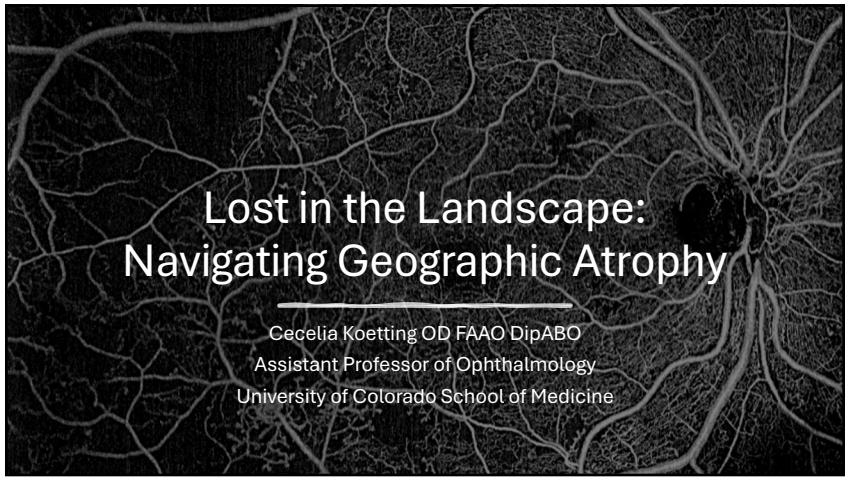


1

Cecelia Koetting Financial Disclosures

"All relevant relationships have been mitigated."

- Ocular Therapeutix -C
- Horizon-C
- Ivantis-C
- Orasis-C
- Otto-C
- Trukera-C
- LENZ-C
- PRN-C,S
- Kala-R
- Tarsus-C,S,R
- Tarcon-C
- Glaukos-C
- B +L- C,S
- Iveric-C
- Aldura-C
- Claris Bio-C
- Aldeyra-C
- Twenty Twenty Therapeutics-C
- Dompe-C,S,R
- Oyster Point/Viatris-C, S,R
- Allergan/Abbvie – C,S,R
- Alcon-C,S
- Visus-C,S
- Harrow-C,S
- Thea-C,R
- Bruder-C
- Blinkjoy-C
- SCOPE-C

Intrepid

KOETTING CONSULTING, LLC

2

Co-Management: Connecting the O's

- Why?
  - Decreased chair time for Retinal specialist
    - Can help allow more surgical time
  - Enhancement to practice and professional development
  - Established patient relationship
    - Better communication
  - Better treatment experience for patient overall

4

When do you refer AMD/GA patients to Retina?

1. All new and previous patients with any level of AMD/GA
2. Only previous patients with signs of progression
3. Any patient with signs of leakage
4. All new and previous patients with signs of leakage
5. It all depends

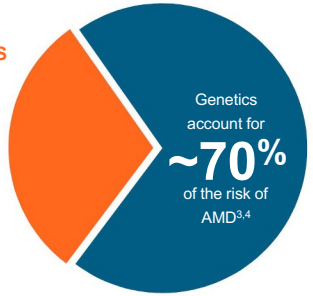
5

5

AMD Risks and Progression

DEMOGRAPHIC AND ENVIRONMENTAL FACTORS

- Age[1,2]
- Smoking[1-4]
- Diet[5]
- High alcohol intake[6]
- High body mass index[2,3]
- Comorbidities[2,3]



GENETIC FACTORS

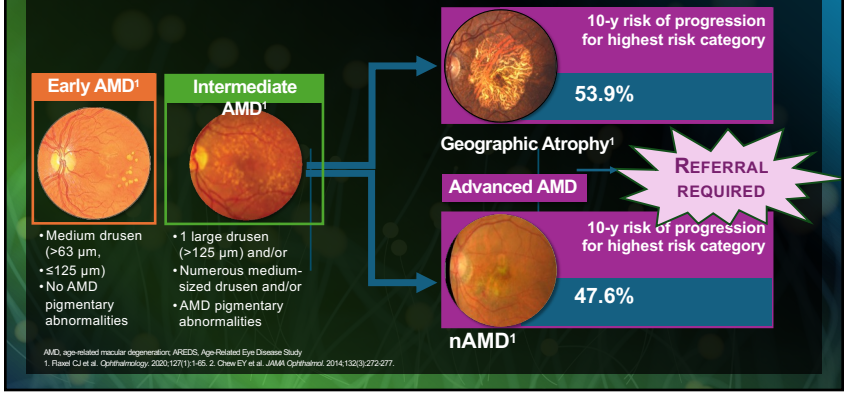
Variants in genes including **CFH, C3,** and **ARMS2/HTRA1** have been associated with GA and may contribute to[1,7]

- Drusen formation
- Oxidation of phospholipids
- Immune response
- Inflammation

AMD, age-related macular degeneration; GA, geographic atrophy.
1. Heesterbeek et al. Ophthalmic Physiol Opt. 2020;40(2):140-170. 2. Chakravarthy et al. BMC Ophthalmol. 2010;10:31. 3. Ersoy et al. Invest Ophthalmol Vis Sci. 2014;55(3):1842-1847. 4. Seddon et al. Arch Ophthalmol. 2005;123(3):321-327. 5. Sobrin and Seddon. Prog Retin Eye Res. 2014;40:1-15. 6. Adams MKM et al. Am J Epidemiol. 2012;176:289-298. 7. Boyer et al. Retina. 2017;37(5):819-835.

6

AMD Staging and Referral



AMD, age-related macular degeneration; AREDS, Age-Related Eye Disease Study
1. Rasel CJ et al. *Ophthalmology*. 2020;127(1):1-65. 2. Chew EY et al. *JAMA Ophthalmol*. 2014;132(3):272-277.

7

Geographic Atrophy Is an Advanced Form of Age-Related Macular Degeneration

- Globally, AMD is among the **leading causes of blindness** in adults aged ≥50 years[1]
- GA is a **progressive, advanced form** of dry AMD characterized by loss of the RPE, photoreceptors, and choriocapillaris leading to **significant, irreversible loss of visual function**[2]

GA affects more than **5 million** people worldwide[2,3]

~973,000 people in the United States have GA in ≥1 eye[4]

4× After age 50, **prevalence of GA approximately quadruples** every 10 years[5]

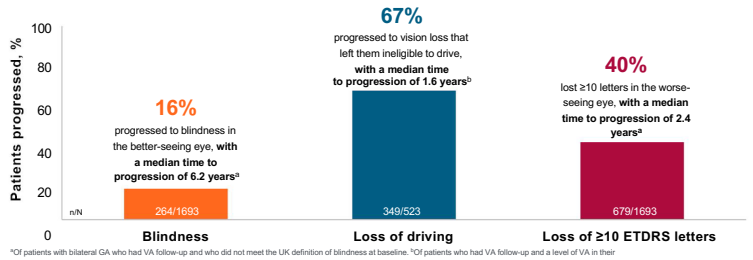
GA accounts for **20%** of all legal blindness attributed to AMD[6,7]

AMD, age-related macular degeneration; GA, geographic atrophy; RPE, retinal pigment epithelium.
1. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study. *Lancet Glob Health*. 2021;9(2):e144-e160. 2. Fleckenstein et al. *Ophthalmology*. 2018;125(3):369-390. 3. Wong et al *Lancet Glob Health*. 2014;2(2):e106-e116. 4. Friedman et al. *Arch Ophthalmol*. 2004;122(4):564-572. 5. Rudnicka et al. *Ophthalmology*. 2012;119:571-580. 6. Biarnés et al. *Optom Vis Sci*. 2011;88(7):881-889. 7. Ferris et al. *Arch Ophthalmol*. 1984;102:1640-1642.

8

Vision Loss in GA Can Progress Quickly and Can Have Profound Impacts

Retrospective cohort analysis of a 10-center EMR database across the UK in patients aged ≥50 years with bilateral GA



[a]Of patients with bilateral GA who had VA follow-up and who did not meet the UK definition of blindness at baseline. [b]Of patients who had VA follow-up and a level of VA in their better-seeing eye that would have placed them in a category of eligible to drive at baseline.
EMR, electronic medical record; ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy; VA, visual acuity.
Chakravarthy et al. Ophthalmology. 2018;125(6):842-849.

9


• Important to identify patients at risk of developing and progressing
• Helps in effective patient management
• Facilitates provision of appropriate education
• Enables offering treatment recommendations aimed at slowing GA, AMD and nAMD advancement
• Preserving vision for an extended period

10


Dilation is STILL IMPORTANT!
• Essential for eyecare practitioners specializing in anterior segment to assess the entire eye comprehensively
• Overlooking other eye segments may lead to missed opportunities for early detection and intervention of ocular pathologies
• Dilating the eyes allows thorough examination of the posterior segment
• Comprehensive eye evaluation ensures all aspects of ocular health are addressed
• Dilation is crucial for proactive identification and management of potential issues

11


Diagnostic Testing
Diagnosing And Monitoring

12


The Most Valuable Retina Tool

13

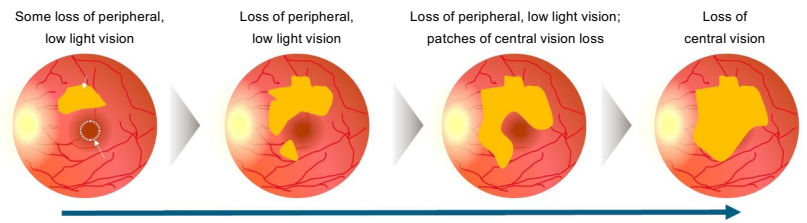
What testing do you utilize to monitor your AMD/GA patients?

1. OCT
2. Fundus FAF
3. Fundus photos
4. FANG
5. All the above
6. Currently refer to a friend for testing

14

Atrophic Lesion Growth and Vision Loss

Even though **central visual acuity is largely preserved** until atrophy encroaches on the fovea, **functional vision continues to decline as lesions grow**[1]



Median* of **2.5 years** from first appearance to foveal GA, with **extrafoveal lesions progressing faster than foveal lesions**[1-3]

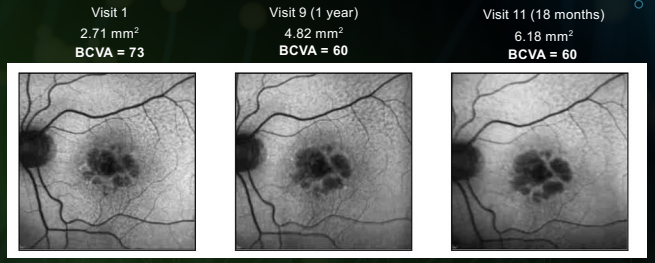
*n=181 of 4757 AREDS participants

1. Boyer et al. Retina. 2017;37(5):819-835. 2. Lindblad et al. Arch Ophthalmol. 2009;127(9):1168-1174. 3. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390.

15

BCVA Doesn't Capture GA Progression

BCVA is poorly correlated to lesion size. Functional vision declines as lesions grow[1,2]

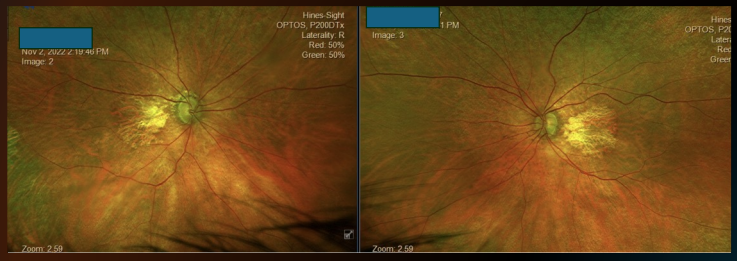


GA progression

BCVA, best-corrected visual acuity; GA, geographic atrophy.
1. Sunness et al. Ophthalmology. 1997;104(10):1677-1691. Sunness et al. Ophthalmology. 2007;114(2):271-277.

16

Fundus Photos



17

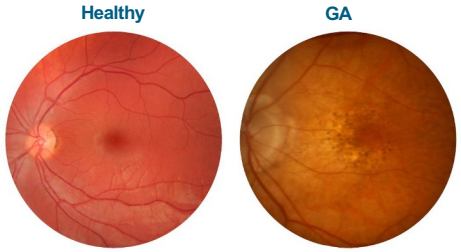
Color Fundus Photography: GA Lesions Clearly Demarcated Areas of Hypopigmentation

What to look for

- Visible choroidal vasculature[1]
- Areas of hypopigmentation with sharply demarcated borders[1]

GA, geographic atrophy.
1. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 2. Boyer et al. Retina. 2017;37(5):819-835.
Healthy fundus image from Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine.

Color fundus photography can define GA lesions; however, it cannot visualize many lesion characteristics associated with progression[1]

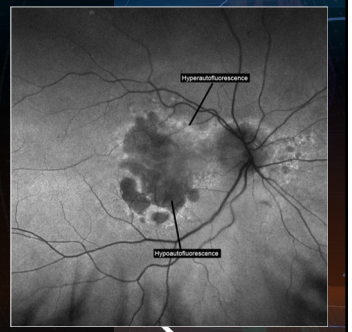


While atrophy encroaches on the foveal center, visual deficits may become more pronounced[2]

18

Fundus Autofluorescence

- Ultra-widefield fundus autofluorescence (FAF)
  - subjective assessment of the overall health of the retinal pigment epithelium as reflected by the amount of lipofuscin component
  - Areas of increased lipofuscin concentration hyperfluorescent,
  - Areas where RPE cells have atrophied or are absent hypofluorescent



19

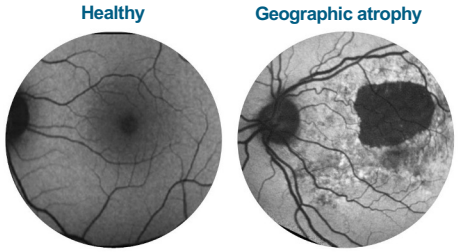
FAF Shows Characteristic Hypoautofluorescence Corresponding To GA Lesions

What to look for

- Depigmented, hypoautofluorescent regions corresponding to RPE atrophy[1,2]
- Abnormal hyperautofluorescence surrounding the atrophic regions representing areas of ongoing RPE cell dysfunction[2]

FAF, fundus autofluorescence; GA, geographic atrophy; RPE, retinal pigment epithelium.
1. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 2. Yung et al. Int J Retina Vitreous. 2016;2:12.
Healthy FAF image from Yung et al. Int J Retina Vitreous. 2016 Apr 8;2:12. Geographic atrophy FAF image courtesy of Nancy Holekamp, MD, Pepose Vision Institute.

FAF is the primary imaging modality used to assess lesion size and progression in GA[1]

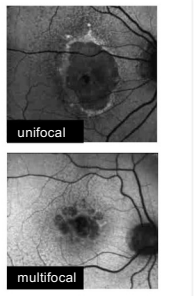


20

FAF Risk Factors Greater GA Progression Rate

Factors associated with increased GA progression rate

Affected eye	• Larger baseline lesion size[1,2]
	• Multifocality[3,4]
	• Abnormal FAF pattern: banded, diffuse FAF phenotypes[2]
	• Nonfoveal location and progression toward periphery; extrafoveal GA lesions progress faster than foveal lesions[4,5]
Fellow eye	• Bilateral GA[3,5,6]
	• Higher progression rate in fellow eye[5]



FAF, fundus autofluorescence; GA, geographic atrophy.
1. Sunness et al. Ophthalmology. 2007;114:271-277. 2. Holz et al. Am J Ophthalmol. 2007;143(3):463-472. 3. Wang and Ying. Ophthalmic Res. 2021;64(2):205-215. 4. Steinle et al. Am J Ophthalmol. 2021;227:116-124. 5. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 6. Lindblad et al. Arch Ophthalmol. 2009;127(9):1168-1174.

21

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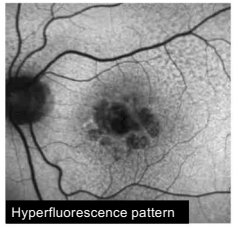

FAF, fundus autofluorescence; GA, geographic atrophy.
1. Sunness et al. Ophthalmology. 2007;114:271-277. 2. Holz et al. Am J Ophthalmol. 2007;143(3):463-472. 3. Wang and Ying. Ophthalmic Res. 2021;64(2):205-215. 4. Steinle et al. Am J Ophthalmol. 2021;227:116-124. 5. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 6. Lindblad et al. Arch Ophthalmol. 2009;127(9):1168-1174.

22

FAF Risk Factors Greater GA Progression Rate

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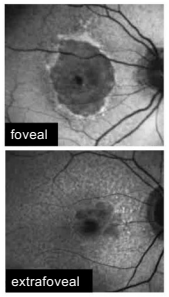


FAF, fundus autofluorescence; GA, geographic atrophy.
1. Sunness et al. Ophthalmology. 2007;114:271-277. 2. Holz et al. Am J Ophthalmol. 2007;143(3):463-472. 3. Wang and Ying. Ophthalmic Res. 2021;64(2):205-215. 4. Steinle et al. Am J Ophthalmol. 2021;227:116-124. 5. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 6. Lindblad et al. Arch Ophthalmol. 2009;127(9):1168-1174.

23

OCT-> GA Lesions Identified by Loss of Outer Retinal Layers

What to look for

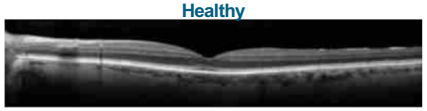
Lesions are identified by
- Loss of RPE and photoreceptor layers[1,2]
- External limiting membrane absence[1,2]
- Increase in choroidal hypertransmission[1,2]

GA, geographic atrophy; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

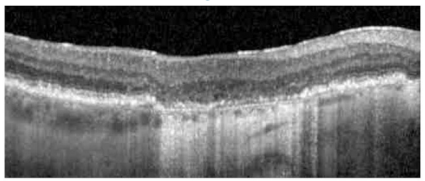
1. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390. 2. Sadda et al. Ophthalmology. 2018;125(4):537-548.
Healthy OCT image from Emmerson Badaró et. al. "Spectral-Domain Optical Coherence Tomography for Macular Edema," The Scientific World Journal.

OCT is emerging as a preferred imaging modality to assess features of lesions in GA[1]

Healthy



GA



24

AMD Progression Predictors on OCT

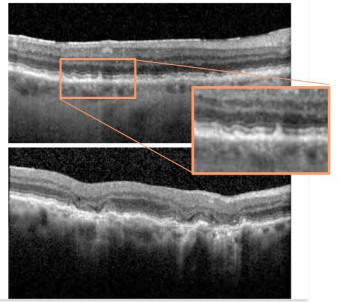
Predictive signs detectable on OCT

Reticular pseudodrusen[1]
- Drusenoid deposits located above the RPE
- May represent a risk factor for the development of late AMD

Subsidence "sinking" of INL and OPL[1]
- Retina layers appear to sink towards the RPE in the area of outer atrophy – appear as a hyporeflective wedge
- A finding at high risk to progress to GA

Hyperreflective Foci[1]
- Appear as discrete well-circumscribed, punctate lesions equal or greater in reflectivity than RPE
- Can indicate higher progression from early to advanced GA

Predictive signs of Geographic Atrophy (GA)



AMD, age-related macular degeneration; OCT, optical coherence tomography; RPE, retinal pigment epithelium; INL, inner nuclear layer; OPL, outer plexiform layer.
1. Jaffe et al.Ophthalmology Retina 2021;1-13

25

AMD Progression Predictors on OCT

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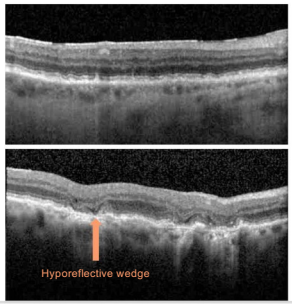

AMD, age-related macular degeneration; OCT, optical coherence tomography; RPE, retinal pigment epithelium; INL, inner nuclear layer; OPL, outer plexiform layer. 1. Jaffe et al. Ophthalmology Retina 2021;1-13

26

AMD Progression Predictors on OCT

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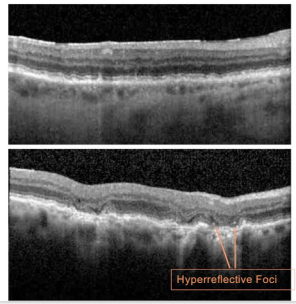
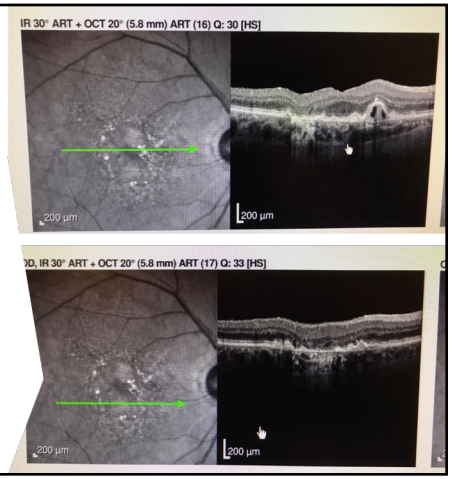


AMD, age-related macular degeneration; OCT, optical coherence tomography; RPE, retinal pigment epithelium; INL, inner nuclear layer; OPL, outer plexiform layer. 1. Jaffe et al. Ophthalmology Retina 2021;1-13

27

Macular Raster

- Optometrist's assessment:
  - Stage 4 dry AMD OU
- Retina specialist's assessment:
  - nAMD with active CNV OD



ART, automatic real-time tracking; CNV, choroidal neovascularization; IR, infrared; OCT, optical coherence tomography; OU, both eyes
Images courtesy of Cecelia Koetting, OD, FAAO, DipABO

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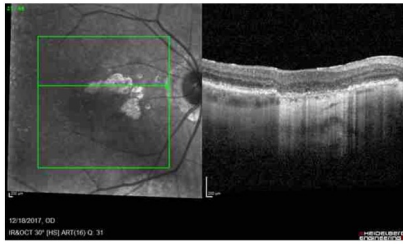
Near-infrared Reflectance (NIR)

- Fundus images acquired simultaneously with SD-OCT
- Drusen/pigmentary changes and areas of GA appear hyperreflective compared to surrounding retinal structures
- More comfortable for patients as compared to the bright flash of fundus photography or the intense blue light of FAF
- Benefit of NIR over many other imaging modalities is minimal light scattering through a hazy media[1]



1. Dolz-Marco et al; Ophthalmol. Vis. Sci. 2016;57(14):6440-6446. doi: https://doi.org/10.1167/iovs.16-20285

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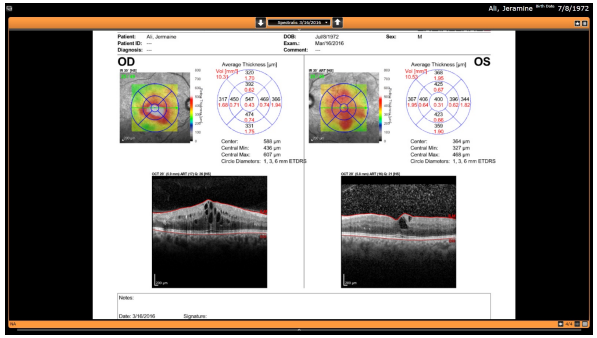
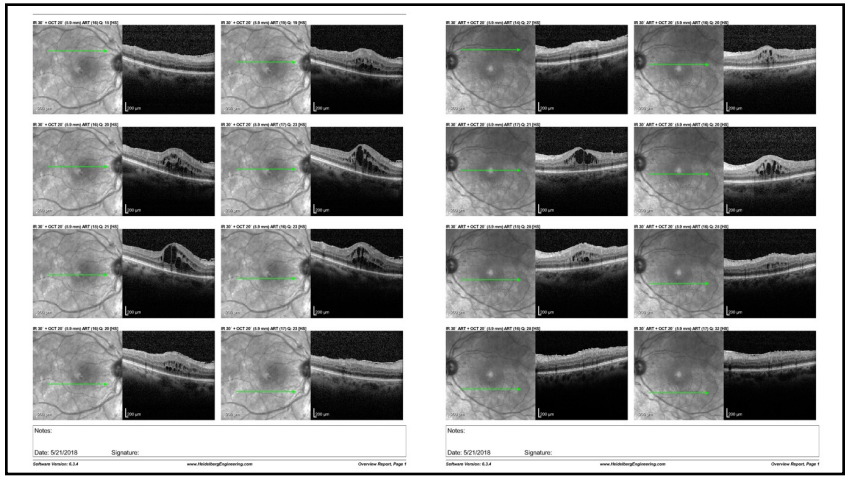
DME



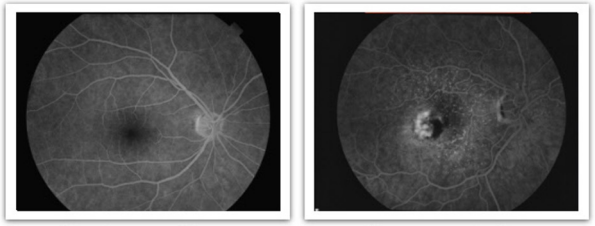
30



31

Fluorescein Angiography

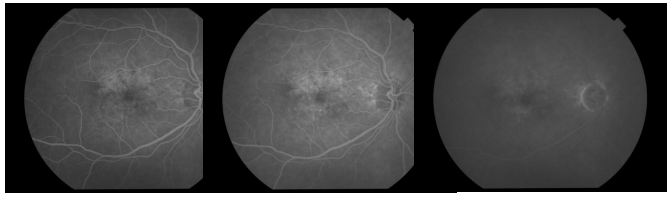
- Analyzing retinal blood flow, retinal perfusion, and choroidal vasculature
- Helps to identify neovascularization and leakage



FA Normal Macula FA Wet AMD

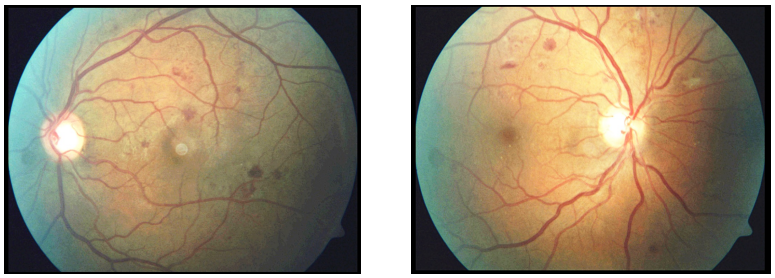
32

FA



Early Mid Late

33



PDR

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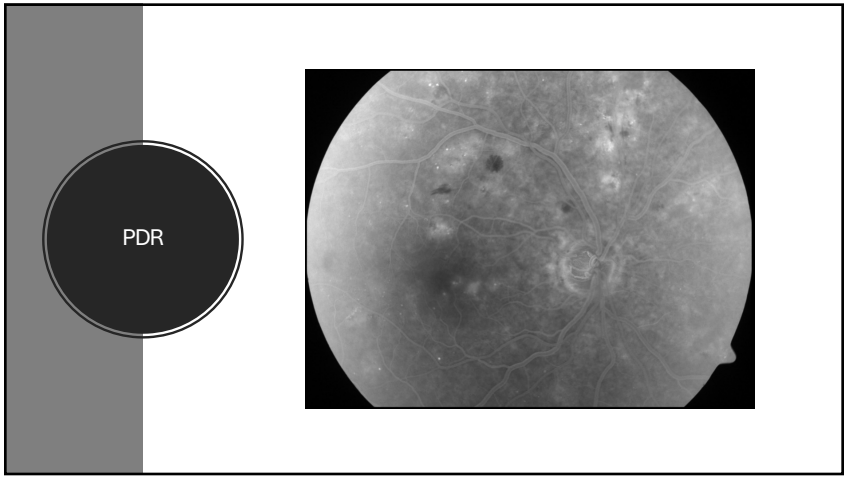
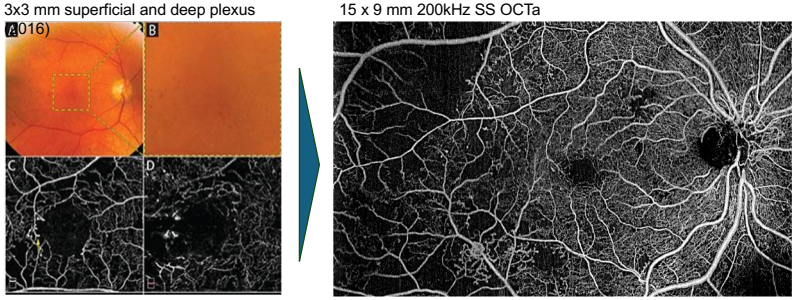


35

OCTA improving rapidly

3x3 mm superficial and deep plexus (2016)

15 x 9 mm 200kHz SS OCTa



Novais E, Baumal C. The Clinical Utility of OCT Angiography. Review of Ophthalmology, Jan 2017.

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Which patients do you talk to about AREDS?

1. Early AMD
2. Intermediate Severe AMD
3. nAMD
4. All the above

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Reminders

- Helps to slow progression of AMD in INTERMEDIATE to LATE AMD
  - Reduced by 25% during a 5-year period
  - Does not reverse or prevent
- No smokers formula
  - beta-carotene (Vitamin A) has been removed
- 2/3rd of patients in AREDS 2 study also took a multivitamin daily

Ingredient	Amount in AREDS 2
Vitamin C	500 milligrams (mg)
Vitamin E	400 International Units (IU)
Copper (cupric oxide)	2 mg
Zinc	80 mg
Beta-carotene	---------
Lutein	10 mg
Zeaxanthin	2 mg

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AREDS II 10-Year Follow UP

JAMA Ophthalmology | Original Investigation

Long-term Outcomes of Adding Lutein/Zeaxanthin and ω-3 Fatty Acids to the AREDS Supplements

Results of this long-term epidemiologic follow-up study of the AREDS2 cohort suggest that lutein/zeaxanthin was an appropriate replacement for beta carotene in AREDS2 supplements. Beta carotene usage nearly doubled the risk of lung cancer, whereas there was no statistically significant increased risk with lutein/zeaxanthin. When compared with beta carotene, lutein/zeaxanthin had a potential beneficial association with late AMD progression

with long-term follow-up.

OBJECTIVE To assess 10-year risk of developing lung cancer and late age-related macular degeneration (AMD).

Scientific findings

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What Can We Do Beyond AREDS2?

Mediterranean diet has been shown to reduce formation and progression of AMD

Omega 3 Fatty Acids and Vitamin B complex have been found to have AMD protective association

Lutein and zeaxanthin (carotenoids) are uniquely protective in the macula (↑MPOD)

AREDS, Age-related Eye Disease Study; MPOD, Macular Pigment Optical Density.

Agrón E et al. *Ophthalmology*. 2021;128(3):425-442. Datta S et al. *Prog Retin Eye Res*. 2017;60:201-218.

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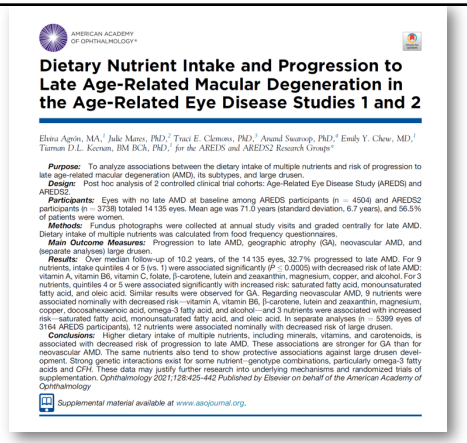

AMERICAN ACADEMY OF OPHTHALMOLOGY

Dietary Nutrient Intake and Progression to Late Age-Related Macular Degeneration in the Age-Related Eye Disease Studies 1 and 2

Elvira Agrón, MA,[1] Julie Mares, PhD,[2] Traci E. Clemons, PhD,[3] Anand Swaroop, PhD,[4] Emily Y. Chew, MD,[1] Tiernan D.L. Keenan, BM BCh, PhD,[1] for the AREDS and AREDS2 Research Groups[5]

Purpose: To analyze associations between the dietary intake of multiple nutrients and risk of progression to late age-related macular degeneration (AMD), its subtypes, and large drusen.
Design: Post hoc analysis of 2 controlled clinical trial cohorts: Age-Related Eye Disease Study (AREDS) and AREDS2.
Participants: Eyes with no late AMD at baseline among AREDS participants (n = 4504) and AREDS2 participants (n = 3738) totaled 14 135 eyes. Mean age was 71.0 years (standard deviation, 6.7 years), and 56.5% of patients were women.
Methods: Fundus photographs were collected at annual study visits and graded centrally for late AMD. Dietary intake of multiple nutrients was calculated from food frequency questionnaires.
Main Outcome Measures: Progression to late AMD, geographic atrophy (GA), neovascular AMD, and (separate analyses) large drusen.
Results: Over median follow-up of 10.2 years, of the 14 135 eyes, 32.7% progressed to late AMD. For 9 nutrients, intake quintiles 4 or 5 (vs. 1) were associated significantly ($P \leq 0.0005$) with decreased risk of late AMD: vitamin A, vitamin B6, vitamin C, folate, β-carotene, lutein and zeaxanthin, magnesium, copper, and alcohol. For 3 nutrients, quintiles 4 or 5 were associated significantly with increased risk: saturated fatty acid, monounsaturated fatty acid, and oleic acid. Similar results were observed for GA. Regarding neovascular AMD, 9 nutrients were associated nominally with decreased risk—vitamin A, vitamin B6, β-carotene, lutein and zeaxanthin, magnesium, copper, docosahexaenoic acid, omega-3 fatty acid, and alcohol—and 3 nutrients were associated with increased risk—saturated fatty acid, monounsaturated fatty acid, and oleic acid. In separate analyses (n = 5399 eyes of 3164 AREDS participants), 12 nutrients were associated nominally with decreased risk of large drusen.
Conclusions: Higher dietary intake of multiple nutrients, including minerals, vitamins, and carotenoids, is associated with decreased risk of progression to late AMD. These associations are stronger for GA than for neovascular AMD. The same nutrients also tend to show protective associations against large drusen development. Strong genetic interactions exist for some nutrient–genotype combinations, particularly omega-3 fatty acids and CFH. These data may justify further research into underlying mechanisms and randomized trials of supplementation. *Ophthalmology 2021;128:425-442 Published by Elsevier on behalf of the American Academy of Ophthalmology*

Supplemental material available at www.aaojournal.org.

Volume 128, Number 3, March 2021

Continued analysis of the AREDS 1 & 2 cohorts 14,000+ eyes

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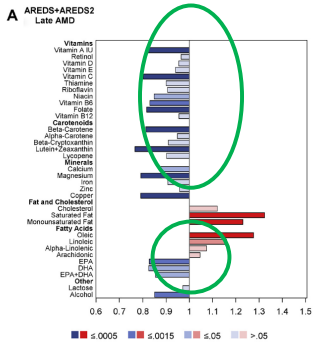
Nutrients and AMD Progression



Hazard Ratio Nutrient in RED
Protective Associations in BLUE
Smaller p values are darker

This graph showed overall AMD progression – both central geographic atrophy and/or neovascular AMD

Revealed the protective associations
- **AREDS 2 ingredients**
- **Vitamin B's**
- **Omega 3's**

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Systemic Disease Management

- Several chronic medical conditions are associated with increased risk of AMD progression
- Managing risk factors closely with the patient's PCP or specialist is part of overall AMD management

Obesity
- ***32% increase in the risk of developing late AMD***
- Higher body fat associated with lower tissue LZ levels

Cardiovascular Disease
- Variable associations with several CVD outcomes, eg, CAD, MI, angina
- Drusen and atherosclerotic plaques have numerous components in common

Diabetes
- Patients with DR at significantly greater risk of subsequent AMD
- Presence of diabetes predicts incident geographic atrophy

High Cholesterol
- Increasing levels of HDL-C inversely related to incident late AMD (RR per SD increase=0.74; 95% CI=0.56-0.99)
- Elevated total/HDL cholesterol ratio predicts late AMD

CAD, coronary artery disease; DR, diabetic retinopathy; HDL-C, high density lipoprotein-cholesterol; LZ, lutein/zeaxanthin; MI, myocardial infarction.

Zhang QY et al. *Invest Ophthalmol Vis. Sci.* 2016;57(3):1276-1283. Pennington KL et al. *Eye Vis (Lond).* 2016;3:34. He MS et al. *Diabetes Care*. 2018;41(10):2202-2211. Tan JSL et al. *Ophthalmology.* 2007;114(6):1143-1150. Bovier ER et al. *Nutrients.* 2013;5:750-757.

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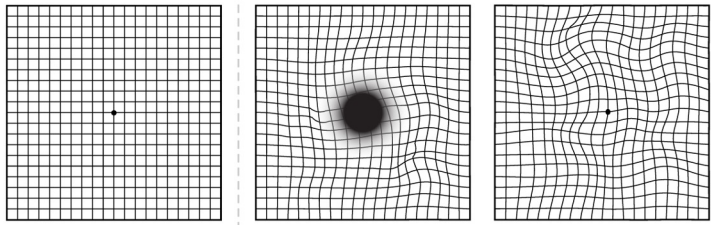
At Home Monitoring : Amsler Grid



Normal | Missing area/blind spot | Distortion/wavy lines

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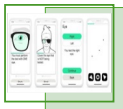
Next Generation: FDA-Cleared Digital Retina Home Monitoring

ForeseeHome
- Detects conversion from dry AMD to nAMD early
- Data from each daily test sent to monitoring center, then to doctor

OdySight Care
- App for home VA testing in patients with retinal disease
- Alerts notify physicians and patients when significant change in VA detected

Home Vision Monitor
- Smartphone app that monitors vision in patients with neovascular retinal diseases



Alleye
- Smartphone app enabling early detection of worsening pathology or need for IVT in patients with neovascular retinal diseases

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Photobiomodulation treatment- Valeda (LumiThera)

FDA approval Nov 2024

Treatment for vision loss in patients with dry AMD

- Low level laser therapy
  - Targeted wavelength NIR 500-1000nm from light emitting diodes or laser
    - Creates chemical reaction at cellular level in electron transport channel- specifically enzyme cytochrome c oxidase within Complex IV
    - Increases mitochondrial activity in cells in retinal layers (RPE, ganglion cell nuclei, IPN, OPN) -→ promotes ATP production
    - Also decreases NO activity increasing complex IV activity, creating PR improved function
- Provides improvement in BCVA over 24 months of >5 letters

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Neovascular AMD

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Why Is Early Detection of nAMD Important?

The longer fluid or hemorrhage is present in or under the retina, the worse the visual outcomes are.

Natural History[1]
- Vision loss over time:
  - 1 line at 3 mo
  - 2.7 lines at 1 y
  - 4 lines at 2 y

Symptoms[2]
- Retrospective study of 45 patients with nAMD treated <1 mo (group 1), 1-6 mo (group 2), or >6 mo (group 3) after visual symptom onset
- Only patients in group 1 achieved significant increase in BCVA (*P*=.007)

Signs[3]
- Retrospective chart review of 1185 eyes with nAMD treated with ranibizumab using separate-day injection protocol (within 16 d) vs same-day injection protocol
- ≈1-line greater vision gain in same-day injection group

BCVA, best-corrected visual acuity; nAMD, neovascular age-related macular degeneration.

1. Wong TY et al. *Ophthalmology*. 2008;115(1):116-126. 2. Rauch R et al. *Retina*. 2012;32(7):1260-1264. 3. Rasmussen A et al. *Acta Ophthalmol*. 2015;93(7):616-620.

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AOA Guidelines for Monitoring AMD

**** Last Updated 2004

Type of patient	Frequency of Examination
Patient with two or more risk factors for AMD, over age 55 (risk for AMD)	Annual examination
Patient with hard drusen and/or pigmentary degeneration (early AMD)	6-12 Months depending on risk **articles published by AOA now say 6 months
Patieint with geographic atrophy, VA 20/30-20/70	6-12 months depending on extent of atrophy
Patient at high risk with soft confluent drusen and pigment degen	4-6 months

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When to Refer to Retina

- New diagnosis of neovascular AMD
  - Should be referred that day to be seen within 1 week
- Changes in existing nAMD including changes in vision or OCT
  - Should be referred that day to be seen within 1 week

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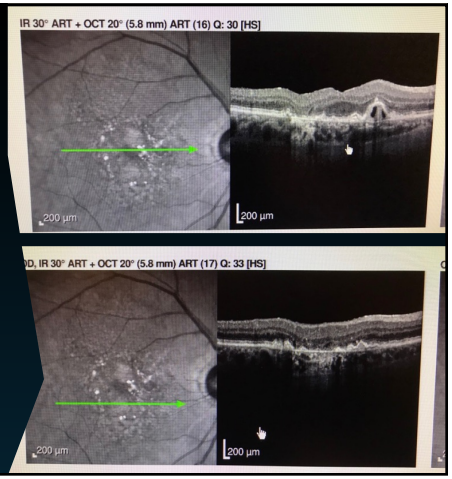
Macular Raster

Optometrist's assessment:

- Stage 4 dry AMD OU

Retina specialist's assessment:

- nAMD with active CNV OD



ART, automatic real-time tracking; CNV, choroidal neovascularization; IR, infrared; OCT, optical coherence tomography; OU, both eyes
Images courtesy of Cecelia Koetting, OD, FAAO, DipABO

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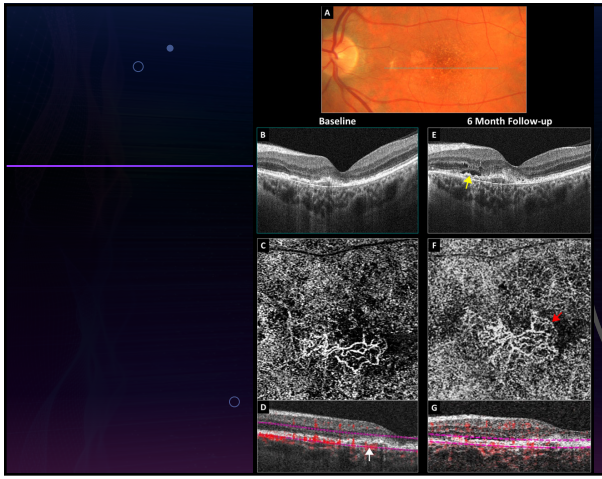

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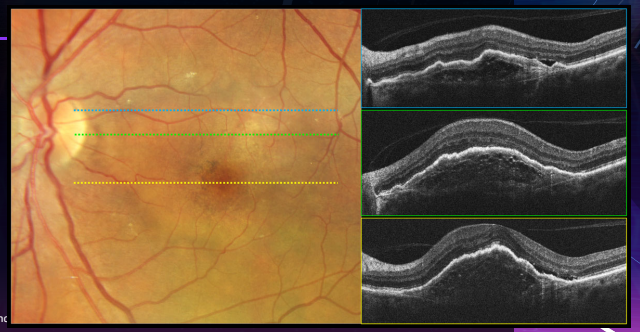
neovascular exudative AMD, fibrovascular PED



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Serous PED subretinal fluid suggestive of exudative AMD

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Current Firstline Treatment for nAMD

Anti- VEGF

- Block a protein called vascular endothelial growth factor (VEGF) that stimulates the growth of abnormal blood vessels.

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Current Options

Pegaptanib (Macugen)	Anti-VEGF	6 weeks
Bevacizumab (Avastin)	Anti-VEGF	4-6 weeks
Ranibizumab (Lucentis)	Anti-VEGF	4-6 weeks
Aflibercept (Eyelea)	Anti-VEGF	4 weeks for first 3 months, then every 8 weeks
Brolucizumab (Beovu)***	Anti-VEGF	1 x month for 3 months, then every 8-12 weeks
Susvimo port with Lucentis	Anti-VEGF	Refill every 6 months
Faricimab (Vabysmo)	Anti-VEGF AND monoclonal antibody	4 weeks for first 4 months, then every 8-12 weeks

***Potential risk for retinal vasculitis and RVO

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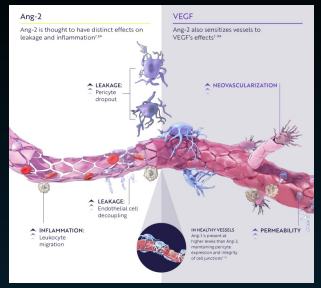
2023 FDA Approved Faricimab(Vabysmo)

- First in class bi-specific monoclonal antibody
  - Dual inhibition of VEGF-A and Angiopoietin-2 (Ang-2)
  - Helps with vascular stability and permeability
- 4 weeks for first 4 months, then every 8-12 weeks



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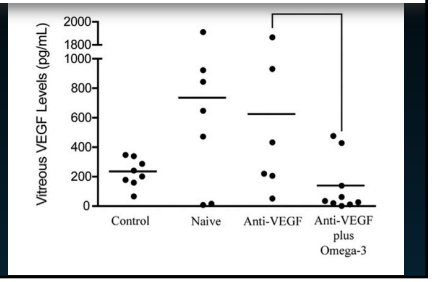
Anti-VEGF + AREDS 2 and Omega 3

- Group 1: Wet AMD receiving anti-VEGF
  - Omega 3 [200 mg of DHA and 400 mg of EPA] + AREDS2
- Group 2: Wet AMD receiving anti-VEGF
  - AREDS2
- Group 3: Wet AMD starting anti-VEGF treatment
  - No Supplement
- Group 4: non-AMD patients with ERM or MH undergoing PPV
  - No Supplement

Omega-3 Supplementation Combined With Anti–Vascular Endothelial Growth Factor Lowers Vitreal Levels of Vascular Endothelial Growth Factor in Wet Age-Related Macular Degeneration

FLAVIO A. REZENDE, ERIC LAPALME, CYNTHIA X. QIAN, LOIS E. SMITH, JOHN PAUL SANGIOVANNI, AND PRZEMYSLAW SAPIEHA



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GA Treatment

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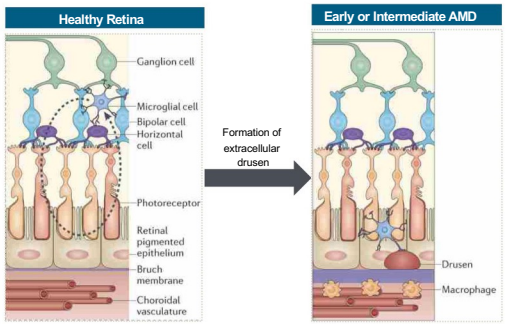
Damage Caused By Intrinsic and Extrinsic Stressors Results in Drusen Formation

- With aging, the **RPE is exposed to oxidative stress** caused by retinal metabolic demands, photo-oxidation, and environmental stressors
- Damage caused by these stressors can accumulate, resulting in formation of **extracellular drusen**



RPE, retinal pigment epithelium.
Boyer et al. Retina. 2017;37(5):819-835.

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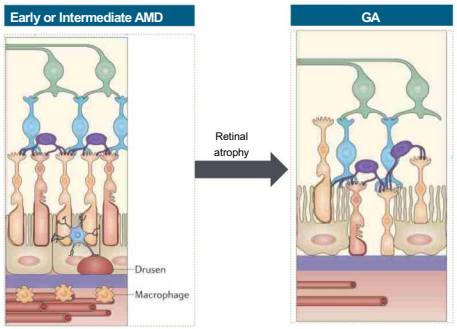
Cumulative Retinal Damage Can Trigger Inflammation and Lead to Widespread Retinal Atrophy

- Excessive drusen accumulation may trigger inflammation via multiple pathways (eg, the complement cascade), leading to **photoreceptor, RPE, and choriocapillaris cell death**[1,2]
- Loss of photoreceptors, RPE, and choriocapillaris results in **sharply defined atrophic lesions**, characteristic of GA[1]



GA, geographic atrophy; RPE, retinal pigment epithelium.
1. Boyer et al. Retina. 2017;37(5):819-835. 2. van Lookeren Campagne et al. Immunobiology. 2016;221(6):733-739. 3. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390.

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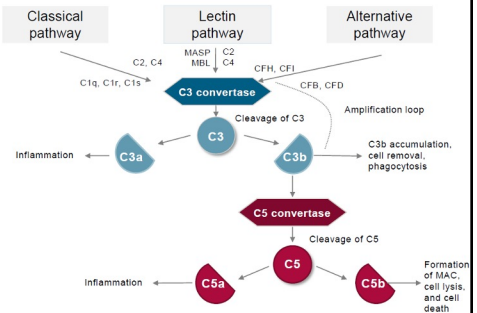
A Leading Contributor to Inflammation in GA Pathogenesis Is Dysregulation of the Complement System

- The complement cascade is controlled by **regulator proteins** and is primarily responsible for **removal of pathogens**[1,2]
- Patients with AMD have been shown to have **increased levels** of activated complement components[3]
- Dysregulation can lead to **excess phagocytosis, inflammation, and cell lysis,** potentially **contributing to lesion growth in GA**[1,2]

AMD, age-related macular degeneration; CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; CFI, complement factor I; GA, geographic atrophy; MAC, membrane attack complex; MASP, MBL-associated protease; MBL, mannose-binding lectin.
1. Boyer et al. *Retina*. 2017;37(5):819-835. 2. Katschke et al. *Sci Rep*. 2018;8(1):13055. 3. Smailhodzic et al. *Ophthalmology*. 2012;119(2):339-346. 4. Mastellos et al. *Trends Immunol*. 2017;38(6):383-384.

The complement cascade consists of 3 distinct pathways[1,4]



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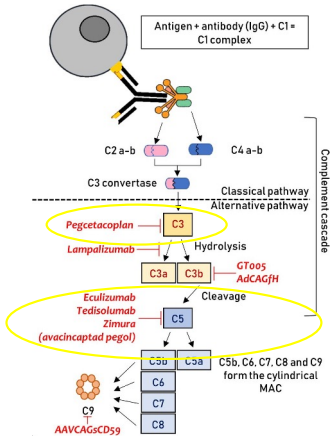

Newly Approved Complement Inhibition Therapy for GA

- **Pegcetacoplan (SYFOVRE®)**
  - Approved February 2023
  - Indication: GA secondary to AMD
  - MOA/Target: C3
  - Clinical Trials: OAKS/DERBY/GALE
  - 15 mg intravitreal injection every 25-60 days
- **Avacincaptad Pegol (IZERVAY®)**
  - Approved August 2023
  - Indication: GA secondary to AMD
  - MOA/Target: C5
  - Clinical Trials: GATHER1/GATHER2
  - 2 mg intravitreal injection monthly for up to 12 months

Cabral de Guimaraes TA, Daich Varela M, Georgiou M, *et al*
Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions. *BJO* 2022;106:297-304.

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How to discuss GA and treatment with patients when referring

- Understand patients may or may not be treated
- Understand what the current treatments do and DON'T do.
  - Will not improve patients current GA
  - Will help decrease RISK of progression

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Comanagement–Setting Expectations

- Educate patient that GA is a progressive, irreversible form of AMD
- Available treatment options can slow progression of GA but don't reverse it
- Vision may continue to worsen, with or without treatment
- Current treatment administered by intravitreal injection every 1-2 months
- Considerations when referring for possible GA treatment:
  - Patient specific - symptoms, age, motivation, comorbidities
  - Imaging specific - progression rate, risk factors for progression
- Don't forget about referral to low vision specialist when appropriate
- Patient will still require primary eyecare services

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Life Adaptation changes

- Small changes can make a big impact
- Best corrected MRX
- Possible low vision devices
- Refer out for low vision training
- Talking with family members
- Using our phones as a device.

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Treatments in Trial

Neovascular age-related macular degeneration
- Aflibercept high dose
- APX3330
- AR-1105 AR13503

Geographic atrophy.
- ALK-001 (Alkeus Pharmaceuticals)
- ANX007 Annexon Biosciences
- Danicopan Alexion Pharm
- Elamipretide Stealth Bio
- Ionis-FB-LRx Ionis pharm
- NGM621 NGM Bio
- Zimura Iveric Bio

Gene therapies for AMD, DR and DME.
- 4D-1550
- ExG102-031 Exergenisis Bio
- FT-003
- GEM103
- RGX-314

Biosimilars.
- Aflibercept biosimiliars
- Bevacizumab biosimilar
- Ranizumab biosimilar

Devices.
- Prima
- Retilux
- SingIMT
- Valeda light delivery system

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Thank you

- Dr.CeceliaKoetting@gmail.com

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SESSION 6
COPE Event 128399
CECELIA KOETTING, OD, FAAO
COPE Course # 95363-TD : Lost in the Landscape: Navigating Geographic Atrophy

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