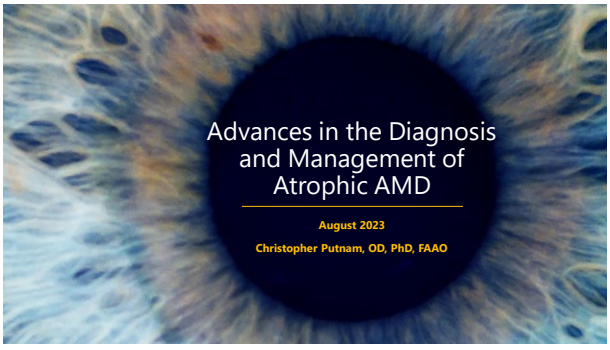
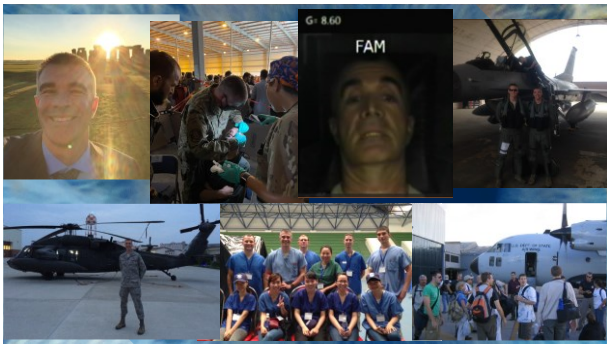

Advances in the Diagnosis and Management of Atrophic AMD
August 2023
Christopher Putnam, OD, PhD, FAAO

1


South Dakota State University
Pacific University Oregon
Department of the Air Force
University of Houston College of Optometry
UMSL Optometry University of Missouri–St. Louis

2


FAM

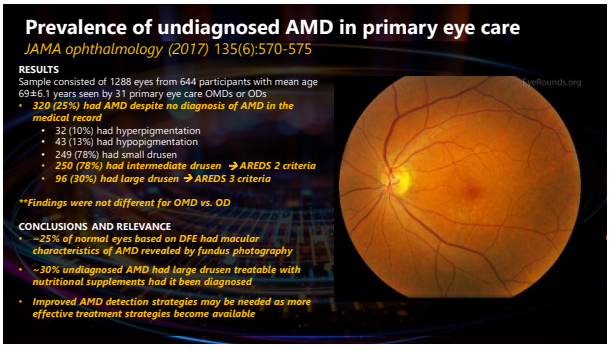
3


Humanitarian / Research / Operational Deployments

4


Clinical Retinopathy
Subclinical and Early Macular Degeneration
THERE'S A LOTTA BAD
DRIVERS OUT THERE

5


Prevalence of undiagnosed AMD in primary eye care
JAMA ophthalmology (2017) 135(6):570-575
RESULTS
Sample consisted of 1288 eyes from 644 participants with mean age 69±6.1 years seen by 31 primary eye care OMDs or ODs
320 (25%) had AMD despite no diagnosis of AMD in the medical record
32 (10%) had hyperpigmentation
43 (13%) had hypopigmentation
249 (78%) had small drusen
250 (78%) had intermediate drusen → AREDS 2 criteria
96 (30%) had large drusen → AREDS 3 criteria
**Findings were not different for OMD vs. OD
CONCLUSIONS AND RELEVANCE
~25% of normal eyes based on DFE had macular characteristics of AMD revealed by fundus photography
~30% undiagnosed AMD had large drusen treatable with nutritional supplements had it been diagnosed
Improved AMD detection strategies may be needed as more effective treatment strategies become available

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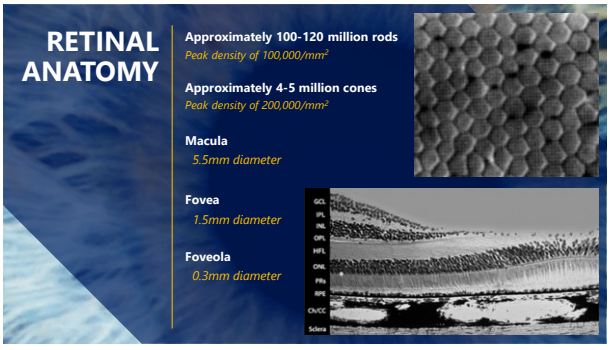
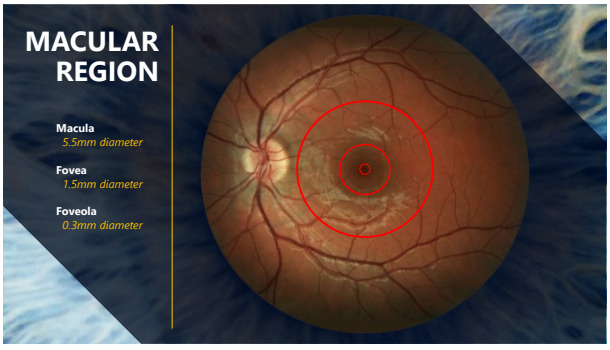

RETINAL ANATOMY
Approximately 100-120 million rods
Peak density of 100,000/mm²
Approximately 4-5 million cones
Peak density of 200,000/mm²
Macula
5.5mm diameter
Fovea
1.5mm diameter
Foveola
0.3mm diameter
GCL
IPL
INL
OPL
HFL
ONL
Ellp
RPE
Ch/CC
Sclera

10


MACULAR REGION
Macula
5.5mm diameter
Fovea
1.5mm diameter
Foveola
0.3mm diameter

11


THE RELATIVE SIZE
OF PARTICLES
HUMAN HAIR 50-180µm
FOR SCALE
FINE BEACH SAND 90µm
GRAIN OF SALT 60µm
WHITE BLOOD CELL 25µm
GRAIN OF POLLEN 15µm
DUST PARTICLE (PM10) <10µm
RED BLOOD CELL 7-8µm
RESPIRATORY DROPLETS 0.1-10µm
DUST PARTICLE (PM2.5) 2.5µm
BACTERIUM 1-3µm
WILDFIRE SMOKE 0.1-0.7µm
CORONAVIRUS 0.1-0.4µm
T4 BACTERIOPHAGE 0.225µm
ZIKA VIRUS 0.045µm
Pollen can trigger allergic reactions and hay fever—which 1 in 5 Americans experience every year.
The visibility limits for what the naked eye can see hovers around 10-40µm.
Respiratory droplets have the potential to carry smaller particles within them, such as dust or coronavirus.
Wildfire smoke can persist in the air for several days, and even months.

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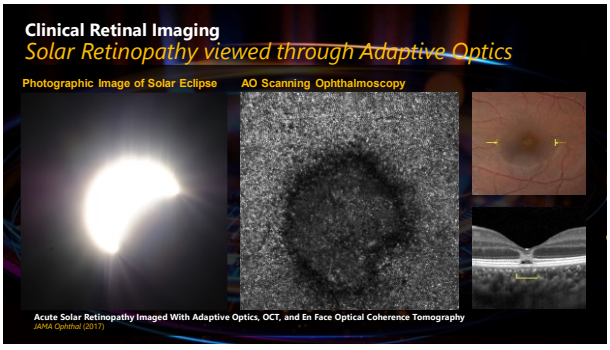
Clinical Retinal Imaging
Solar Retinopathy viewed through Adaptive Optics
Photographic Image of Solar Eclipse
AO Scanning Ophthalmoscopy
Acute Solar Retinopathy Imaged With Adaptive Optics, OCT, and En Face Optical Coherence Tomography
JAMA Ophthal (2017)

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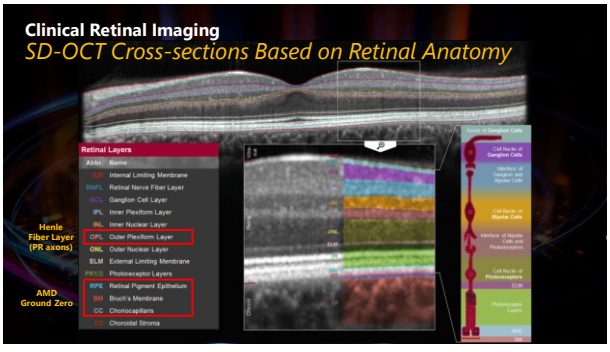
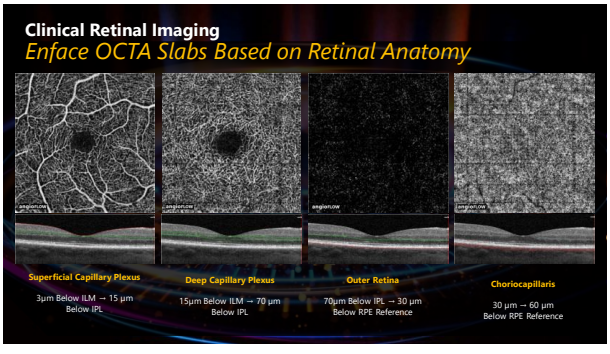

Clinical Retinal Imaging
SD-OCT Cross-sections Based on Retinal Anatomy
Retinal Layers
ILM Internal Limiting Membrane
RNFL Retinal Nerve Fiber Layer
GCL Ganglion Cell Layer
IPL Inner Plexiform Layer
INL Inner Nuclear Layer
OPL Outer Plexiform Layer
ONL Outer Nuclear Layer
ELM External Limiting Membrane
PR1/2 Photoreceptor Layers
RPE Retinal Pigment Epithelium
BM Bruch's Membrane
CC Choriocapillaris
CS Choroidal Stroma
Henle Fiber Layer (PR axons)
AMD Ground Zero

16


Clinical Retinal Imaging
Enface OCTA Slabs Based on Retinal Anatomy
Superficial Capillary Plexus
3μm Below ILM → 15 μm Below IPL
Deep Capillary Plexus
15μm Below ILM → 70 μm Below IPL
Outer Retina
70μm Below IPL → 30 μm Below RPE Reference
Choriocapillaris
30 μm → 60 μm Below RPE Reference

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Applying a Familiar Standard of Care
Side-by-Side Multifactorial Diseases

	Glaucoma		AMD
Structure	 C/D Ratio RNFL Macular GCC	→	 Drusen PIL (PR mitochondria) RPE / Bruch's Interface
Function	 Visual Field	→	 Dark Adaptation Contrast Sensitivity Color Sensitivity
Risk	Age / Race Family history / Genetic Risk Health and Lifestyle (Diabetes) Intraocular Pressure (IOP) Corneal Thickness / Hysteresis	→	Age / Race Family History / Genetic Risk Health and Lifestyle (Smoking) Macular Pigment Optical Density (MPOD) RPE Health / Choroidal Perfusion

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Age-Related Macular Degeneration

- Epidemiology
- Age Related Eye Disease Study Criterion

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Age Related Macular Degeneration
Epidemiology

25 Million Americans show clinical evidence of AMD
- 14% of patients over 55 ***(Age of enrollment for AREDS)***
- 25% of patients over 65
- 37% of patients over 75
- 66% of patients over 90
- 100% of patients over 100

55 Million Americans have clinical risk factors for AMD development
- Age
- Family History ***(Genetic Predisposition)***
- Ethnicity
- Smoking
- Cardiovascular Disease ***(Severe and Exudative AMD)***
- Obesity ***(Chronic Inflammation and Mitochondrial Dysfunction)***
- Sunlight Exposure*
- Diet low in fruits/vegetables ***(Carotenoids, Polyphenols and Ω-3 FAs)***

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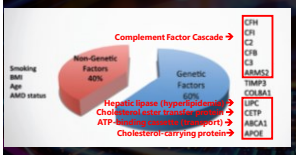
Age Related Macular Degeneration
Epidemiology



- Leading cause of blindness >55yrs in US
  - 2020 - 11 million have AMD findings
  - 2050 - 22 million (projected)
- ***More cases of AMD (~11M) than POAG (~2.7M) and DR (~4.8M) combined***
- Approximately 1 in 14 persons >40yrs has ***some degree of macular degeneration***
  - Affects 1 in 5 families
- Strongest genetic linkage of any major disease

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Age Related Macular Degeneration
Epidemiology

Genetic and environmental factors strongly influence risk, severity and progression of age-related macular degeneration

Signal Transduction and Targeted Therapy (2016) e16016; doi:10.1038/sigtrans.2016.

- **Genotyped 25 SNPs in 983 cases with advanced AMD and 271 cases with intermediate AMD**
- **Built AMD life-risk score model for assessment of progression from intermediate to advanced AMD**
- **Analyzed performance of prediction model for GA progression or choroidal neovascularization progression**

Lifetime Risk	7-Year Progression to GA Risk
1) CFH	*1) BMI*
2) BMI	*2) Smoking*
3) VEGFA	*3) ABCA1*
4) Smoking	*4) CETP*
5) C3	*5) CFI*
6) ARMS2	*6) CFH*
7) HTRA1	*7) VEGFA*
8) APOE	*8) ARMS2*

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Age Related Macular Degeneration
AREDS Criterion

FIRST EYE (Must have VA >20/32, no advanced AMD and no disqualifying lesions)				SECOND EYE
AMD Category	Drusen Size*	Drusen Area*	Pigment Abnormalities**	
1	None or <63um	<125um diameter	None	Same as 1st
2	<63um Or >63um, <125um None if pigment abnormalities	>125um diameter Or >1 druse	Absent or Present **WITHOUT** GA	Same as 1st or Category 1
3a	>63um, <125um Or >125um None if GA present	>360um diameter (if soft drusen present) >656um diameter (if soft drusen absent) Or At least 1 druse	Absent or Present **WITHOUT central** GA	Same as 1st or Category 1,2
4a	Category 1,2 or 3			Advanced AMD***

* ***Drusen*** or ***GA*** within 2DD of fovea

** Pigment abnormalities within 1DD of fovea

*** Advanced AMD is:
1) GA involving fovea
2) CNVM development

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Retinal Findings Related to Age-Related Macular Degeneration

- Microvascular Changes
- RPE Dysfunction
- Drusen Formation
- Geographic Atrophy

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Retinal Findings Related to Age-Related Macular Degeneration

Microvascular Changes

Quantitative analysis of inner retinal structural and microvascular alterations in intermediate AMD: SS-OCTA study

Photodiag and Photodynamic Therapy (2020) 32:102030

Methods

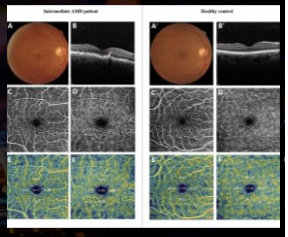
58 eyes of iAMD patients and 64 control eyes were enrolled. RNFL, GCL, IPL, INL, OPL thicknesses were analyzed in the central and parafoveal region. FAZ area and vessel density of the SCP and DCP in the fovea and parafoveal region were obtained

Results

- ***RNFL, GCL, and IPL were significantly thinner compared to controls***
- ***Parafoveal SCP vessel density significantly decreased compared to controls***
- ***GCC was significantly correlated with SCP vessel density measurements***

Conclusion

- ***Inner retina is affected in iAMD in terms of structural and microvascular components***
- ***Inner retinal thinning is significantly correlated with vessel density reduction suggesting a cause-and-effect relationship***



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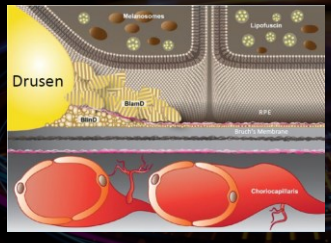
Retinal Findings Related to Age-Related Macular Degeneration

RPE Dysfunction



- Cholesterol accumulation leads to macular deposits
  - **BlamD (Basal laminar deposits)**
    - Between RPE and BM
    - Histopathologic drusen
  - **BlinD (Basal linear deposits)**
    - Within collagenous layer
    - Clinically-visible drusen
- Extracellular cholesterol deposits:
  - Impact PR health
  - Initiate inflammation
  - Create CNV predisposition
  - Limit retinol transport across Bruch's membrane

***** Leads to localized Vit A (retinol) deficiency and impaired dark adaptation***

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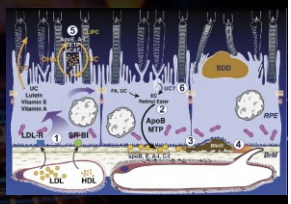
Retinal Findings Related to Age-Related Macular Degeneration
Drusen Formation

Soft Drusen in AMD: Biology and Targeting Via the Oil Spill Strategies
IOVS (2018) 59(4):160-181

- *Vascular-metabolic-inflammatory disease*
  - *Soft drusen/basal linear deposit (BLinD) and subretinal drusenoid deposit (SDD) confer risk of atrophy and neovascularization*
- *BLinD (cone-specific) and SDD (rod-specific) suggest exchange pathways*
  - *Outer retinal cells -> Bruch's membrane -> subretinal space*
- *BLinD is large apoB and apoE secreted by the RPE that offloads lipids creating atherosclerosis-like progression in the subRPE-basal lamina space*
  - *Soft drusen/BLinD impaire transport across Bruch's membrane-choriocapillary endothelium*



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Retinal Findings Related to Age-Related Macular Degeneration
Drusen Formation

- *Healthy Choriocapillaris, Bruch's, RPE and PR*

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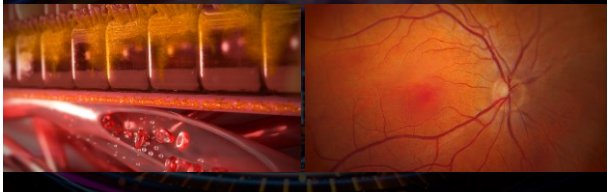
Retinal Findings Related to Age-Related Macular Degeneration
Drusen Formation

- *Cholesterol barrier deposited along Bruch's and RPE*

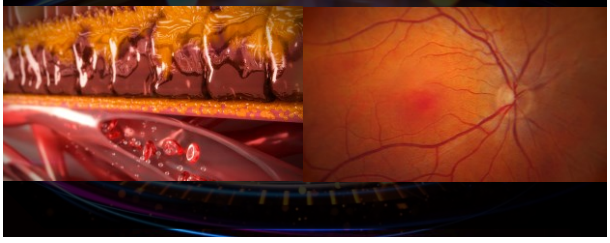


31

Retinal Findings Related to Age-Related Macular Degeneration

Drusen Formation

- *RPE continues to secrete cholesterol and degenerates*

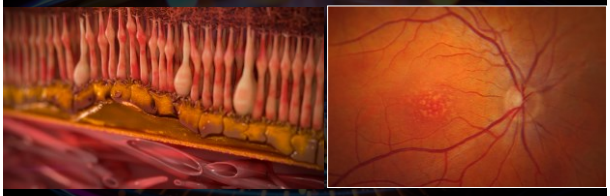


32

Retinal Findings Related to Age-Related Macular Degeneration

Drusen Formation

- *Visibly evident drusen on fundus evaluation*



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Retinal Findings Related to Age-Related Macular Degeneration

Geographic Atrophy

Natural history of GA progression secondary to AMD (GA Progression Study)

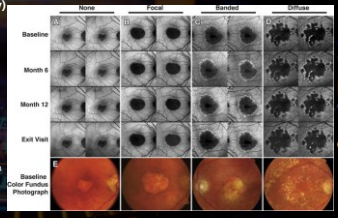
Ophthalmology (2018) *123*(2):361-368

- Mean change in lesion size from baseline to month 12 was significantly greater in:
  - ***Multifocal atrophic spots compared with unifocal spots***
  - ***Extrafoveal lesions compared with foveal lesions***
  - ***FAF and CFP were highly correlated***

Choriocapillaris Degeneration in GA

American Journal of Pathology (2019)

- Choriocapillaris loss was observed in early AMD with greater loss in GA even in areas of intact RPE.
  - ***Choriocapillaris changes are more prevalent in outer choroid in GA***
  - ***Choroidal microvascular degeneration contributes to atrophic AMD progression***



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Retinal Findings Related to Age-Related Macular Degeneration

*Early Onset Pathogenesis – **Take Home***

1. **Drusen are not markers for early stage AMD**
   - ***Visible structural evidence indicates pathogenesis underway for quite some time***
2. **Cholesterol deposits exist beneath the surface long before drusen form**
   - ***Cannot be seen with structure-based methods (…. but functional testing can ID)***
   - Cholesterol produced by RPE deposits into Bruch's membrane
3. **As cholesterol accumulates, outer retina compromise occurs as:**
   - Inflammation
   - Oxidative stress
   - Disruption of oxygen and nutrients transport
   - Drusen formation
4. **Impaired retinol (Vit A) across Bruch's membrane**
   - Functional impairment can occur to dark adaptation

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Age-Related Macular Degeneration Studies

- ***Eye Disease Case Control Study (EDCC)***
- ***Age-Related Eye Disease Study (AREDS)***
- Lutein Antioxidant Supplement Trial (LAST)
- Carotenoids in Age-Related Eye Disease Study (CAREDS)
- Lutein Xanthophyll Eye Accumulation (LUXEA)
- Taurine, Omega-3, Zinc, Antioxidant and Lutein (TOZAL)
- ***Age-Related Eye Disease Study II (AREDS2)***
- Carotenoids in Age-Related Eye Disease Study II (CAREDS2)
- Lutein for Vision in Albinism (LUVIA)
- Maculopathy Optic Nerve Nutrition Neurovascular/Heart Disease study (MONTRACHET)
- Lutein Influence on Macula of Persons Issued from AMD Parents study (LIMPIA)
- ***Dietary Flavonoids and 15-year Incidence of AMD****

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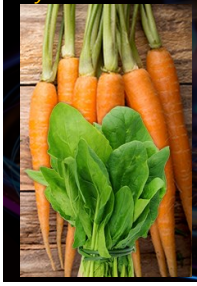
Age Related Macular Degeneration Studies

Eye Disease Case Control (1994)



Design:
- 356 subjects (ages 55-80) with advanced AMD within 1-yr of enrollment
  520 control subjects
  ** Frequency matched to cases of same age and sex **

Methods:
- Multiple Regression analysis controlled for smoking and other risk factors

Results:
- Highest quintile dietary intake of carotenoids (specifically L and Z) showed 43% lower risk than lowest quintile in the development of advanced AMD

***INTERESTING NOTE: Vit A, Vit C and Vit E showed NO significant relationship to AMD development**

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Age Related Macular Degeneration Studies

Age Related Eye Disease Study (AREDS) [2001]

Design:
5-year longitudinal, randomized, placebo-controlled study

Methods:
3640 subjects were divided into 4 groups:
1) antioxidants+ zinc
2) antioxidants ONLY
3) zinc ONLY
4) placebo

Results:
- AREDS formulation reduced advanced AMD rate by 25% over a 5-year period
- AREDS formulation ***DID NOT*** show prevention of early signs of AMD

AREDS formula:
Vit A (15mg) / Vit C (500mg) / Vit E (400IU) / zinc (80mg) / copper (2mg)

***** 20-year results still support antioxidant + zinc formulation*****

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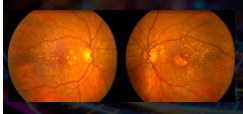
Age Related Macular Degeneration Studies

Age Related Eye Disease Study II (AREDS2) [2013]

Design:
6 year longitudinal, placebo-controlled study released in May 2013



Methods:
4203 men and women ages 50-85 were divided into 4 groups:
1) 10mg L and 2mg Z + AREDS
2) 350mg DHA and 650mg EPA + AREDS
3) 10mg L and 2mg Z and 350mg DHA and 650mg EPA + AREDS
4) control (AREDS formulation only) ****No true placebo group****

All participants were offered:
- Original AREDS formula (Standard of Care)
- Variation of the AREDS formulation (former smokers)

In contrast to AREDS, AREDS II subjects were previously diagnosed with moderate to advanced AMD

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Age Related Macular Degeneration Studies

Age Related Eye Disease Study II (AREDS2) [2013]

Results:

L/Z plus AREDS formula:
- Reduced progression to advanced AMD 10% over AREDS formulation alone in total cohort
  - ✓ ***L/Z substitution for β-carotene resulted in a 18% risk reduction of advanced AMD within 5 years***
- Reduced progression to nvAMD by 11% of AREDS formulation alone in total cohort
  - ✓ **Reduced progression to nvAMD by 26% in subjects with lowest intake of L/Z**
  - ✓ ***L/Z substitution for β-carotene resulted in a 22% risk reduction of nvAMD within 5 years***
- ***NO*** **apparent effect of β-carotene elimination or reduction of zinc to 25mg**

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Age Related Macular Degeneration Studies

Dietary Flavonoids and 15-yr Prevalence of AMD [2018]

Dietary flavonoids and the prevalence and 15-year incidence of age-related macular degeneration

Am J Clin Nutrition (2018) 108.2:381-387

Design

- 2856 adults aged ≥49 y at baseline and 2037 followed up 15 years later were included in prevalence and incidence analyses. Dietary intake was assessed by using a semi-quantitative FFQ and AMD was assessed from retinal photographs using AREDS criterion

Results

- Each 1-SD increase in total flavonoid, flavonol and flavanone intake was associated with a reduced prevalence of AMD ***[OR: 0.75]***

Conclusions

- ***Independent and protective association between dietary intake of flavonoids and the reduced likelihood of developing AMD***

	Adjusted OR (95% CI)[2]		
Flavonoids, mg/d	Any AMD (n=177)	Early AMD (n=130)	Late AMD (n=47)
All flavonoids			
First quartile (≤410.6)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Second quartile (412.4–881.5)	0.63 (0.31, 1.29)	0.51 (0.23, 1.14)	1.37 (0.31, 6.13)
Third quartile (881.6–1232.3)	0.62 (0.31, 1.24)	0.63 (0.30, 1.32)	0.60 (0.11, 3.10)
Fourth quartile (≥1232.4)	0.52 (0.25, 1.06)	0.52 (0.24, 1.12)	0.45 (0.08, 2.60)

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Why not use anti-oxidant therapy on every high-risk AMD patient?

Age-Related Macular Degeneration Studies

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- ***Dietary Flavonoids and 15-year Incidence of AMD****

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Zinc Daily Dosage

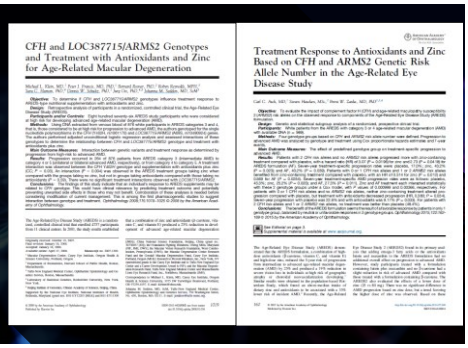
Upper Limit: 40mg

RDA: ~10mg

High doses associated with:

- ***Prostate hypertrophy***
- ***Genitourinary complications***

- **Food and Nutrition Board of the Institute of Medicine (2020)**



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

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

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Age Related Macular Degeneration Studies
Journal of Vitreo-Retinal Disease (2017)

Methods:
- Genetic risk and antioxidant treatment were analyzed as independent and interacting risk factors for development of iAMD in 554 AREDS individuals
- Genetic risk was determined using an allele dosage model based on the total number of CFH and ARMS2 risk alleles.

Conclusion:
Antioxidant treatment has little to no impact on the development of iAMD in patients without AMD and may reduce the risk of developing iAMD in patients with high genetic risk

- ***Antioxidant treatment may increase the risk of developing iAMD in patients with low genetic risk***
  - ***i.e: Absence of both CFH and ARMS2 alleles***
- ***Genotype-directed antioxidant treatment of patients without AMD may ultimately lead to fewer cases of advanced AMD***

Progression From No AMD to Intermediate AMD as Influenced by Antioxidant Treatment and Genetic Risk: An Analysis of Data From the Age-Related Eye Disease Study Cataract Trial

48

Age Related Macular Degeneration Studies
Ophthalmology (2018)

METHODS
- Team 1
  - Focused on data concordance between conflicting studies
- Team 2
  - Focused on replicating the key claim of an interaction between genotype and treatment
- Team 3
  - "Blank slate" approach in attempting to find baseline predictors of treatment response

RESULTS
- Evidence confirmed that higher risk patients had more to gain from treatment, unable to replicate any genotype treatment interactions after adjusting for multiple testing
- ***Did not find evidence to support the claim that supplementation leads to a large increase in the risk of advanced AMD in some genotype subgroups.***

HHS Public Access

Genetic polymorphisms of CFH and ARMS2 do not predict response to antioxidants and zinc in patients with age-related macular degeneration: independent statistical evaluations of data from the Age-Related Eye Disease Study

49

(Sub)Clinical Retinal Imaging

- Macular Pigment Optical Density
- *En Face* Swept Source OCT
- Dark Adaptometry
  - AdaptDx
- Preferential Hyperacuity Perimetry
  - Foresee

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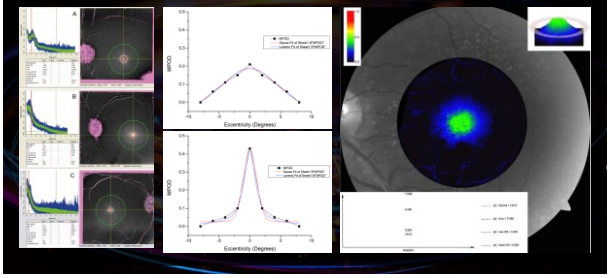
Clinical Retinal Imaging
Macular Pigment Optical Density



51

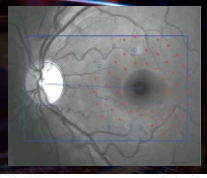
Clinical Retinal Imaging
Macular Pigment Optical Density

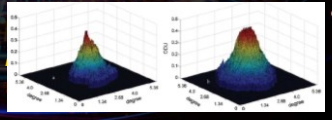
Simple and objective method for routine detection of macular pigment
J Biomed Optics (Nov 2010)

Methods
1-λ reflectometry vs. 2-λ FAF Visucam NM/FA (Zeiss Meditec) vs. Spectralis HRA+OCT Multicolor (Heidelberg)

Conclusion
Strong correlation (R^2=0.86) of the 1-λ and 2- λ FAF method in MPOD measurements of normal and AMD patients both with pseudophakic eyes and eyes with a crystalline lens.

- ***Despite the high individual variability, the MPOD was significantly lower in atrophic AMD than in age-matched healthy subjects***
- ***Supplementation by L, MZ and Z may be subjects with a FHx of AMD***





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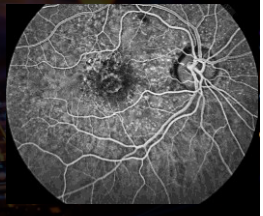
Clinical Retinal Imaging
En Face Optical Coherence Tomography

Multimodal Imaging and *En Face* OCT Detection of Calcified Drusen in Eyes with AMD
American Journal of Ophthalmology (2020) 212: 7-16.

Results
220 eyes with nonexudative AMD were studied with 43% of eyes containing calcified drusen either at baseline or during follow-up visits

- On the *en face* SS OCT images, calcified drusen appeared as dark focal lesions that were detected in the choroid using a sub–RPE slab
- Lesions were associated with significant attenuation of the overlying retina and the corresponding FAF images showed hypoautofluorescence at the location of these lesions
- Lesions indicated complete RPE and outer retinal atrophy

Conclusions
En face OCT imaging is a useful method for the detection and monitoring of calcified drusen and can be used to document the evolution of these drusen



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Clinical Retinal Imaging
Dark Adaptometry (Adapt Dx)

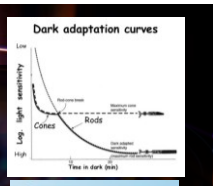
Diagnostic Sensitivity and Specificity of Dark Adaptometry Detection of AMD

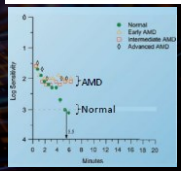
IOVS (2014) 55(3):1427-1431

- Multisite study of 127 AMD patients and 21 normal adults
- Clinical diagnosis confirmed by retina specialist grading fundus photographs

Patients classified as having AMD if dark adaptation >6.5 minutes
- **91% sensitivity**: confirmed AMD cases
- **91% specificity**: confirmed normal cases

Comparisons:
- HVF testing in glaucoma diagnosis:
  - 83% sensitive
  - 95% specific
- SLE diagnosis of AMD by retina specialists:
  - 82% sensitive
  - 91% specific





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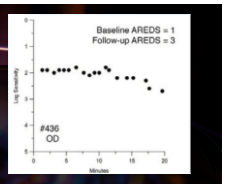
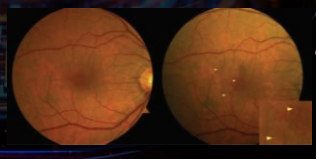
Clinical Retinal Imaging
Dark Adaptometry (Adapt Dx)

Delayed Rod-Mediated Dark Adaptation as Functional Biomarker for Incident Early AMD

Ophthal (2016) 123(2):344-351

- Study sample of 325 adults without clinically detectable AMD
- Baseline testing showed impaired dark adaptation in 24% of subjects
- AMD status determined at 3-year F/U visit
  - Impaired dark adaptation:
    - ***2X more likely to develop clinically evident AMD***
    - ***8X more likely to reach intermediate AMD***





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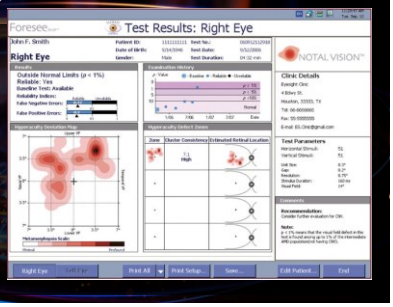
Clinical Retinal Imaging
Foresee



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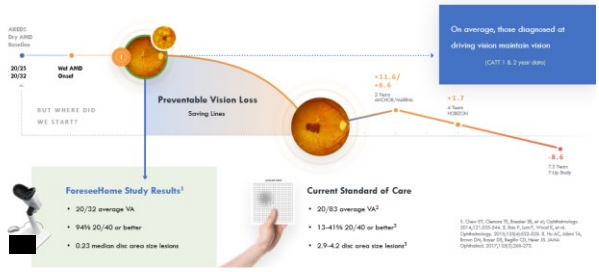
Readjusting our point of view to preventable vision loss



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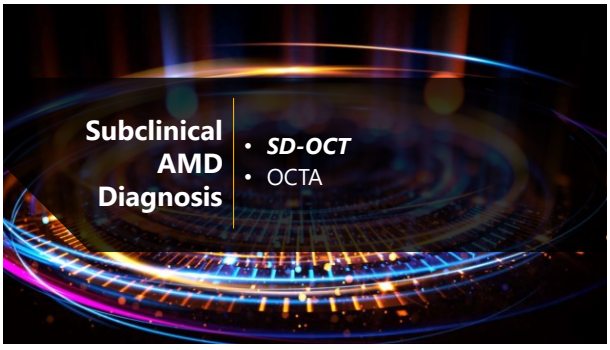

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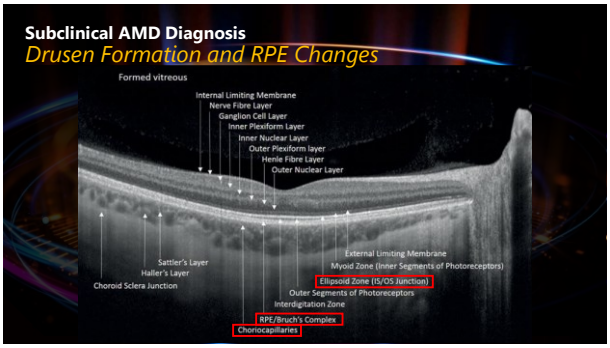

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Subclinical AMD Diagnosis
Clinical Predictors of Advanced AMD Progression

- Visual loss (BCVA and CS)
- Reticular pseudodrusen
- ***Drusen load***
- ***Hyper-reflective foci***
- ***RPE hypo-reflectance***
  - ***Nascent geographic atrophy***
- ***Sub-RPE hyper-reflective columns***

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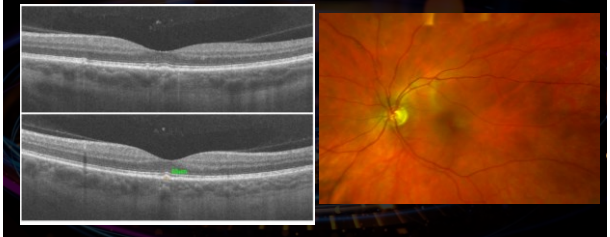
Subclinical AMD Diagnosis
SD-OCT Drusen Identification and Measurement



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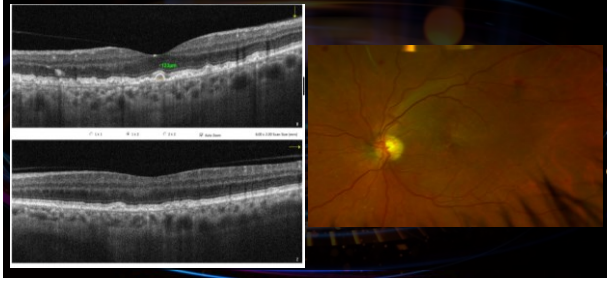
Subclinical AMD Diagnosis
SD-OCT Drusen Identification and Measurement



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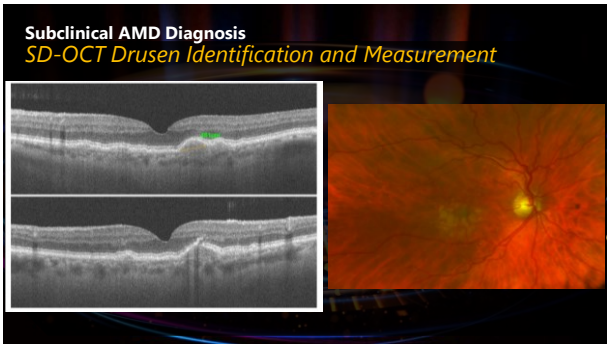
Subclinical AMD Diagnosis
SD-OCT Drusen Identification and Measurement

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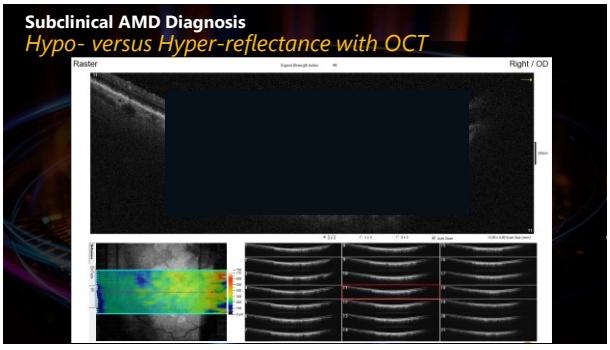
Subclinical AMD Diagnosis
Hypo- versus Hyper-reflectance with OCT
Raster
Right / OD

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Subclinical AMD Diagnosis
SD-OCT
OCTA

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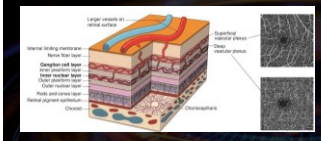
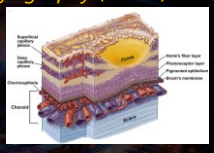
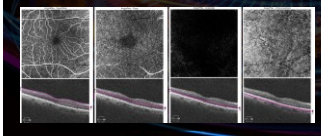
Subclinical AMD Diagnosis

Optical Coherence Tomography Angiography (OCTA)







Superficial capillary plexus (SCP)
Within NFL and GCL at the same level as the arterioles and major venules

Deep capillary plexus (DCP)
Between the INL and the OPL

Avascular outer retina
Comprises the ONL and PR nuclear layer and photoreceptors.
normally avascular where any apparent flow is a projection artifact or results from* ***pathology*

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Subclinical AMD Diagnosis

Optical Coherence Tomography Angiography

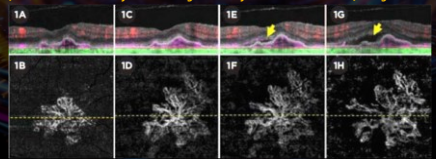
OCTA studies showing early neovascular changes in atrophic AMD

American Academy of Ophthalmology EyeNet (2018)

Methods:
Prospective monitoring of 160 eyes with intermediate AMD or GA with exudative AMD in the fellow eye

- ***Baseline: 15% of atrophic AMD eyes showed subclinical macular neovascularization***
- ***1-year: 24% of eyes with subclinical macular neovascularization developed exudative disease***

Conclusion:
Relative risk of exudative disease at 1 year was 15X greater in eyes with subclinical NV findings



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Subclinical AMD Diagnosis

Optical Coherence Tomography Angiography

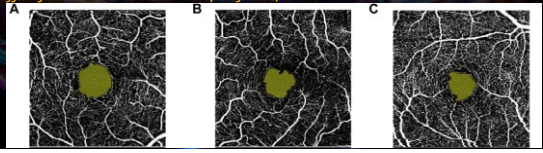
Retinal vessel density in exudative and nonexudative AMD on OCTA

American Journal of Ophthalmology (2020) 212:7-16

Results

- In eyes with AMD, vessel density (VD) decreases with age in the foveal, parafoveal and full macular regions
- Exudative AMD demonstrated lower VD especially in the parafoveal (30%±6% vs 33%±6%, and full regions (28%±6% vs 31%±6%) compared with atrophic AMD

Conclusion
Retinal VD is decreased in eyes with exudative AMD compared with atrophic AMD but is unaffected by anti-VEGF treatments suggesting a retinal vascular contribution to the pathogenesis of AMD.



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Subclinical AMD Diagnosis

Choroidal Neovascularization (CNV)

- **Type 1 – Occult**
  - New vessels develop in the choroid located BELOW RPE and ABOVE Bruch's
- **Type 2- Classic**
  - New vessels develop in choroid located ABOVE RPE and ABOVE Bruch's
- **Type 3- RAP (Retinal Angiomatous Proliferation)**
- **Type 4- Mixed**

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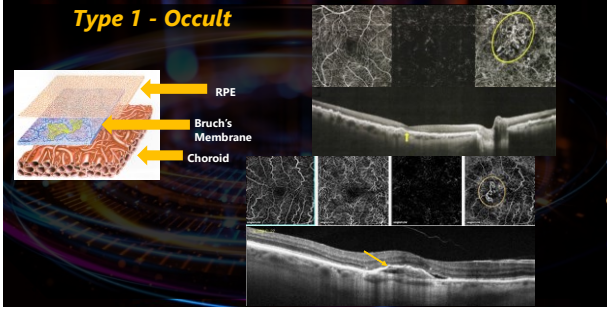
Choroidal Neovascularization (CNV)

Type 1 - Occult



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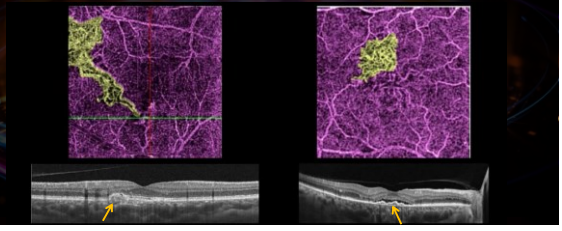
Choroidal Neovascularization (CNV)

Type 1 – Occult

- ***Below RPE***
- ***Wider than Type 2***
- ***Avascular Zone Typically Not Involved***



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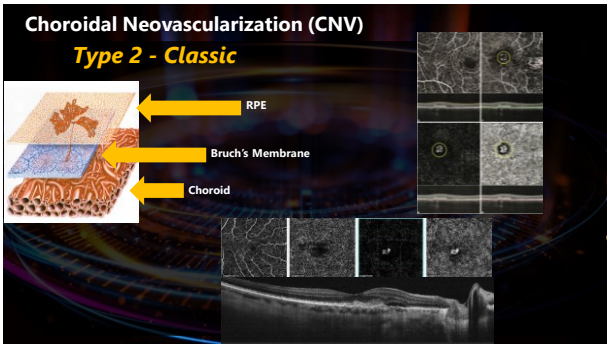
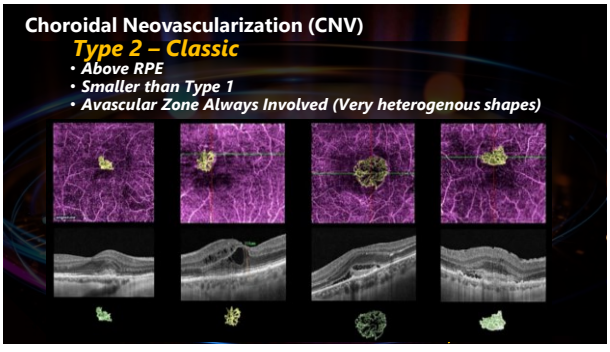

Choroidal Neovascularization (CNV)
Type 2 - Classic
RPE
Bruch's Membrane
Choroid

85


Choroidal Neovascularization (CNV)
Type 2 – Classic
• Above RPE
• Smaller than Type 1
• Avascular Zone Always Involved (Very heterogenous shapes)

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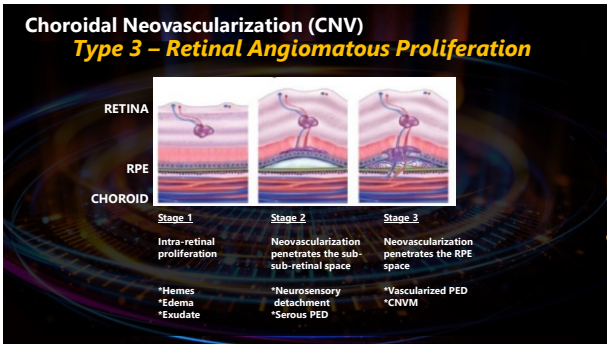
Choroidal Neovascularization (CNV)
Type 3 – Retinal Angiomatous Proliferation
RETINA
RPE
CHOROID
Stage 1
Intra-retinal proliferation
*Hemes
*Edema
*Exudate
Stage 2
Neovascularization penetrates the sub-sub-retinal space
*Neurosensory detachment
*Serous PED
Stage 3
Neovascularization penetrates the RPE space
*Vascularized PED
*CNVM

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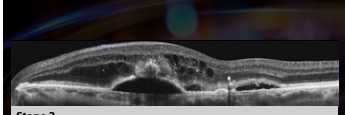
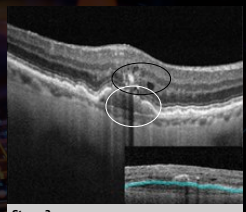
Choroidal Neovascularization (CNV)

Type 3 – Retinal Angiomatous Proliferation

- ***Intraretinal proliferation followed by sub-RPE penetration***



Stage 2
- Hyper-reflective lesion above PED
- Intraretinal cysts
- Serous PED / Neurosensory detachment



Stage 3
- Anastomosis through RPE
- Neovascular PED with CNVM formation

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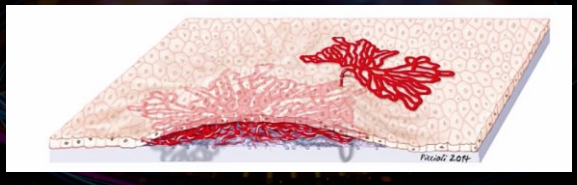
Choroidal Neovascularization (CNV)

Type 4 – Mixed Sub-Retinal and Sub-RPE

- Two or more CNV layers affected
- One above the RPE, one below the RPE
- High flow lesions



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Choroidal Neovascularization (CNV)

Type 4 – Mixed Sub-Retinal and Sub-RPE

Angio - Deep | Angio - Outer Retina | Angio - Choroid Capillary

Initially located below RPE then NV spreads into outer-retina

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Treatments for Choroidal Neovascularization (CNV)

- **Current Anti-VEGF treatments**
  - *Bevacizumab (Avastin)*
    - Humanized full length monoclonal antibody
    - AMD
  - *Ranibizumab (Lucentis)*
    - Humanized monoclonal antibody fragment
    - AMD, DME, DR, RVO
  - *Pegaptanib (Macugen)*
    - RNA aptamer
    - AMD
  - *Aflibercept (Eylea)*
    - Fusion protein
    - AMD, DME, DR
  - *Brolucizumab-dbll (Beovu)*
    - Humanized single-chain antibody fragment
    - Up to 3 months dosing intervals, most are 4-6 weeks
      - 50% remained 3-month intervals after 1 year

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Clinical Treatments Related to Atrophic Age-Related Macular Degeneration

- Systemic Disease Management
- Photobiomodulation (PBM)
- Nutraceuticals

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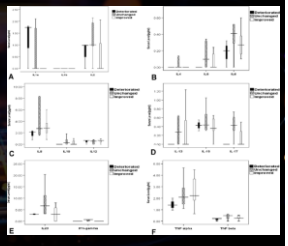
Clinical Treatment

Systemic Disease Management

Serum cytokines as biomarkers for age-related macular degeneration

Clin Exp Ophthal (2015) 253(5), 699-704

- Serum samples from 30 AMD patients and 15 age-matched controls identified elevation of 7 discrete ILs
- **AMD is ultimately an inflammatory disease and cytokines may be used as easy-to-obtain risk biomarkers**



Early AMD with Cardiovascular and Renal Comorbidities: NHANES 2005–2008

Ophthal epidemiology (2017) 24(6), 413-419.

- Age-adjusted OR for having early AMD was 2.6 for any type of heart disease (AP, CHD, MI, CHF, CKD)
- **Strongest association (OR=6.3) was combination of heart disease and stroke.**

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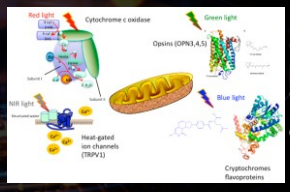
Clinical Treatment
Photobiomodulation (PBM)

- Exposure to low-intensity visible to NIR (500-1000 nm) allows for high tissue penetration and offers a non-invasive approach for the treatment of atrophic AMD
- NIR enhances the mitochondrial cytochrome C oxidase activity and retinal ATP production leading to a reduction of free radical production and oxidative damage
- Mitochondrial cytochrome C oxidase acts as a photo-acceptor for resulting in the enzymatic oxidation reduction
- Reduces gene protein expression of outer retinal stress and inflammatory markers



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Clinical Treatment
LumiThera (PBM)

LIGHTSITE II Randomized Multicenter Trial: Evaluation of Multiwavelength PBM in Non-exudative AMD

Ophthal Therapy (2023) *12*(2):953-968

Methods

Multicenter LIGHTSITE II study was a randomized clinical trial evaluating safety and efficacy of PBM in intermediate non-exudative AMD. LumiThera Valeda® Light Delivery System delivered multiwavelength PBM (590, 660 and 850 nm) 3X per week over 3–4 weeks (9 treatments per series)

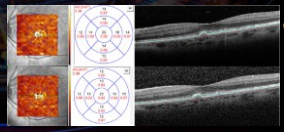
Results

LIGHTSITE II enrolled 44 non-exudative AMD subjects.

- ***PBM-treated eyes showed statistically significant BCVA improvement at 9-mos with 4-letter gain for patients receiving all 27 treatments***
- ***35% of PBM-treated eyes showed ≥ 5-letter improvement at 9 months***
- ***Macular drusen volume remained stable in PBM-treated group but did show increases in the sham-treated group***
- ***20% less GA lesion growth in the PBM group over 10-mos***

Conclusion

Results confirm previous clinical testing of multiwavelength PBM and support treatment as a potential treatment for non-exudative AMD



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Nutraceuticals Related to Atrophic AMD

- Oral Supplementation
  - Polyphenols
    - Flavonoids
    - Non-Flavonoids
  - Carotenoids
    - Xanthophylls

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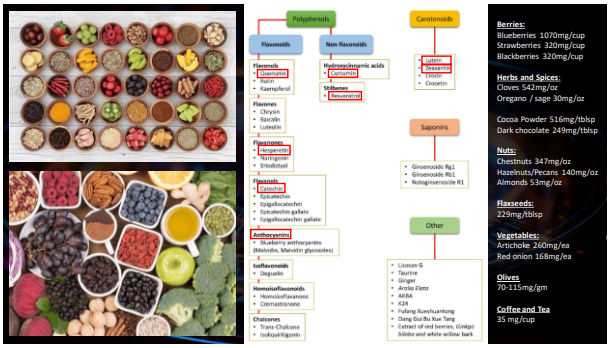

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Dietary flavonoids and the prevalence and 15-year incidence of age-related macular degeneration.

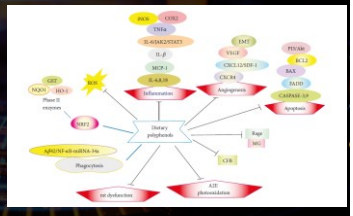
Am J Clin Nutrition (2018) 108.2:381-387

Results

- Each 1-SD increase in total flavonoid intake was associated with a reduced AMD incidence **[OR: 0.76]**
- Each 1-SD increase in total flavonols intake was associated with reduced AMD prevalence **[OR: 0.75]**
- Each 1-SD increase in total flavanones was associated with reduced prevalence of any AMD **[OR: 0.77]**

Conclusions

- ***Independent and protective association between dietary intake of flavonoids and the reduced likelihood of developing AMD***



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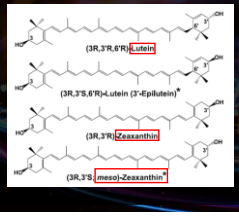
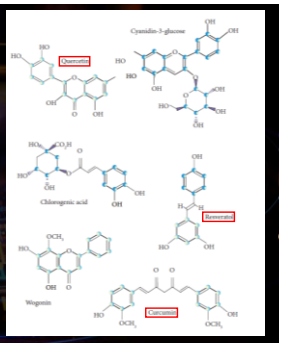
Retinal nutraceuticals share a common thread....





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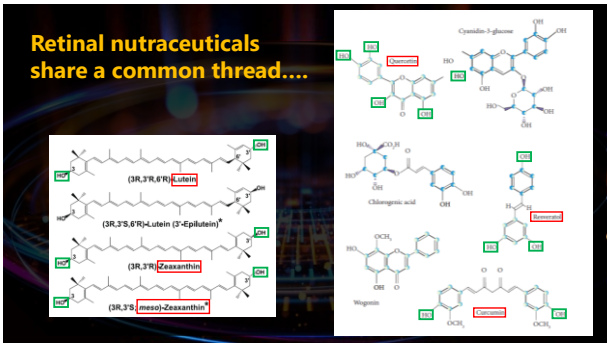
Retinal nutraceuticals share a common thread....
(3R,3'R,6'R)-Lutein
(3R,3'S,6'R)-Lutein (3'-Epilutein)*
(3R,3'R)-Zeaxanthin
(3R,3'S,meso)-Zeaxanthin*
Quercetin
Cyanidin-3-glucose
Chlorogenic acid
Resveratrol
Wogonin
Curcumin

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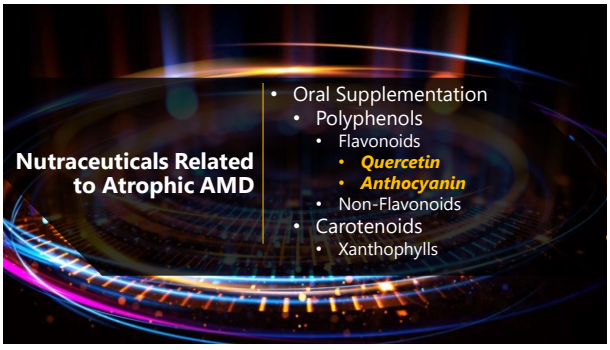
Nutraceuticals Related to Atrophic AMD
Oral Supplementation
Polyphenols
Flavonoids
Quercetin
Anthocyanin
Non-Flavonoids
Carotenoids
Xanthophylls

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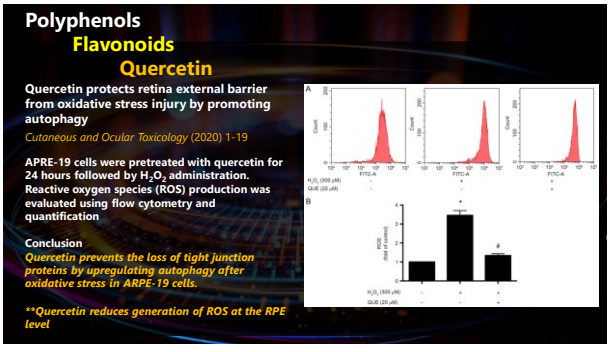
Polyphenols
Flavonoids
Quercetin
Quercetin protects retina external barrier from oxidative stress injury by promoting autophagy
Cutaneous and Ocular Toxicology (2020) 1-19
APRE-19 cells were pretreated with quercetin for 24 hours followed by H2O2 administration. Reactive oxygen species (ROS) production was evaluated using flow cytometry and quantification
Conclusion
Quercetin prevents the loss of tight junction proteins by upregulating autophagy after oxidative stress in ARPE-19 cells.
**Quercetin reduces generation of ROS at the RPE level

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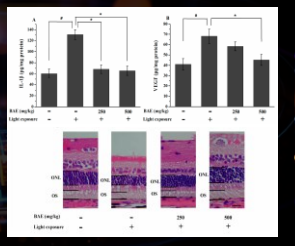
Polyphenols
Flavonoids
Anthocyanins

Retinoprotective Effects of Anthocyanins via Anti-Inflammatory and Anti-Apoptotic Mechanisms in a Visible Light-Induced Retinal Degeneration Model
Molecules (2015) 20:22395–22410



Results
Anthocyanins exhibited protective effects:
- ***Increasing antioxidant defense mechanisms***
- ***Suppressing lipid peroxidation and***
- ***Downregulating proinflammatory cytokines***
- ***Inhibiting retinal cells apoptosis***

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Nutraceuticals Related to Atrophic AMD

- Oral Supplementation
  - Polyphenols
    - Flavonoids
    - Non-Flavonoids
      - ***Curcumin***
      - ***Resveratrol***
  - Carotenoids
    - Xanthophylls

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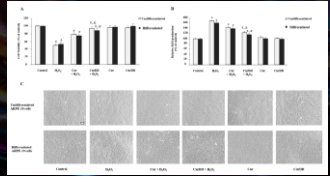
Polyphenols
Non-Flavonoids
Curcumin

Protective Effects of Curcumin Ester Prodrug Against H_2O_2-Induced Oxidative Stress in RPE: Potential Therapeutic Avenues for AMD
Inter J Molecular Sci (2019) 20(13):3367

Protective effects of curcumin against ROS production and cytotoxicity in ARPE-19 cells
(A) ARPE-19 cells were pre-treated with Cur or CurDD for 24 h, followed by H2O2 treatment for 6 hr
(B) ROS generation was determined by assay and average cell viability (mean ± SD values)



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Polyphenols
Non-Flavonoids
Resveratrol

Longevinex® Improves Atrophic AMD Photoreceptor and RPE-Mediated Dark Adaptation
J Adv Med and Med Res (2017) 1-19

Table 1. Demographic post-hoc clinical review

Case (Figure # & initials)	Age	Gender	AMD duration	Current smoker	Current alcohol	Retinal /Corneal dystrophy? (yes / no)	DA improving medication?	Supplements
1 (NS)	86	M	2 years	N	N	N	40 mg simvastatin	1000IU Vit D3 Centrum Silver QD 1000 mg Fish oil BID 420 mg Mg Oxide
2 (RS)	64	F	5 years +	N	N	Retinal Pavingstone	20 mg lovastatin	Centrum®
3 (HJ)	82	M	8 years	N	N	N	40mg atorvastatin	
4 (HJ)	89	M	9 years+	N	N	N	20 mg simvastatin	MaxiVision® AREDS 2, Krill Oil
5 (CJ)	86	F	1 year	N	N	Corneal Pellucid	20 mg atorvastatin	Bright Eyes®
6 (KW)	88	M	1 year	N	N	N/A	N/A	1000 IU Vit D AREDS2 500 mg Vit C, 1000 mg Fish oil
7 (DR)	84	M	New	N	N	N/A	N/A	Vitamin D3

Table 3. Clinical dark adaptation clinical data continued

Case (Figure # & initials)	Duration prescribed longevinex®	Rod intercept (OD)	Rod intercept (OS)	Baseline log sensitivity (OD)	Baseline log sensitivity (OS)	#Eyes improved OR remained stable in at least 1 DA factor
1 (SN)	5 Weeks	17.39→8.34	2.57→6.10	−1.9→−2.2	2.8→2.1	1 (L eye parameters worse)
2 (SR)	7 Months	5.73→8.84	2.04→3.90	−1.3→−1.2	−2.1→−2.3	2 (L eye remains normal)
3 (JH)	4.5 Months	>6.5→>6.5	>6.5→N/A (Cannot be calculated)	−1.9→−2.3	−2.2→−2.6	2
4 (JH)	4 Months	>20→>20	>20→>20	−1.1→−1.4	−1.2→−1.6	2
5(JC)	1 Month	>20→>6.5	>20→>6.5	1.2→1.2	1.0→1.1	2
6 (KW)	4 Months	11.9→18.85	>20→>20	−1.5→1.0	−0.9→−1.2	1 (R eye parameters worse)
7 (RD)	~4 Months	>20→>20	>20→>20	−1.1→−0.9	−1.0→−1.1	2

#Eyes improved or remained stable in at least 1 DA factor (12/14) Rod intercept data (n = 9/14 same/ improved; n = 4/14 worse; 1 unavailable. Baseline Log Sensitivity +/- 0.2 (11/14 = same / improved; 3/14 = worsened)

Conclusion:
Dark adaptation stability and improvement are consistent with previous beneficial effects of resveratrol including enhanced choriocapillaris circulation

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Nutraceuticals Related to Atrophic AMD

- Oral Supplementation
  - Polyphenols
    - Flavonoids
    - Non-Flavonoids
  - Carotenoids
    - Xanthophylls
      - ***Lutein***
      - ***Meso-zeaxanthin***
      - ***Zeaxanthin***

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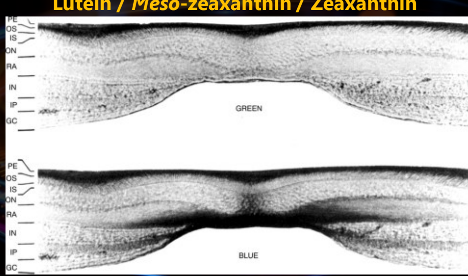
Carotenoids
Xanthophylls
Lutein / *Meso*-zeaxanthin / Zeaxanthin



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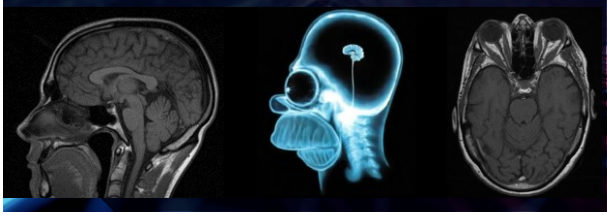
Carotenoids

Xanthophylls

Lutein / *Meso*-zeaxanthin / Zeaxanthin

Proxy for cortical levels?



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Association between MPOD and visual function outcomes: systematic review and meta-analysis

Eye (2021) 35(6):1620-1628

METHODS

MEDLINE®, Cochrane and PubMed databases were searched for correlations of MPOD and visual function in adults with healthy eyes at all timepoints and all designs. Visual function outcomes reviewed included photostress recovery, contrast sensitivity, visual acuity, glare sensitivity/disability and dark adaptation.

RESULTS

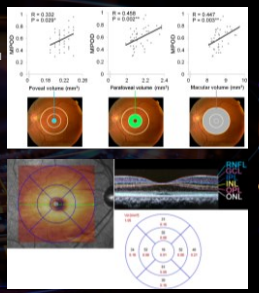
Meta-analysis of 22 publications, MPOD was found to be significantly correlated with:

- ***Foveal CS with a spatial frequency of 7, 11 and 21 cpd***
- ***Foveal photostress recovery at 10 cpd and 16% contrast***
- ***Foveal glare disability at 460 nm***

CONCLUSIONS

Identified link between MPOD and visual function with

1) ***Photostress recovery***
2) ***Glare disability***
3) ***Contrast sensitivity***



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Effect of Lutein/Zeaxanthin Intake on MPOD: Systematic Review and Meta-Analysis

Adv Nutrition (2021) 12(6):2244-2254

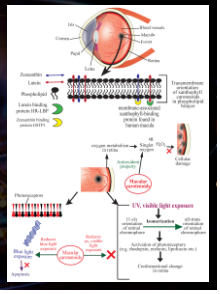
ABSTRACT

L, Z, and MZ are the only carotenoids found in the human macula and are reported to protect the retina as antioxidants and by acting as a blue light filter.

Our objective was to determine a minimum concentration of lutein/zeaxanthin intake that is associated with a statistically significant and/or clinically important change in MPOD among adults with healthy eyes. We searched Ovid MEDLINE, CENTRAL and Google Scholar and screened 46 studies (*n*=3189) that evaluated supplements or dietary sources of L/Z on MPOD among adults with healthy eyes

- ***No statistically significant change in MPOD among studies <5mg/d of total L/Z***
- ***Pooled mean MPOD increase was 0.11 units among studies ≥20mg/d of total L/Z***

MPOD increased with lutein/zeaxanthin intake, particularly at higher doses (***≥20mg***), among adults with healthy eyes. The effects of lutein/zeaxanthin intake at doses <5 mg/d or from dietary sources is less clear.



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Ocular Nutraceutical Roles

- ***Deposition/Transport Enhancement***
- Supplement Synergy
- Protein Expression Augmentation
- Not Just for AMD…..

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Feasibility study of a DHA optimized nutraceutical formulation on the macular levels of lutein in a healthy Mediterranean population

Ophthalmic Research (2020)

Methods:

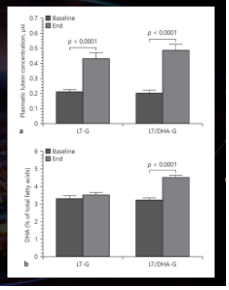
- 100 healthy participants with mean age 49.3 ±13.7 years randomized in a 1:1 ratio to receive one of following supplements daily for 3 months: [1] L or [2] L + DHA
- MPOD measured at baseline and at 3-month F/U by retinography
- Lutein in plasma was determined by HPLC
- DHA in red blood cell membranes was analyzed by gas chromatograph

Results:

- MPOD significantly higher in Lutein/DHA group than in the L group @ 3 months
- Significantly higher L in plasma and DHA levels in cell membrane were seen in L/DHA group than in L group at the 3-month F/U

Conclusions:

- ***L supplementation improves MPOD in healthy subjects and is significantly increased in the presence of DHA***
- ***Adjunctive role of DHA for a better lutein availability***



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Ocular Nutraceutical Roles

- Deposition/Transport Enhancement
- ***Supplement Synergy***
- Protein Expression Augmentation
- Not Just for AMD…..

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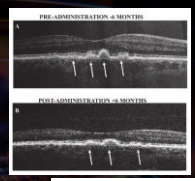
Nutraceuticals for dry AMD: Case report based on novel pathogenic and morphological insights

Arch. Ital. Biol 158 (2020): 24-34

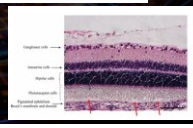


RESULTS

- OCT indicated a number of drusen beneath the macular region
- 6 month diet + intervention decreased drusen volume and thickness in the central area of the macula and was associated with a more regular macular profile
- Subjective improvement in color contrast and reduction in Amsler grid distortion
- Monocular CS(Pelli-Robson) improved from 1.8 to 2.0

CONCLUSIONS AND RELEVANCE

- ***AMD dysfunction occurs on both sides of the RPE suggesting basal membrane accumulation of proteins such as unesterified cholesterol, apoE, CFH and vitronectin***
- ***Generalized defects in protein handling by the retina-choroid junction is best targeted by a pharmacological synergism at multiple levels***



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Ocular Nutraceutical Roles

- Deposition/Transport Enhancement
- Supplement Synergy
- ***Protein Expression Augmentation***
- Not Just for AMD.....

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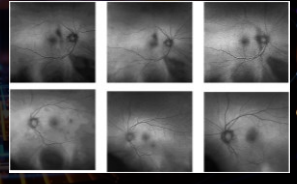
Characterizing the effect of supplements on the phenotype of cultured macrophages from AMD patients

Molecular vision (2017) *23*:889

- Macrophages may exert oxidative, inflammatory and angiogenic effects in the presence of AMD
- Combinations of L carnosic acid, Zn and β-carotene resulted in ***upregulation of antioxidative genes and downregulation of angiogenic and inflammatory genes***
- ***Combinations of supplements can modify the expression genes and proteins that may modulate macrophage phenotype in AMD***



Resveratrol-based supplement produces long-term beneficial effects on structure and visual function

Nutrients (2014) 6(10):4404-4420

- Low dose OTC resveratrol-based matrix of red wine solids, vitamin D_3 and inositol hexaphosphate (IP6) was evaluated using FAF and SD-OCT EDI and BCVA, CS and glare recovery
- ***Broad bilateral improvements in ocular structure and function were observed suggesting application of epigenetics may have a role in long-term efficacy against AMD***

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Ocular Nutraceutical Roles

- Deposition/Transport Enhancement
- Supplement Synergy
- Protein Expression Augmentation
- ***Not Just for AMD.....***

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Clinical Treatment
Oral Supplementation for Diabetic Retinopathy

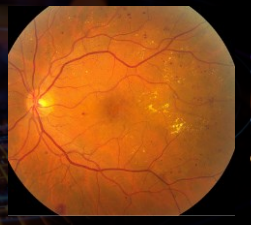
Application of Lutein and Zeaxanthin in non-proliferative diabetic retinopathy.
Int. J. Ophthal (2021) 4, 303–306.

Effect of lutein supplementation on visual function in nonproliferative diabetic retinopathy.
Asia Pac. J. Clin. Nutr. (2017) 26, 406–411.

Plasma carotenoids and diabetic retinopathy.
Br. J. Nutr. (2019) 101, 270–277.

MPOD Measured by Dual-Wavelength Autofluorescence Imaging in Diabetic and Nondiabetic Patients: A Comparative Study.
IOVS (2020) 51, 5840–5845.

Effect of carotenoids dietary supplementation on macular function in diabetic patients.
Eye Vis. (2017) 4.



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Hypothesized Roles of Macular Pigment

Optical Hypothesis
Protection Hypothesis
Neural Hypothesis

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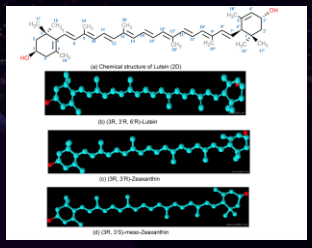
Lutein, *Meso*-zeaxanthin & Zeaxanthin
Macular Pigment



Macular pigment (MP) is the collective name for the isomeric carotenoids **lutein, *meso*-zeaxanthin** and **zeaxanthin**
(Bone et al., 1997)

Accumulated within the sensory retina at levels 1000X higher than found in serum to the exclusion of all other carotenoids
(Landrum et al., 1997)

Primary Metabolites:
3'-oxolutein
3'-epilutein

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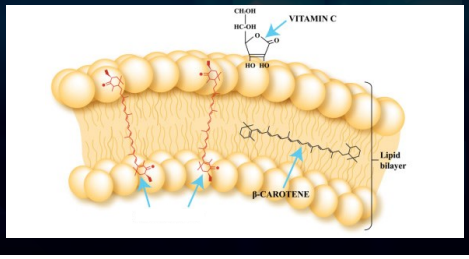
Protection Hypothesis
Macular Pigment



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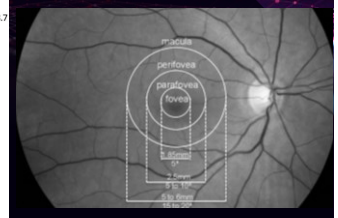
Take Home Points:
Clinical Macular Pigmentation supplementation

Food (1 cup cooked)	Lutein & zeaxanthin (mg)
Kale	23.7
Spinach	20.4
Swiss chard	19.3
Mustard greens	14.6
Turnip greens	12.2
Collards	11.8
Garden cress	11.3
Dandelion greens	9.6
Green peas	4.2
Summer squash	4.0
Beet greens	2.6
Brussels sprouts	2.4
Sweet corn	2.2
Broccoli	2.1

Source: USDA National Nutrient Database for Standard Reference, Release 22 (2009)



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Take Home Points:
Clinical Macular Pigmentation supplementation

MPOD in top quartile correlated with:
- Improved neural efficiency
- Improved peak visual performance
- Decreased risk of progression to advanced AMD
- Mitigation of CSME and CME

Lutein (20mg), *meso*-zeaxanthin (20mg) and Zeaxanthin (4mg) supplementation correlated with:
- Visual improvements at 3 months
- Improved visual peak performance at 6 months
- Visual performance plateau at 12 months

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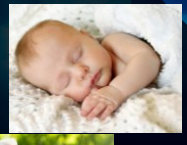
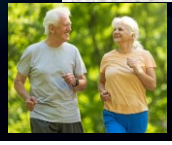
Take Home Points:
Clinical Nutraceutical supplementation – Step 1





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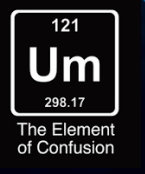
Take Home Points:
Clinical Nutraceutical supplementation – Step 2



https://www.consumerlab.com/reviews/lutein_zeaxanthin_supplements_review/lutein

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Take Home Points:
Clinical Nutraceutical supplementation – Step 2

PreserVision*

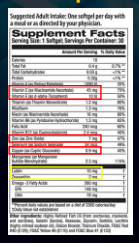
Vitamin A:
1 IU = 0.3 mcg (retinol)
1 IU = 0.6 mcg (β-carotene)

Vitamin C:
1 IU = 50 mcg

Vitamin D:
1 IU = 0.025 mcg

Vitamin E:
1 IU = 0.67 mg

I-Caps



Ocuvite

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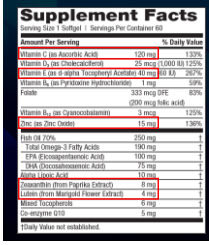
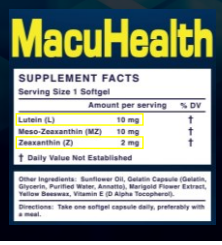
Take Home Points:
Clinical Nutraceutical supplementation – Step 2

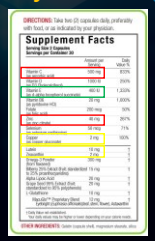
EyePromise



MacuHealth



EyeScience



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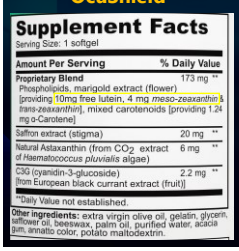
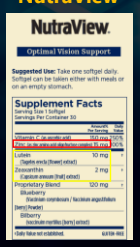
Take Home Points:
Clinical Nutraceutical supplementation – Step 2

OcuShield



NutraView



Vision MD

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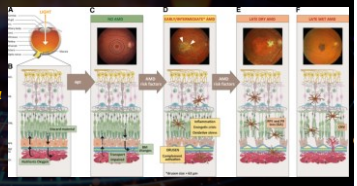
Take Home Points: Clinical Nutraceutical supplementation – Step 2

Nutritional, Alternative, and Complementary Therapies for AMD
Integrative Medicine (2019) 18:6



Abstract
AMD is the leading cause of blindness in patients >65 particularly in those who are smokers, obese, Caucasian, genetically predisposed and environmentally exposed

- ***Root cause is thought to be photochemical damage causing oxidative stress to the macula coupled with low grade inflammation***

- AREDS2 formulation consisting effective for slowing the progression iAMD
  - ***Subsequent studies suggest higher dietary dosages of L / MZ / Z and supplementing with Vit D, Vit B12, and Ω-3 fatty acids may further reduce the progression of the disease***

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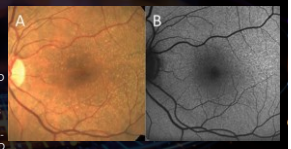
Take Home Points: Clinical Nutraceutical supplementation – Step 2

Association of plasma Ω-3 fatty acids with early AMD in the Multi-Ethnic Study of Atherosclerosis (MESA)
Retina (2022) doi:10.1097/IAE.0000000000003465



Methods
MESA participants with baseline PUFA measurements and retinal photography at exam 5 (n=3,772). Fundus photographs were assessed for AMD using a standard grading protocol. Relative risk regression determined associations between PUFA levels and AMD

Results
There was a significant association between increasing DHA levels and increasing DHA + EPA levels with reduced risk for early AMD (n=214 participants with early AMD, of which n=99 (46%) are non-white). EPA levels alone were not significantly associated with AMD

Conclusion
- ***Increasing levels of DHA are associated with reduced risk for early AMD in a multi-ethnic cohort***
- ***Represents the first racially diverse study demonstrating an association between Ω-3 PUFAs and AMD risk***

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Take Home Points: Clinical Nutraceutical supplementation – Step 2

Therapeutic Role of Carotenoids in Diabetic Retinopathy: Systematic Review
Diabetes Metab Syndr Obes. 2020;13:2347-2358

Methods
Six online databases (Medline/PubMed, Scopus, Web of Knowledge, Embase, ScienceDirect, and ProQuest) were searched until September 2019. The systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Results
25 studies revealed relationship between carotenoids and management of DR. Findings also demonstrated that the underlying mechanism of beneficial effects of these compounds was ***antioxidant, anti-inflammatory, anti-angiogenic and neuroprotective properties.***

Conclusion
Carotenoids potentially delay the initiation and prevent the progression of DR

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Take Home Points:
Clinical Nutraceutical supplementation – Step 2

L (20mg), MZ (20mg) and Z (4mg) [OSL: 40mg/d]
Ω-3 FA (1000mg)
- **DHA (350mg)**
- **EPA (650mg)**

Resveratrol (500mg) [OSL: 4000mg*]
Curcumin (500mg) [OSL: 3000mg*]
Quercetin (500mg) [OSL: N/A]
Anthocyanin (500mg) [OSL: N/A]

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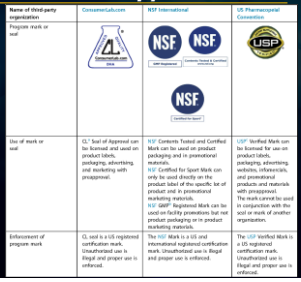
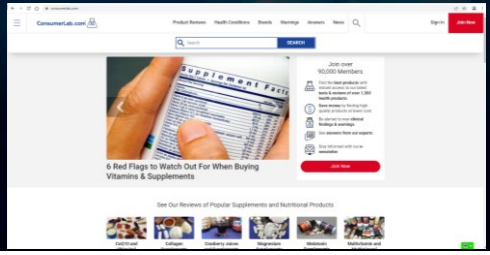
Take Home Points:
Clinical Nutraceutical supplementation – Step 3



149

Take Home Points:
Clinical Nutraceutical supplementation – Step 3

https://www.consumerlab.com/



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Take Home Points: Clinical Nutraceutical supplementation – Step 3

https://ods.od.nih.gov

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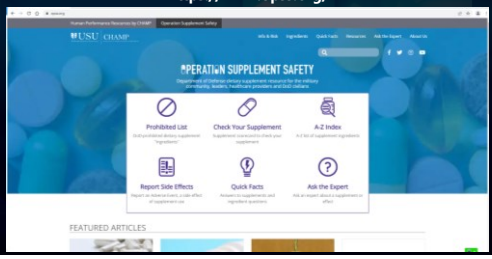
Take Home Points: Clinical Nutraceutical supplementation – Step 3

https://www.opss.org/



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What's now?

1. Family history (genetic predisposition), age, systemic health, and carotenoid status are all risk factors
2. **NOTHING** will replace:
   1. Healthy diet high in fruits/vegetables (Mediterranean diet)
   2. Moderate exercise 4 times/week
   3. Adequate rest targeting 8 hours/night
3. Impaired dark adaptation is an early manifestation of AMD
4. Oral supplementation has been firmly established in treatment and management of non-proliferative AMD
   1. Mild, non-proliferative maculopathy = 20mg L / 5mg Z + 1000mg Ω-3
   2. Intermediate, non-proliferative maculopathy = AREDS2 + 20mg L / 5mg Z + 1000mg Ω-3
   3. Severe, non-proliferative maculopathy = AREDS2 + 20mg L / 5mg Z + 1000mg Ω-3
5. Have a bottle or example of the recommended supplement in-office

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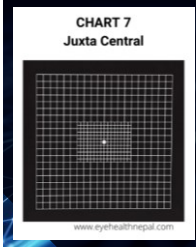
What's now?



AMD Category	Drusen Size*	Drusen Area*
1	None or <63um	<125um diameter
2	<63um Or >63um, <125um	>125um diameter Or >1 druse
3a	>63um, <125um Or >125um	>360um diameter (if soft drusen present) >656um diameter (if soft drusen absent) Or At least 1 druse
4a	Category 1,2 or 3	

Grid = 10cm x 10cm
- 33cm fixation
  - 20° field
  - Each square = 1°
  - ***1° = 300µm***

- **Chart 7**
  - 20° field
  - Foveal detail @ 0.5°
  - ***0.5° = 150µm***

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What's now?

Regression of some high-risk features of AMD in patients receiving intensive statin treatment

Ebio Medicine (2016) 4.5: 198-203

Design

Prospective, multicenter clinical pilot study
- 26 patients with diagnosis of AMD and the presence of large, soft drusenoid deposits
- Patients received atorvastatin 80mg QD and monitored at baseline and every 3 months with complete exam to include:
  - BCVA
  - Fundus photographs
  - SD-OCT
  - Blood panel
    - AST, ALT, CPK, total cholesterol, TSH, creatinine

Results
- 23 subjects completed 12 months of follow-up
- ***High dose atorvastatin resulted in regression of drusen deposits associated with increase of 3.3 letters***
- ***No patients progressed to exudative AMD***

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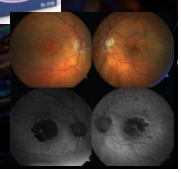
What's now? – FDA Approved (Feb2023)

Efficacy of intravitreal pegcetacoplan in GA patients: 12-month results from the Phase 3 OAKS and DERBY studies

IOVS (2022) 64:1500



Methods

OAKS and DERBY are phase 3, randomized, double-masked, sham-controlled studies
Enrolled patients:
- ≥60 years old, with
- BCVA ≥24 letters
- GA area between 2.5 and 17.5 mm^2 (including foveal and extrafoveal lesions)
- Primary endpoint was lesion size change from baseline to 1yr measured by FAF

Results
- OAKS showed statistically significant reductions in GA lesion growth by 16-22%
  - Foveal reduction: 16%
  - Extrafoveal reduction: 21-35%
- DERBY did not reach statistical significance: decreased GA lesion growth 11-12%
  - Foveal reduction: 7%
  - Extrafoveal reduction: 16-25%

Conclusions

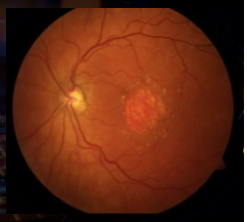
Pegcetacoplan met primary endpoint in OAKS with positive trends observed in DERBY. Pegcetacoplan demonstrated greater efficacy in patients with baseline extrafoveal lesions. Taken together with Phase 2 FILLY study, these findings support the efficacy of pegcetacoplan in slowing the progression of GA lesions

156

What's now? – FDA Phase III Trials

Avacincaptad pegol for geographic atrophy secondary to age-related macular degeneration: 18-month findings from the GATHER1 trial

IOVS (2022) 64:1500



Methods

International, prospective, randomized, double-masked, sham-controlled, phase 2/3 clinical trial

- Part 1: 77 participants were randomized 1:1:1 to receive monthly intravitreal injections of ACP 1 mg, ACP 2 mg or sham
- Part 2: 209 participants were randomized 1:2:2 to receive monthly ACP 2 mg, ACP 4 mg or sham
- Mean GA rate of change over 18 months was measured by FAF

Results

Monthly ACP treatment reduced the mean GA growth over 18 months by 28% for the 2 mg cohort and 30% for the 4 mg cohort

Macular neovascularization was more frequent in both 2 mg (12%) and 4 mg (16%) cohorts than their respective sham control groups (3% and 2%)

Conclusions

- Over 18 months, ACP 2 mg and 4 mg showed continued reductions in the progression of GA growth
- Phase 3 GATHER2 trial is currently underway to support the efficacy and safety of ACP as a potential treatment for GA

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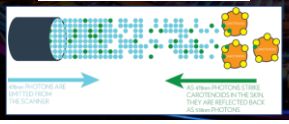
What's next?

Pharmanex *S3 BioPhotonic Scanner*



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Correlations Between Macular, Skin and Serum Carotenoids

Invest Ophthal Vis Sci (2017) 58(9):3616-3627

Correlations Between Macular, Skin and Serum Carotenoids

Invest Ophthal Vis Sci (2017) 58(9):3616-3627

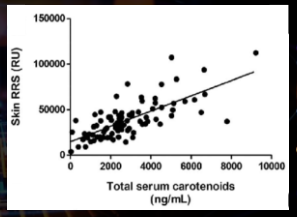
METHODS

88 patients were recruited from general ophthalmology and excluded only if they had a diagnosis of MacTel or Stargardt disease or had poor AFI image quality. Skin, macular, and serum carotenoid levels were measured by RRS, AFI, and HPLC

RESULTS

Skin RRS measurements and serum Z concentrations correlated most strongly with AFI macular pigment volume under the curve (MPVUC) measurements up to 9° eccentricity

- ***Measurements were reproducible and not significantly affected by cataracts***
- ***Techniques could readily identify subjects taking oral carotenoid-containing supplements***



CONCLUSIONS

- ***AFI and skin RRS measurements are noninvasive, objective, and reliable methods to assess ocular and systemic carotenoid levels***
- ***Skin RRS and MPVUC at 9° are both reasonable biomarkers of macular carotenoid status that could be readily adapted to research and clinical settings***

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What's next?

1. Serum-based testing for:
   - ***AMD risk alleles*** (CFH, VEGFA, C3, ARMS2, HTRA1 and apoE)
   - StARD3 and GSTP1
   - Serum-based cytokines (IL-1α, IL-1β, IL-4, IL-5, IL-10, IL-13, IL-17, IL-18)
2. Patient-tailored health plans for at-risk populations
   - Integrated systemic / supplementation strategies
3. Enhanced bioavailability
4. Risk calculator to incorporate:
   - Clinical biomarkers + Genetic risk + Environmental Factors
5. ***AMD shares characteristics with neurodegenerative disease…***

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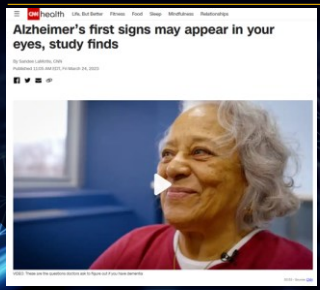
What's next?



Retinal pathological features and proteome signatures of Alzheimer's disease
Acta Neuropathologica (2023) 145:409-438

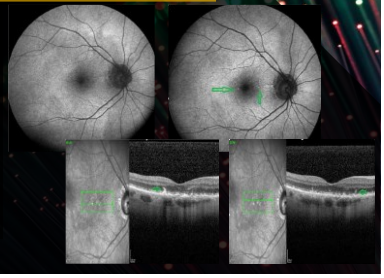
- Retinal and brain tissue samples over 14 years from 86 human donors with Alzheimer's disease (AD) and mild cognitive impairment (MCI)
- Retinal correspondence of structural effects with brain and cognitive effects in AD
  - Entorhinal and temporal cortex
- Microglial cells declined by 80% in those with cognitive issues
  - Responsible for repair and maintenance including clearing β-amyloid from the brain and retina.

161

What's next?

Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease
JCI Insights (2017) 2(16)

- Curcumin is a lipophilic polyphenol derived from turmeric and a fluorophore with a high affinity to A_β
- Aβ in AMD Lesions isolated in patient diagnosed with Alzheimer's Disease in 4 separate studies since 2017
- High bioavailability, proprietary blend used in conjunction with cSLO:
  - ***100% sensitivity***
  - ***81% specificity***
- ***Retinal Aβ load was strongly correlated with brain amyloid plaque burden confirmed through PET imaging***



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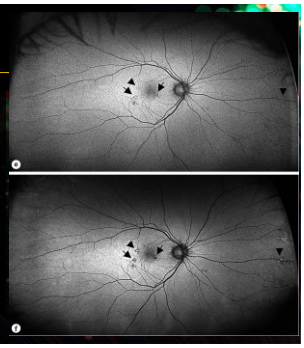
What's next?

Peripheral Retinal Imaging Biomarkers for Alzheimer's Disease: A Pilot Study
Ophthalmic Research (2018) 24.5

Results:
- Baseline analysis showed a significantly higher prevalence of peripheral hard drusen in AD subjects (25%) vs. control subjects (4%)
- Marked increase in drusen number at the 2-year follow-up in AD subjects vs. control subjects

Conclusions:
- ***UWF retinal imaging revealed a significant association between AD and peripheral hard drusen formation beyond the posterior pole at baseline and over 2-year progression***



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What's next?

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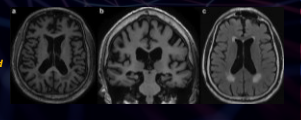
What's next?

Neuroimaging Biomarkers of Chronic Traumatic Encephalopathy: Targets for the Academic Memory Disorders Clinic
Neurotherpeutics (2021) 18:772-791

Abstract
CTE is a neurodegenerative disease associated with exposure to repetitive head impacts, such as those from contact sports.

- Pathognomonic lesion for CTE is the ***perivascular accumulation of hyper-phosphorylated tau*** in neurons and cell bodies
- Optimal tau PET radiotracer with high affinity for the ***3R/4R neurofibrillary tangles*** is lacking
- ***Amyloid PET scans have tended to be negative***
- Structural and functional imaging show ***frontotemporal and medial temporal lobe neurodegeneration***



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Safety and therapeutic effects of orally administered AKST4290 in newly diagnosed neovascular age-related macular degeneration
Retina (2022) doi: 10.1097/IAE.0000000000003446

Methods
In this prospective, multicenter, open-label Phase 2a pilot clinical study, 30 patients with newly diagnosed nAMD self-administered AKST4290 (400 mg) orally twice daily for 6 weeks. Patients were examined weekly for safety, to measure best corrected visual acuity (BCVA), and to perform exploratory morphological assessments. The primary endpoint was the mean change in BCVA from baseline to end of treatment, and the secondary endpoint was safety. Exploratory endpoints investigated potential changes in macular morphology.

Results
Mean BCVA improved by +7.0 letters (95% CI, 2.2–11.7); 24 patients (82.8%) had stable or improved BCVA, with 6 (20.7%) gaining ≥ 15 letters. No patients experienced severe or serious adverse events

Conclusions
In this 6-week study, AKST4290 treatment was associated with improved BCVA scores in patients with treatment-naïve nAMD. All adverse events (AEs) were mild or moderate in severity and no safety issues were identified. Treatment of nAMD with AKST4290 warrants further investigation in randomized, placebo-controlled trials.

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If there's time remaining…

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Genetic Testing for Ophthalmic Conditions

170

Generalized Ocular Genetic Testing

Inherited Retinal Disease and Spark Therapeutics

- Panel tests for mutations in approximately 300 genes associated with inherited retinal disease (IRD)
  - More commonly tested for:
    - ***Retinitis pigmentosa***
    - ***Leber congenital amaurosis***
    - ***Stargardt disease***
  - Commonly associated symptoms
    - Nyctalopia
    - Central and/or peripheral field loss
    - Color vision deterioration and/or loss
    - Severe photophobia

ID YOUR IRD
INHERITED RETINAL DISEASE GENE TESTING INITIATIVE

*****ID your IRD does NOT currently test for genes associated with AMD*****

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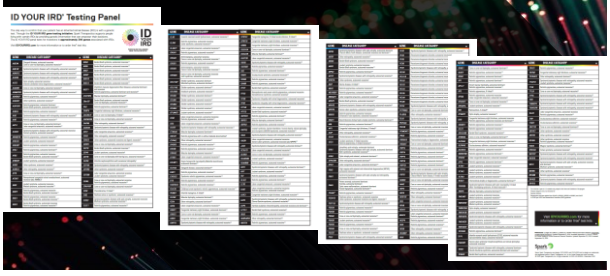
Generalized Ocular Genetic Testing
Inherited Retinal Disease and Spark Therapeutics



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Age-Related Macular Degeneration Genetic Testing

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Age-Related Macular Degeneration Genetic Testing
Peer-Reviewed Published Studies

Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multistate Markov models. *IOVS* 53.3 (2012): 1548-1556.

CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration. *Ophthalmology* 120.11 (2013): 2317-2323.

Validation of a prediction algorithm for progression to advanced macular degeneration subtypes. *JAMA ophthalmology* 131.4 (2013): 448-455.

Treatment response to antioxidants and zinc based on CFH and ARMS2 genetic risk allele number in the Age-Related Eye Disease Study. *Ophthalmology* 122.1 (2015): 162-169.

Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis. *British Journal of Ophthalmology* 100.12 (2016): 1731-1737.

CFH and ARMS2 genetic risk determines progression to nvAMD after antioxidant and zinc supplementation. *Proc National Academy of Sciences* 115.4 (2018): E696-E704.

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Age-Related Macular Degeneration Genetic Testing

Arctic Medical Laboratories (https://arcticdx.com)

Vita Risk
PREDICT AND PROTECT

Vita Risk® is a DNA test measuring the two main genetic variations (three genetic variations in two genes) that interact with common vitamin/mineral supplements containing zinc. People in one genetic group have increased risk of progression of age-related macular degeneration, to wet AMD.

Does my patient carry the genetic variations associated with vision loss when using chronic supplements such as AREDS?

***Patients positive for VitaRisk are advised to avoid long-term AREDS/AREDS2 supplements**

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Age-Related Macular Degeneration Genetic Testing

Arctic Medical Laboratories (https://arcticdx.com)

Macula Risk
PREDICT AND PROTECT

Macula Risk® is a DNA test combining many of the genes (15 genetic variations in 12 genes) associated with the progression of age-related macular degeneration (AMD). The genetic result is integrated into a formula developed from research at Tufts Medical Center and includes a patient's age, AMD disease status, height, weight, sex, age, and smoking history, which provides a basis for progression risk.

What is the likelihood of my patient progressing to advanced AMD?

Should my patient avoid chronic zinc supplementation?

***Predictive algorithm touts 89% accuracy @ 2, 5 and 10-year time points**

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Age-Related Macular Degeneration Genetic Testing

Visible Genomics (https://www.visiblegenomics.com)

AMDiGuard DNA Risk Test

The AMDiGuard Risk Test is designed to use DNA through a simple swab combined with patients' basic health factors and provide a risk level of aged-related macular degeneration based on our scientific analysis of both factors.

AMDiGuard DNA Progression Test

The AMDiGuard Progression Test is designed to learn more about the risk of advanced AMD for patients who have early to intermediate AMD.

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Age-Related Macular Degeneration Genetic Testing

Take Home Points

Excerpts from AAO Recommendations for Genetic Testing of Inherited Eye Diseases

- Use CLIA-approved laboratories
  - Avoid direct-to-consumer genetic testing without involvement of ECP
  - Request estimates of pathogenicity of observed genetic variants
- Avoid unnecessary parallel testing
  - Order DDx-specific testing
- Avoid routine genetic testing for complex disorders
  - Specific treatment or surveillance strategies are required to show benefit
- Avoid testing asymptomatic patients with untreatable disorders

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