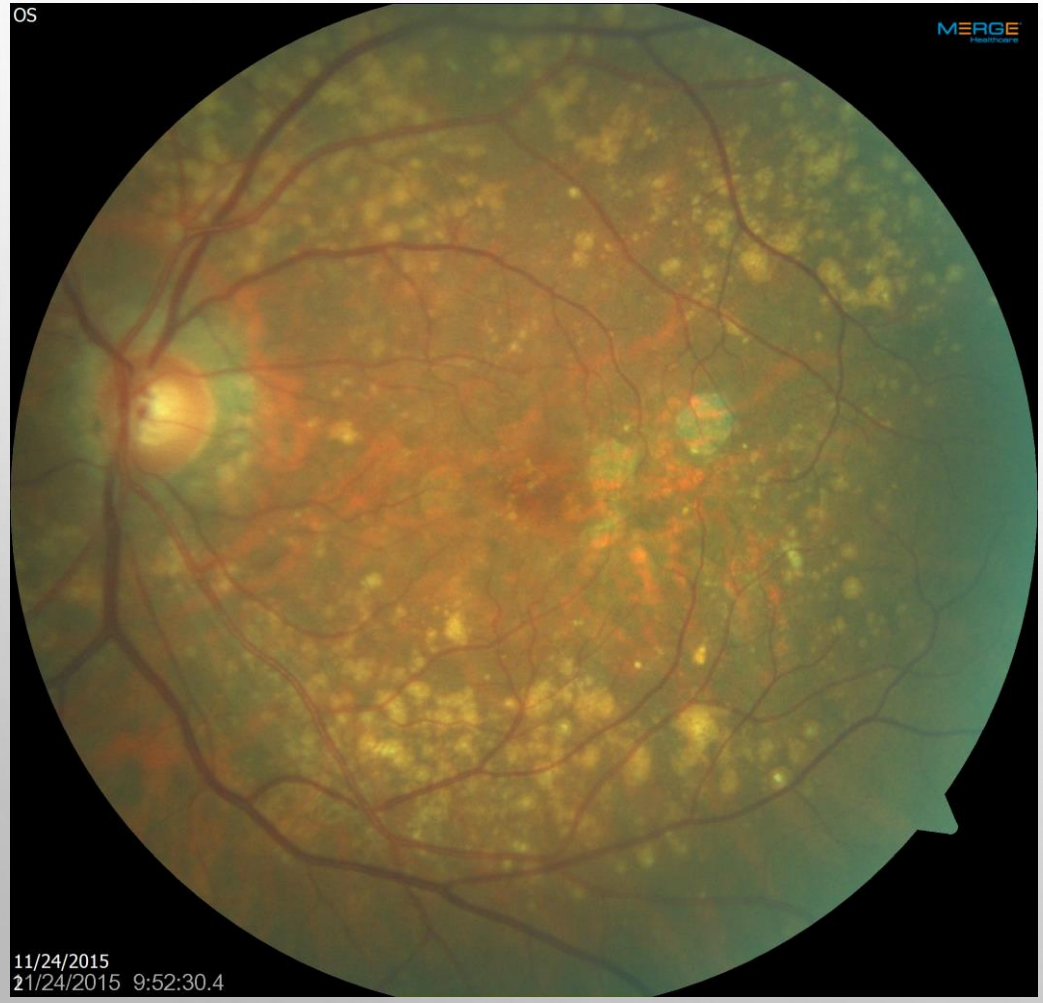


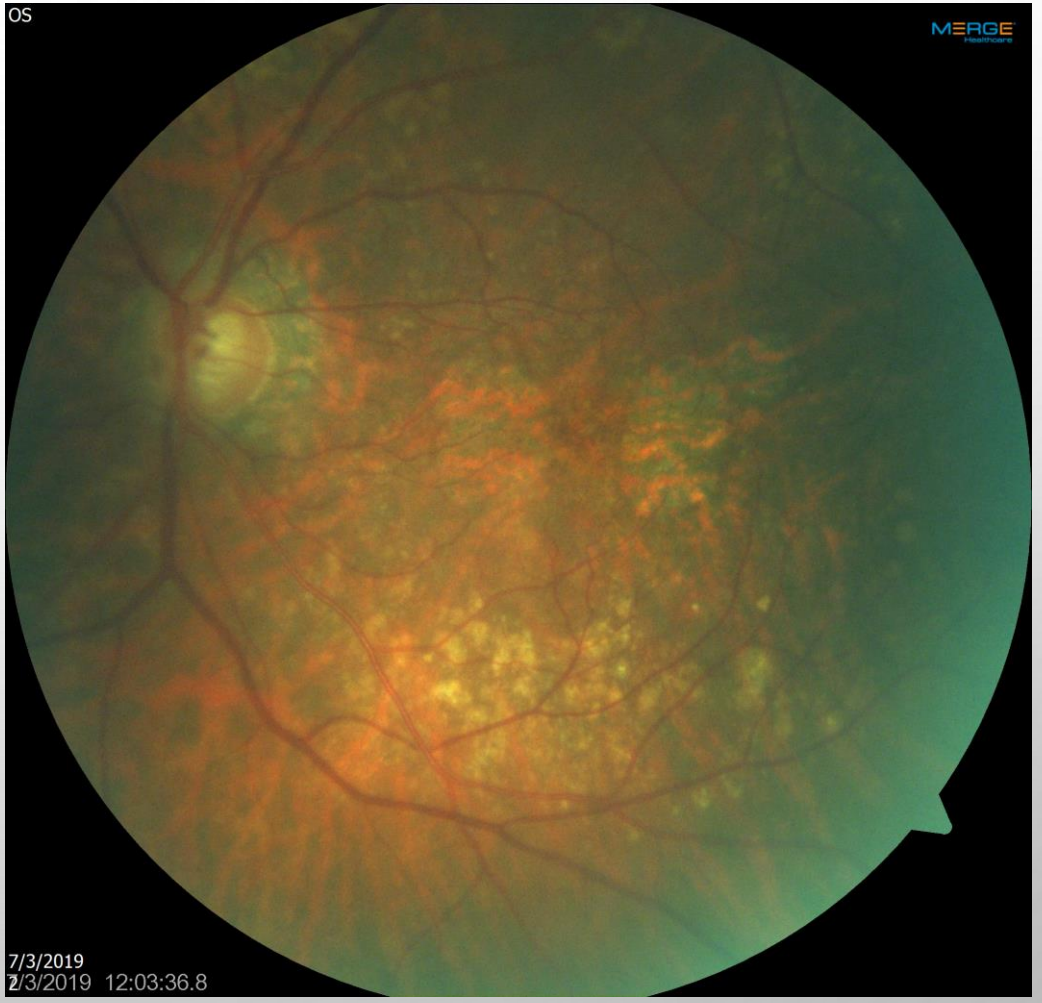
DRUSEN REGRESSION OD 2015-2019 WITH GA



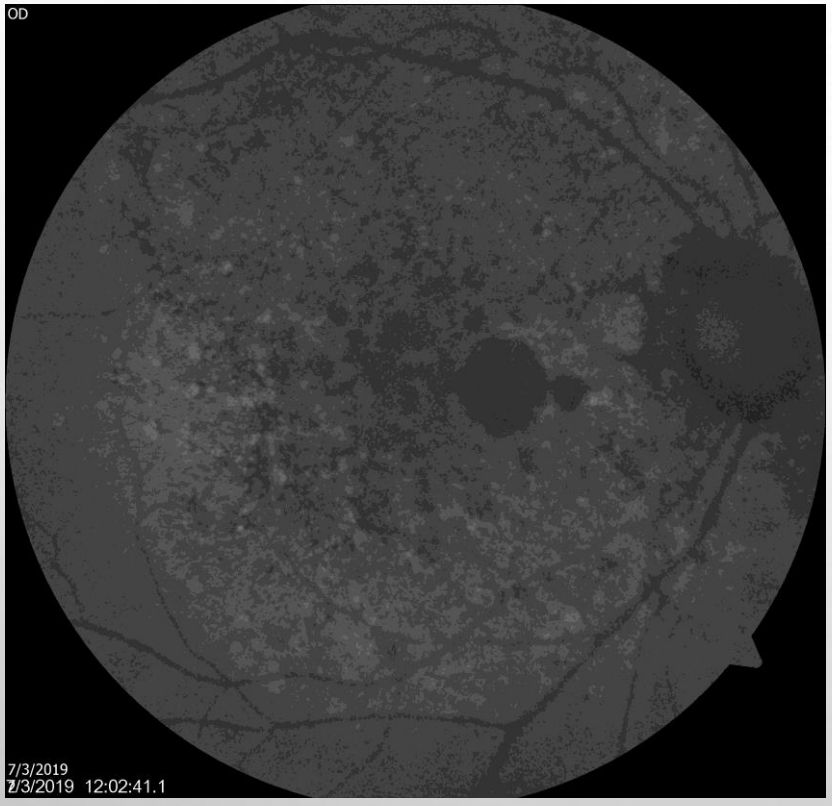


DRUSEN REGRESSION OS 2015-2019 WITH GA





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 HARBOUR TRIAL
- INCREASED CNV RISK WITH……..
- INCREASED CENTRAL DRUSEN VOLUME, CONFIRMING PREVIOUS FINDINGS
- INCREASED REFLECTIVITY OF DRUSEN
- FEMALE
- AGE (OF COURSE!)
- PRESENCE OF THE GENE VARIANT RS61941274 @ THE ACAD10 LOCUS