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OCT – Advanced Retina Applications and Grand Rounds

DAMON DIERKER, OD, FAAO

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Disclosures - Damon Dierker, OD, FAAO

- Aerie - A
- Alcon - A/C/S
- Allergan - A/C/R/S
- ArcticDx - R
- Avellino Lab - A
- Azura - A
- Bausch & Lomb - A/C/S
- Bio-Tissue - A/C/R/S
- Carl Zeiss Meditec - A
- Dompe - S
- Dry Eye Boot Camp - Founder
- Eyes On Dry Eye - Co-Founder
- Eyevance - A/C/S
- Genentech - A
- Glaukos - A/C/S
- Gyroscope - R
- Johnson & Johnson - C
- Kala - A/C/S
- Lumenis - C/S
- MacuHealth - S
- MacuLogix - A/C/S
- Notal Vision - A/C/R/S
- NovaBay - C
- Novartis - A/C/S
- NuSight Medical - C
- Ocular Therapeutix - A/R
- Ocuphire - A
- OcuTerra - A
- Optovue - S
- Oyster Point Pharma - A/C/R/S
- Quidel - A/C
- RVL Pharmaceuticals - A/C/S
- ScienceBased Health - A/C/S
- Scope - C
- Shire - A/C/S
- Sight Sciences - A/C/R/S
- Sun Pharma - A/S
- Tarsus - A/C/R
- Thea Pharmaceuticals - A/C
- Trukera Medical - Chief Medical Advisor, Optometry

A - Advisory Board
C - Consultant
R - Research
S - Speaker Bureau

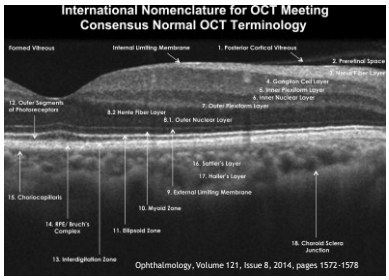
Eye Surgeons of Indiana

3

Outline

- Complications of Early Stage PVD
- Inner Retinal Disease
- Outer Retinal Disease
- Grand Rounds

4



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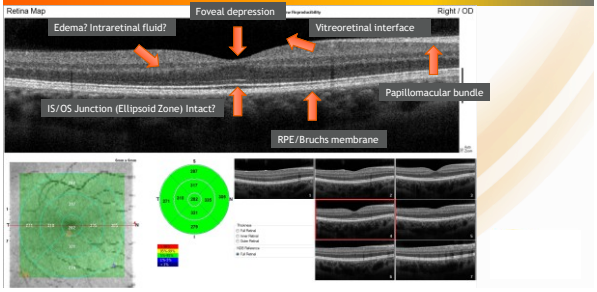
Retina OCT - What is Normal?



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Complications of Early Stage PVD

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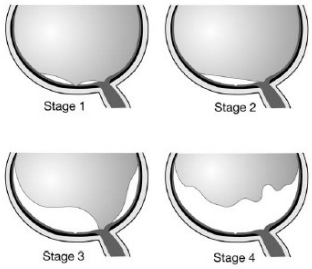
PVD - Stages



Johnson MW. PERIFOVEAL VITREOUS DETACHMENT AND ITS MACULAR COMPLICATIONS. *Transactions of the American Ophthalmological Society*. 2005;103:537-567.

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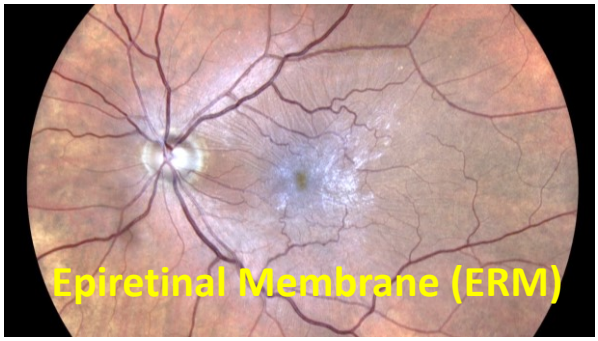

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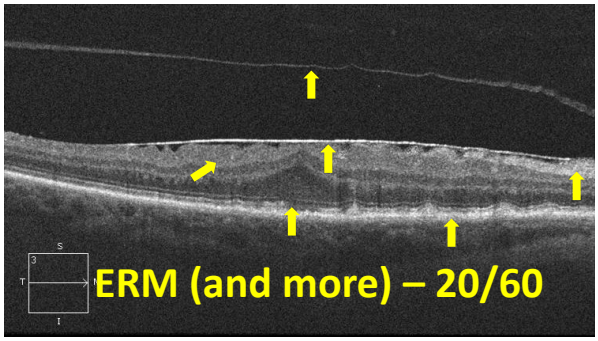

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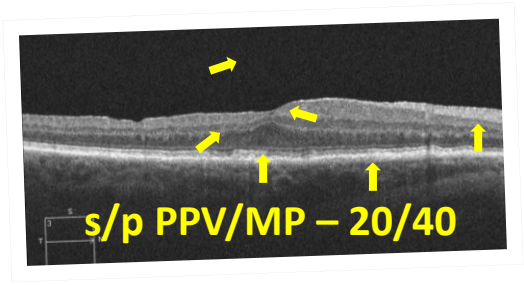

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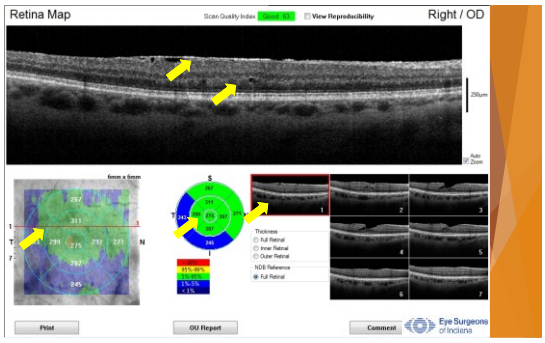

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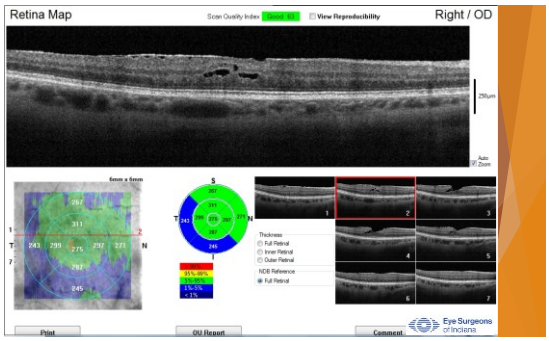

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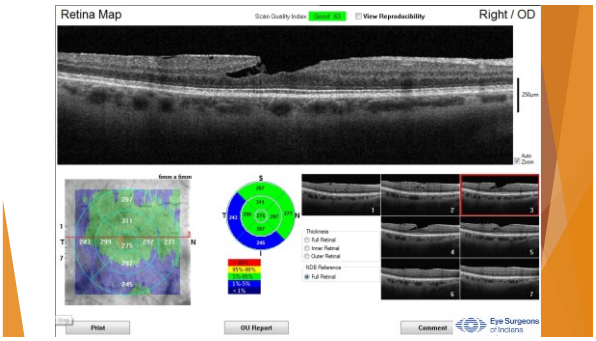

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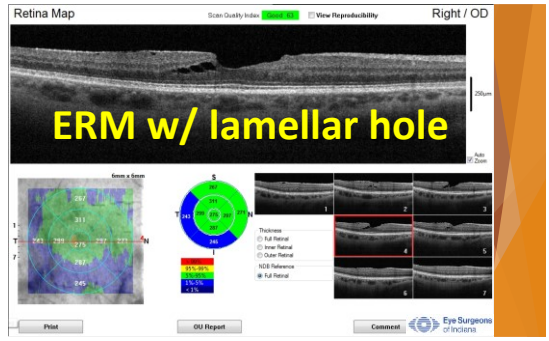

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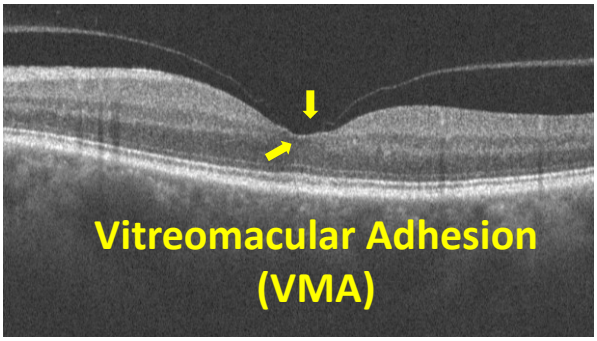

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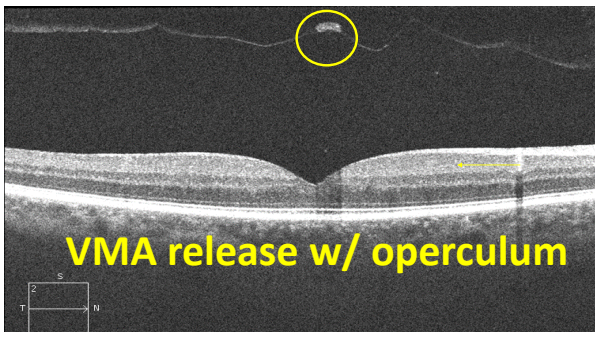

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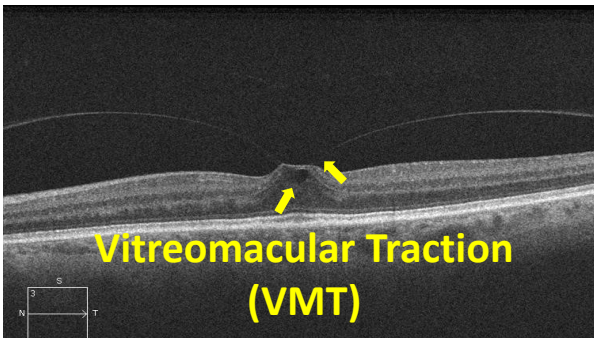

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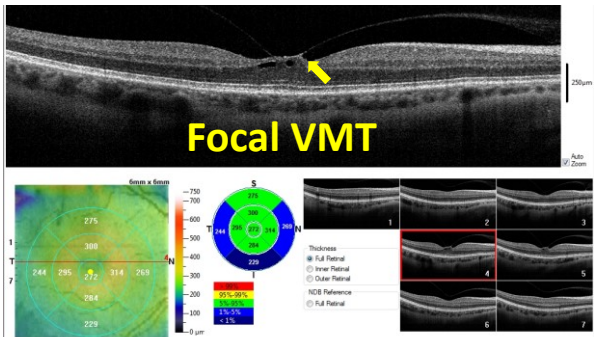

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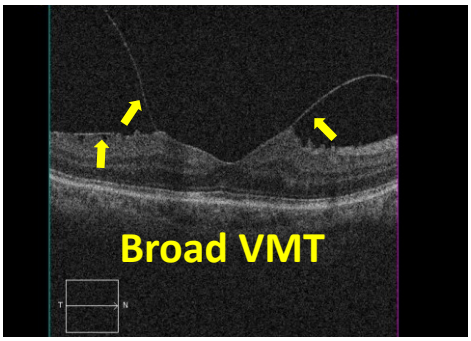

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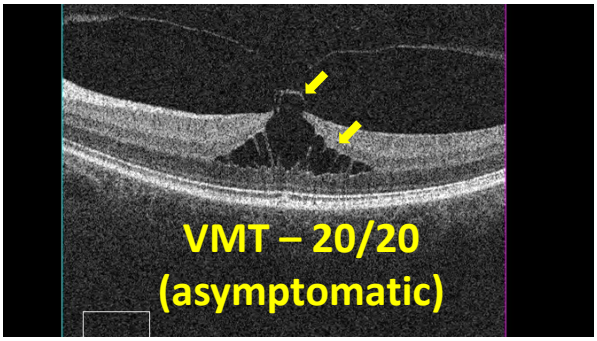

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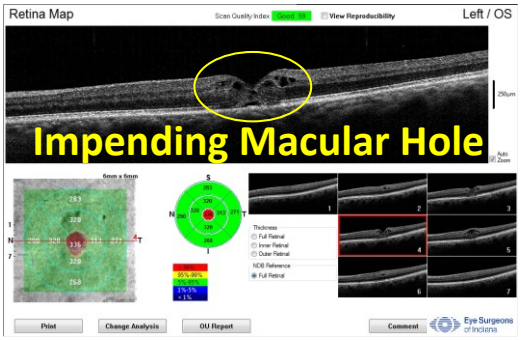

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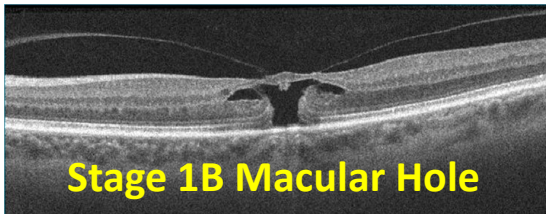
1/30/12 – 68 BM 20/50 OS



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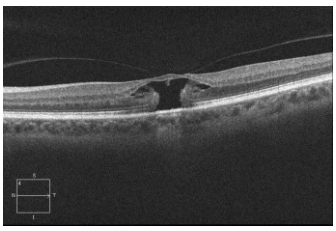
2/20/12 – 20/70



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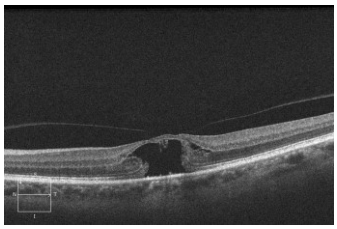
4/5/12 – 20/100



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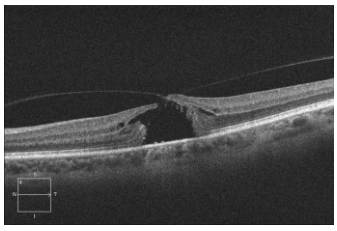
6/11/12 – 20/200



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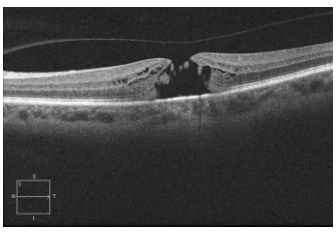
11/12/12 – Patient elects PPV OS – 20/150



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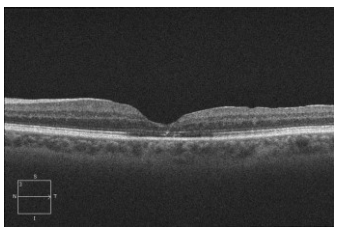
2/18/13 – 3 mo s/p PPV OS – 20/70



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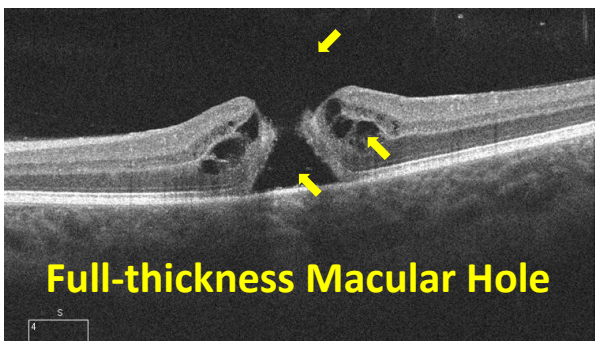

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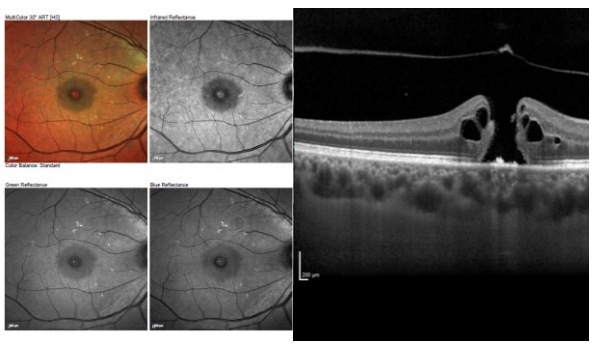

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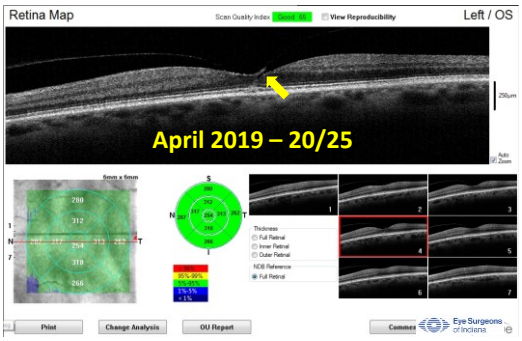

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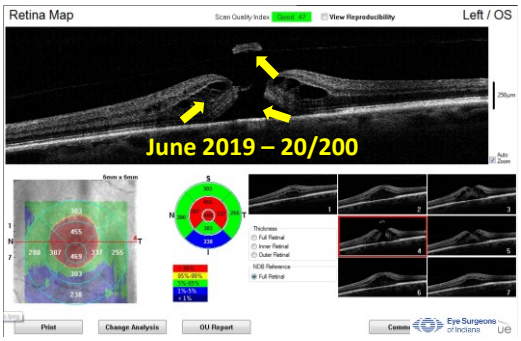

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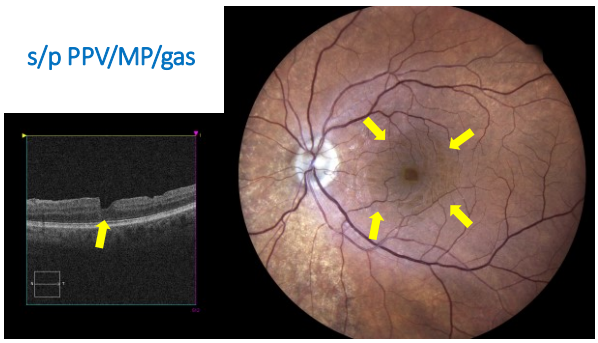
s/p PPV/MP/gas



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CLASSIFYING VMA

CLINICAL STAGES	ATTRIBUTES	COMMENTS
VMA	Vitreous adhesion to central macula with no demonstrable retinal morphologic changes.	Has been called stage 0 in the past when contralateral eye has FTMH; normal appearance on clinical examination; no symptoms.
VMT	Vitreous adhesion to central macula with demonstrable changes by OCT but no full-thickness tissue dehiscence; may include the following: tissue cavitation, cystoid changes in macula, loss of foveal contour, elevation of fovea above the RPE.	May or may not have yellow changes in central macula on examination; can be referred to as impending macular hole if FTMH is present in contralateral eye.
Small FTMH	Hole ≤ 250 µm, may be round or have a flap adherent to vitreous; operculum may or may not be present.	Visual acuity may be relatively good; optimal size for successful repair by pharmacologic vitreolysis; very high probability of success with vitrectomy surgery.
Medium FTMH	Hole > 250 but ≤ 400 µm; may be round or have a flap adherent to vitreous; operculum may or may not be present.	High probability of success with vitrectomy surgery.
Large FTMH	Hole > 400 µm; vitreous more likely to be fully separated from macula.	Slightly less probability of successful closure with vitrectomy surgery.

FTMH, full-thickness macular hole; OCT, optical coherence tomography; RPE, retinal pigment epithelium; VMA, vitreomacular adhesion; VMT, vitreomacular traction.

SOURCE: Adapted from Duker JS et al. *Ophthalmology*. 2013;120(12):2611-2619.

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› Acta Ophthalmol. 2023 May 10. doi: 10.1111/aos.15682. Online ahead of print.

Macular hole Delphi consensus statement (MHOST)

Abstract

Purpose: To derive a Delphi method-based consensus for the surgical management of Full Thickness Macular Hole (FTMH) and Lamellar Macular Hole (LMH).

Methods: 37 expert VR surgeons from 21 mainly European countries participated in Delphi method-based questionnaire for diagnosis and treatment of FTMHs and LMHs.

Results: A total of 36 items were rated in round 1 by 37 participants, of which 10 items achieved consensus: intraoperative verification of PVD; clinical superiority of OCT-based FTMH classification; practical ineffectiveness of ocriplasmin; circular 360° ILM peeling for small macular holes; use of regular surgical technique for the size of the hole in concomitant retinal detachment; performing complete vitrectomy; SF6 gas as preferred tamponade; cataract surgery if crystalline lens is mildly/moderately opaque; removal of both ILM and LHEP in LMH surgery. In round 2, 18 items with moderate consensus (45-70% agreement) in round 1 were rated by 35 participants. Final consensus was reached in 35% of questions related to both diagnosis and surgical procedures.

Conclusions: This Delphi study provides valuable information about the consensus/disagreement on different scenarios encountered during FTMH and LMH management as a guide tosurgical decision-making. High rate of disagreement and/or variable approaches still exist for treating such relatively common conditions.

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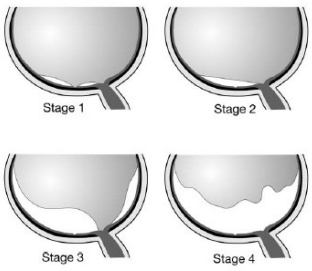


PVD - Stages

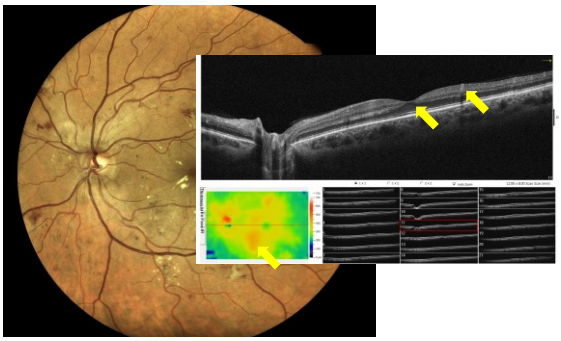
Macular pathology

Peripheral pathology

36

Examples of Inner Retinal Disease

37



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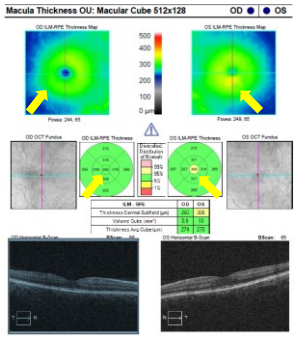

- 52 yo WM
- Referred by PCP
- Type 2 DM x 7 years
- Last HbA1c 7.8%
- No visual complaints
- BCVA 20/20 OD, OS
- DFE: mild NPDR w/o DME
- OCT reveals mild center-involved DME OS

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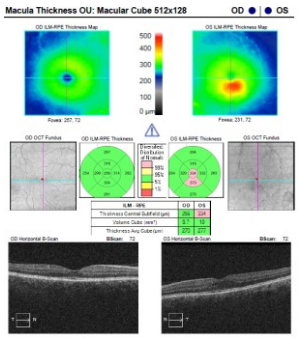


- 4 month F/U
- Last HbA1c 8.2%
- No visual complaints
- BCVA 20/20 OD, 20/25 OS
- DFE: mild NPDR w/ no visible DME
- OCT reveals worsening center-involved DME OS

41

42

JAMA Ophthalmol. 2020 Apr; 138(4): 341–349. PMCID: PMC7042938
Published online 2020 Feb 20. doi: 10.1001/jamaophthalmol.2019.6035 PMID: 32077907

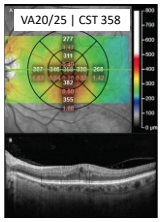
Assessment of the DRCR Retina Network Approach to Management With Initial Observation for Eyes With Center-Involved Diabetic Macular Edema and Good Visual Acuity

Findings

In this secondary analysis of a randomized clinical trial, during 2 years, 80 of 236 eyes (34%) assigned to initial observation received aflibercept. Participants who had thicker retinas, more severe diabetic retinopathy, or a nonstudy eye receiving diabetic macular edema treatment within 4 months of baseline were more likely to receive aflibercept.

Risk Factors for Worsening Diabetic Macular Edema or Vision Loss[7]

- Central subfield thickness of 300 µm or more
- Moderately severe nonproliferative diabetic retinopathy (DRSS level 47 or higher)
- Required treatment in fellow eye
- Hemoglobin A_{1c} ≥7.5%



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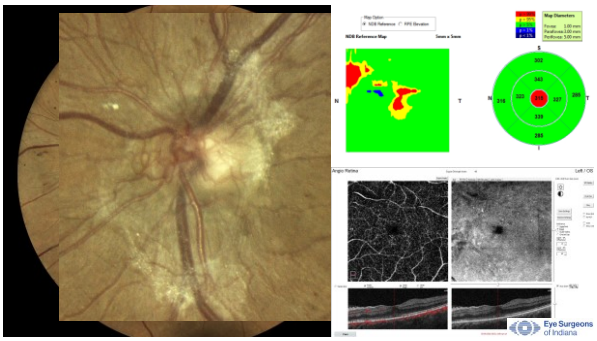

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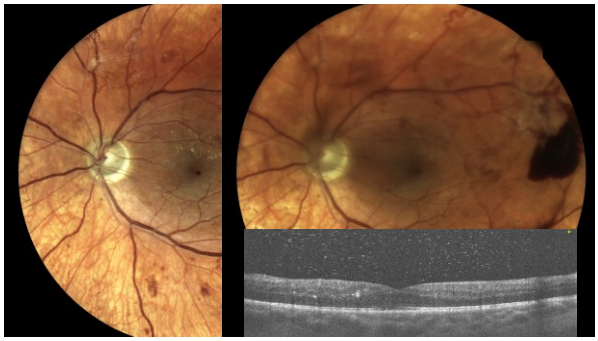

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DR Management – ADA Position Statement

Table 4—Recommended follow-up

Indication	Referral to ophthalmologist	Follow-up	Recommended intraocular treatment*
No diabetic retinopathy	Within 1 year	Every 1–2 years	None
Mild NPDR	Within 1 year	Every year	None
Moderate NPDR	Within 3–6 months	Every 6–9 months	None
Severe NPDR	Immediate	Every 3–6 months	Can consider early PRP for patients with type 2 diabetes
PDR	Immediate	Every 3 months	PRP or intravitreous anti-VEGF therapy, especially if HRCs are present
No DME	Within 1 year	Every 1–2 years	None
Non-CIDME	Within 3–6 months	Every 6 months	None, but observe carefully for progression to CIDME
CIDME	Immediate	Every 1–4 months	Anti-VEGF as first-line therapy for most eyes. Consider macular laser as an adjunctive therapy in eyes with persistent CIDME despite anti-VEGF therapy. Intravitreous steroid treatment can be used as an alternative in selected cases.

*In addition to optimizing systemic control of blood glucose, cholesterol, and hypertension, as well as educating the patient about importance of routine follow-up regardless of whether visual symptoms are present or absent.

Diabetes Care 2017;40:412-418.

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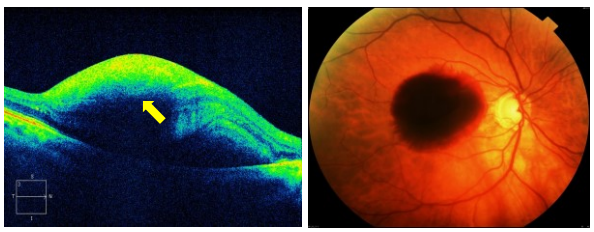
89 yo WF – sudden vision loss OD



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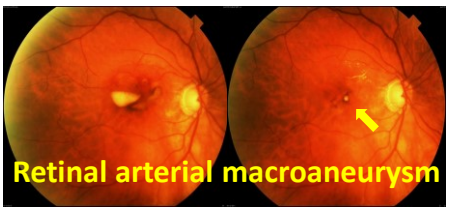
89 yo WF – 2 mos & 6 mos later



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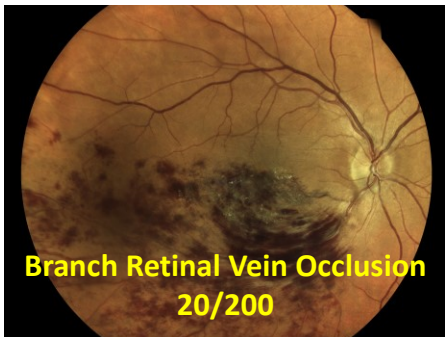

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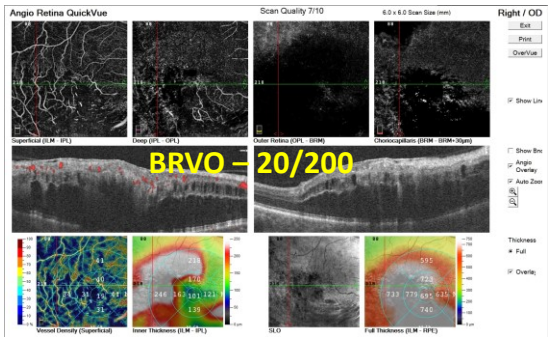

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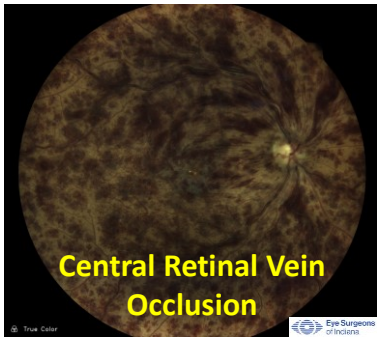

- 55 yo WM
- Referred by her OD
- Type 2 DM x 7 years
- Last HbA1c 7.8%
- ↓VA x 2 weeks OD
- BCVA 20/60 OD

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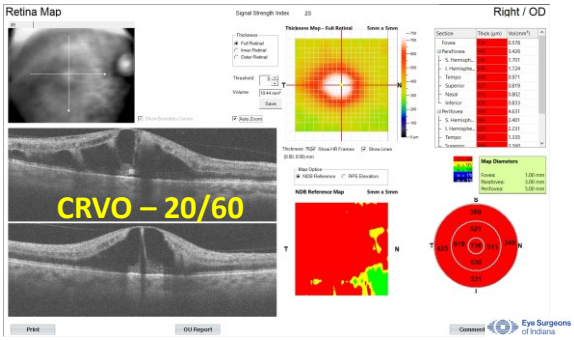

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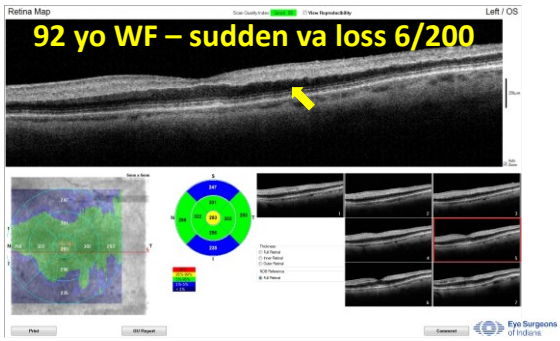

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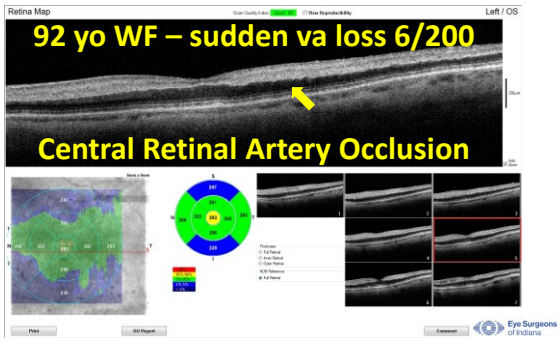

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AHA SCIENTIFIC STATEMENT

Management of Central Retinal Artery Occlusion

A Scientific Statement From the American Heart Association

PURPOSE: Central retinal artery occlusion (CRAO) is a form of acute ischemic stroke that causes severe visual loss and is a harbinger of further cerebrovascular and cardiovascular events. There is a paucity of scientific information on the appropriate management of CRAO, with most strategies based on observational literature and expert opinion. In this scientific statement, we critically appraise the literature on CRAO and provide a framework within which to consider acute treatment and secondary prevention.

METHODS: We performed a literature review of randomized controlled clinical trials, prospective and retrospective cohort studies, case-control studies, case reports, clinical guidelines, review articles, basic science articles, and editorials concerning the management of CRAO. We assembled a panel comprising experts in the fields of vascular neurology, neuro-ophthalmology, vitreo-retinal surgery, immunology, endovascular neurosurgery, and cardiology, and document sections were divided among the writing group members. Each member received an assignment to perform a literature review, synthesize the data, and offer considerations for practice. Multiple drafts were circulated among the group until consensus was achieved.

RESULTS: Acute CRAO is a medical emergency. Systems of care should evolve to prioritize early recognition and triage of CRAO to emergency medical attention. There is considerable variability in management patterns among practitioners, institutions, and subspecialty groups. The current literature suggests that treatment with intravenous tissue plasminogen activator may be effective. Patients should undergo urgent screening and treatment of vascular risk factors. There is a need for high-quality, randomized clinical trials in this field.

Stroke. 2021;52:e282–e294.

55

Examples of Outer Retinal Disease

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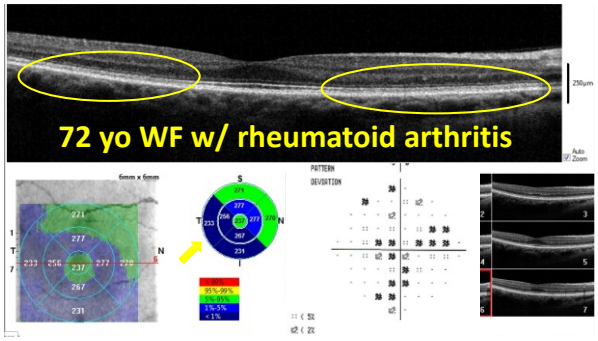

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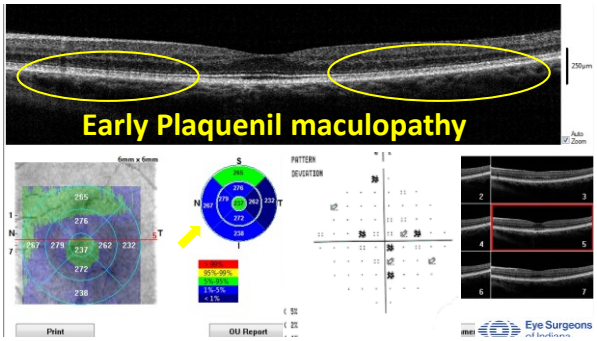


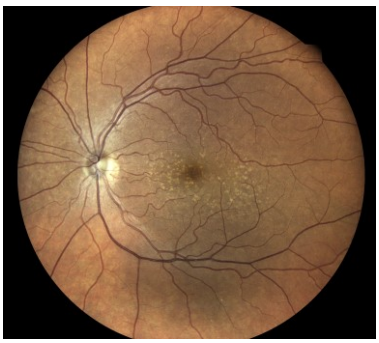
58

TABLE 2. 2016 REVISED RECOMMENDTIONS FOR HCQ AND CHLOROQUINE SCREENING[5]

Recommended Screening Tests	· Visual fields: white SITA testing with pattern deviation plots »10-2 for non-Asian patients »24-2 or 30-2 for Asian patients · Spectral-domain OCT (widefield for Asian patients) · Other objective tests »FAF (widefield for Asian patients) »Multifocal electroretinogram
Newer Screening Tests in the Future	· Microperimetry · Adaptive optics retinal screening
Not Recommended for Screening	· Fundus examination · Time-domain OCT · Fluorescein angiography · Full-field ERG · Amsler grid · Color testing · Electro-oculogram

https://www.reviewofoptometry.com/article/plaquenil-toxicity-how-to-avoid-this-bullseye; accessed 9/4/23

59



- 68 yo WM
- 6 month AMD F/U
- BCVA 20/20 OD, OS
- Trace NS cataract OU

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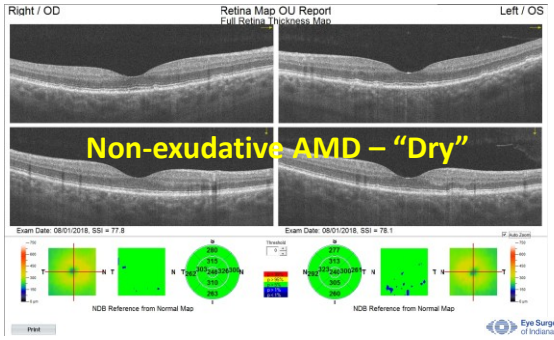

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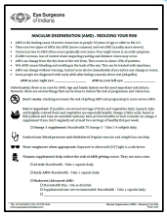
Risk Reduction Strategies – Early AMD

- Smoking cessation
- Diet
- Nutritional supplements
- HTN/cholesterol control
- Exercise/weight control
- UV/blue light protection



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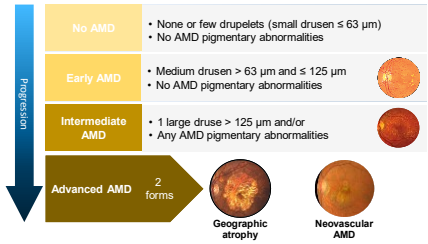
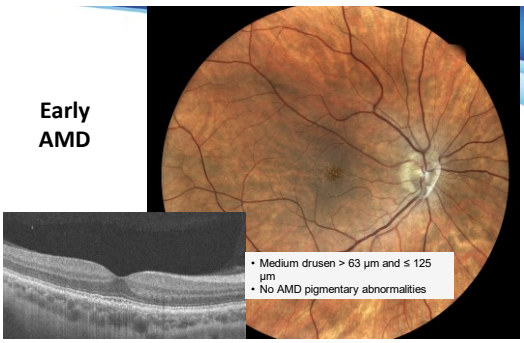
The Beckman Committee Classifies AMD Into 4 Stages



Ferris FL, et al. Ophthalmology. 2013;120(4):844-851.

63

Early AMD



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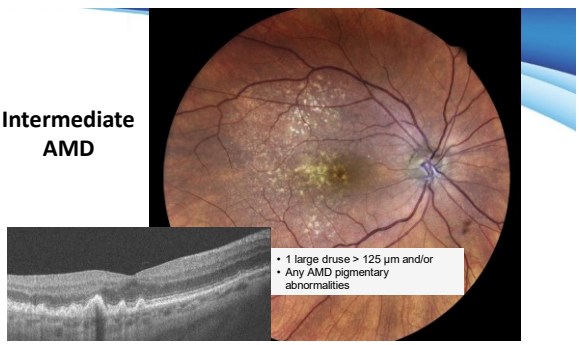
Intermediate AMD



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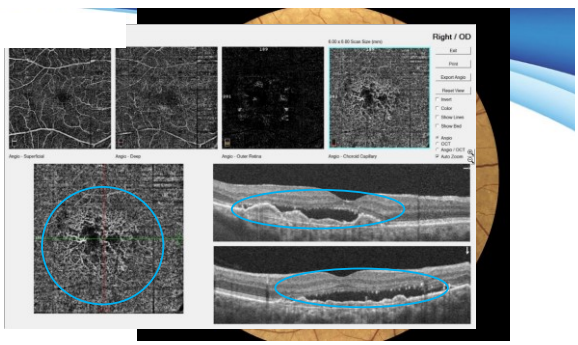

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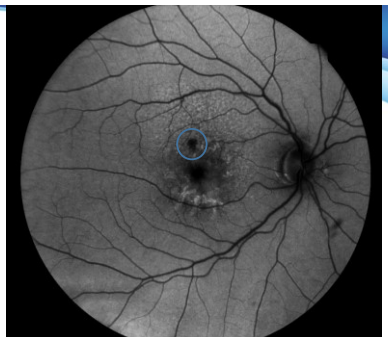
Advanced AMD

GA



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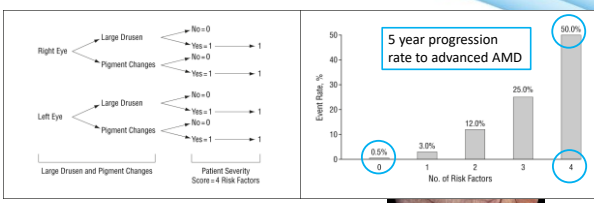
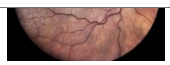
Predicting AMD progression





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Predicting AMD progression w/ OCT

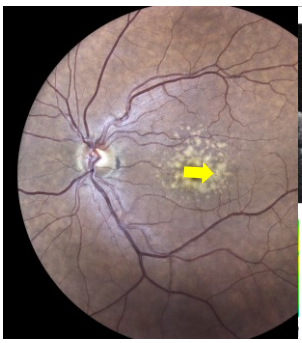
CLINICAL AND EXPERIMENTAL OPTOMETRY

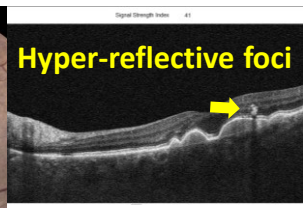
REVIEW

Developing prognostic biomarkers in intermediate age-related macular degeneration: their clinical use in predicting progression

- **Hyper-reflective foci**
- **Reticular pseudodrusen**
- **Nascent geographic atrophy**
- **Sub-RPE hyper-reflective columns**
- **Drusen with subretinal fluid**
- **Drusen substructures**
- **Drusen load**
- **Drusen regression**

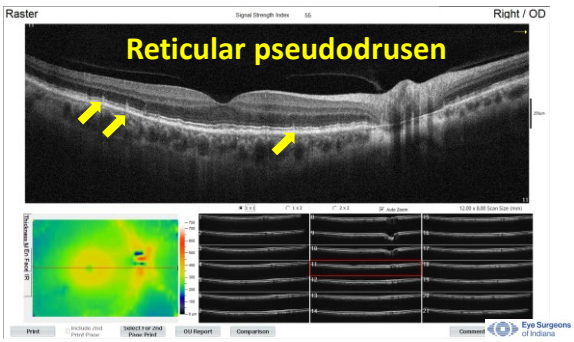
69





- Intraretinal lesion overlying drusen
- Often correspond to focal hyperpigmentation
- Likely represents pigment granules
- 5X ↑ risk of GA over 2 years
- No increased risk of CNV

70



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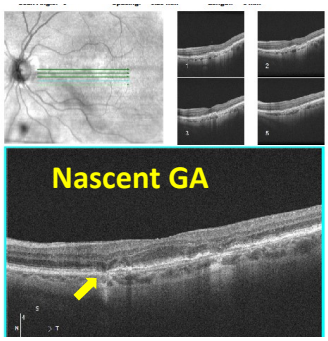
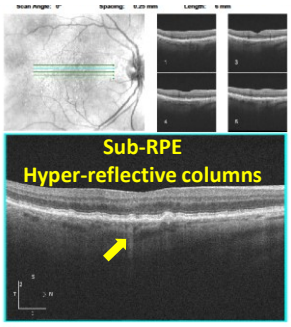


- Thinning of OPL/INL w/ hyporeflective wedge
- "Impending" geographic atrophy
- No extra risk of CNV

72



- Increased transmission of signal columns beneath the RPE
- Overlying RPE appears intact
- May represent fine cracks in the RPE
- Opposite appearance of shadows cast by retinal blood vessels
- Increased risk of geographic disease and CNV

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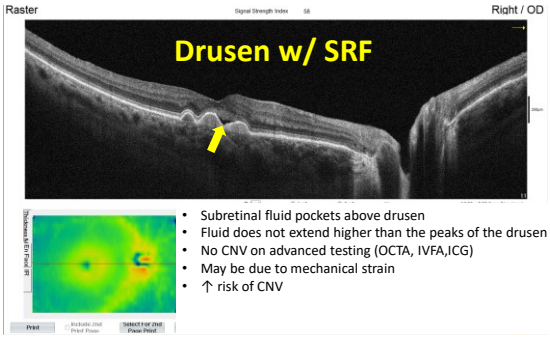

- Subretinal fluid pockets above drusen
- Fluid does not extend higher than the peaks of the drusen
- No CNV on advanced testing (OCTA, IVFA,ICG)
- May be due to mechanical strain
- ↑ risk of CNV

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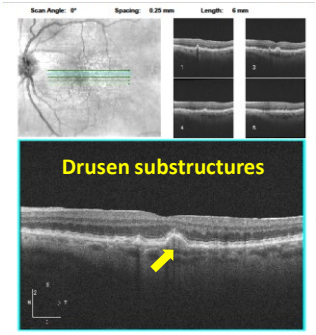

- Non-homogeneous internal reflectivity of soft drusen
- All look the same on examination / photos, but have differing OCT reflectivity
- May precede drusen regression
- Increased risk of GA but not CNV

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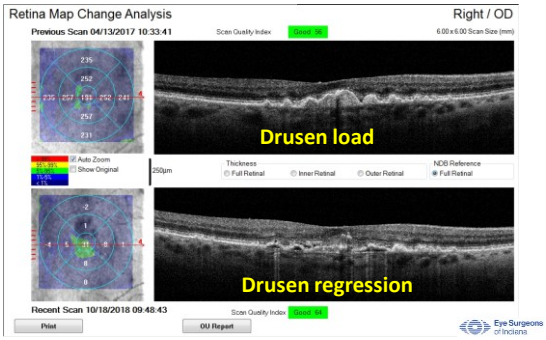

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Case Report – AMD

- 72 yo WF c/o vision loss OU, difficulty driving, glare
- Patient had been told they "may have early AMD"
- Visually significant cataract 20/40 BCVA OU
- Dry AMD discussed at surgical eval, OCT done
- Successful surgery w/ 20/20 BCVA OU – "my vision is perfect"
- Plan: further assessment of AMD @ final PO visit

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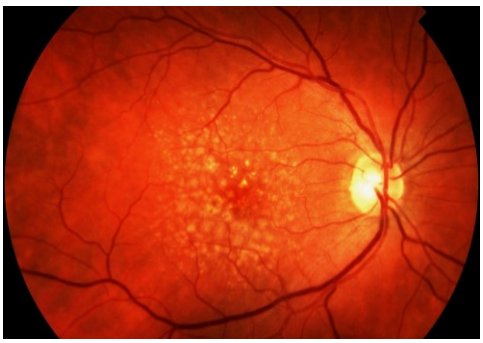

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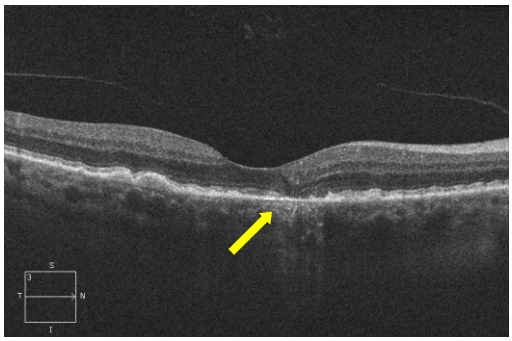

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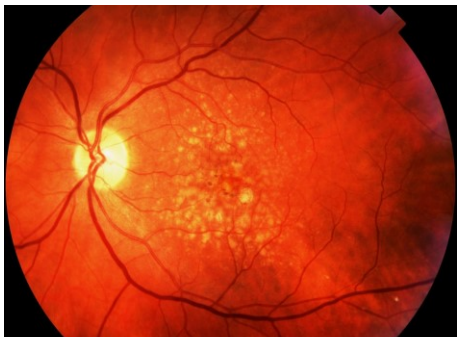

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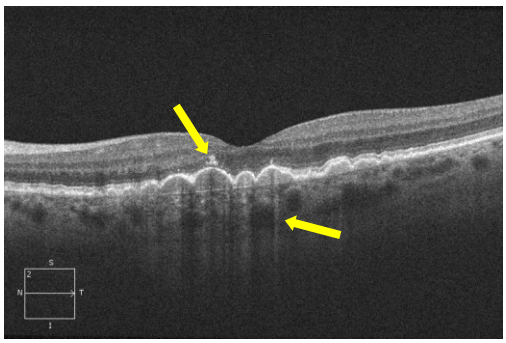

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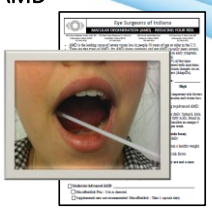
What Else Can Be Done NOW to Improve Outcomes in Intermediate AMD?

82

Risk Reduction – Intermediate AMD

- Smoking cessation
- Diet
- Nutritional supplements
- HTN/cholesterol control
- Exercise/weight control
- UV/blue light protection



Addition #1 - Consider genetic testing

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Zinc controversy

- 80 mg zinc in AREDS showed benefit in patients w/ intermediate AMD by reducing risk of progression to CNV
- Further analysis of AREDS has shown that some patients w/ a specific genotype may be harmed by 80 mg zinc (i.e. more likely to progress to wet)
- AREDS2 showed equal benefit in patients taking 80 mg vs. 25 mg zinc
- 80 mg is 700% RDA
- High-dose zinc has been linked to:
  - Urinary tract infections
  - Benign prostate hypertrophy
  - Prostate cancer
  - Alzheimer's

AREDS Report No. 8. *Arch Ophthalmol.* 2001;119:1417-1436.
Vavvas D et al. *PNAS.* 2018;115(4):E696-E704.
AREDS2 Research Group. *JAMA.* 2013;309(19):2005-2015.
https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/ accessed 9/1/19
Tolentino et al. *J Pharmacovigil.* 2016;4(1):1-5.

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Gene – AREDS Science – Only CNV is Relevant

First four studies incorrectly included GA patients

First studies isolate genetic interaction w AREDS

1. Awh C. et al ; CFH and ARMS2 genetic polymorphisms predict response to antioxidants and zinc in patients with age-related macular degeneration; *Ophthalmology*, November 2013
2. Awh C. et al ; Treatment Response to Antioxidants and Zinc Based on *CFH* and *ARMS2* Genetic Risk Allele Number in the Age-Related Eye Disease Study; *Ophthalmology*, January 2015

Measuring Progression to Geographic Atrophy (Wrong Disease) and CNV

3. Chew E. Y. et al. No Clinically Significant Association between CFH and ARMS2 Genotypes and Response to Nutritional Supplements: *Ophthalmology*, November 2014
4. Assel M. et al ; Genetic Polymorphisms of CFH and ARMS2 Do Not Predict Response to Antioxidants and Zinc in Patients with Age-Related Macular Degeneration; *Ophthalmology*, November 2017

All Studies 5-8 prove AREDS interaction for CNV

CNV - Validating Studies – Demonstrate Genetic Interaction and 'HARM' (AREDS vs. Placebo)

5. Seddon J.M. et al. Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis; *BJO*, July 2016
6. Vavvas D. et al; *CFH* and *ARMS2* genetic risk influences the safety and efficacy of AREDS against progression to Wet AMD (NV); *PNAS*, January 2018:
7. Zanke B. Letter to the Editor re: Assel et al., *Ophthalmology*, May 2018

ASRS 2019 - Genetic Interaction with AREDS against CNV

8. Kaufman S. et al. Multiple Practice analysis of Harm with C2A0 genotype and AREDS against wet AM

85

THE GAIN STUDY:

GENETICS AND AREDS FORMULA INTERACTION IN NEOVASCULAR AMD

Stephen R. Kaufman, MD
Pradeepa Yoganathan, MD FRCSC

Kent W. Small, MD
Deepam Rusia, MD
Sophia I. Pachydaki, MD
Stephen M. Conti, MD
Robert E. Wenz, MD
Mark A. Gersman, MD
Fadi S. Shaya, BS
Rafal Kustra, PhD

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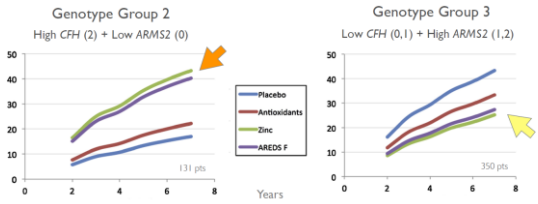
BACKGROUND

Progression rate to advanced AMD when exposed to AREDS F or Zinc vs Placebo



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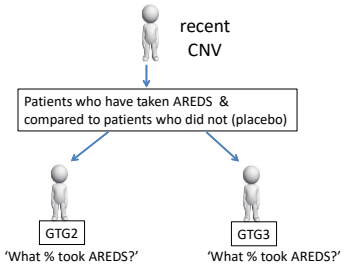

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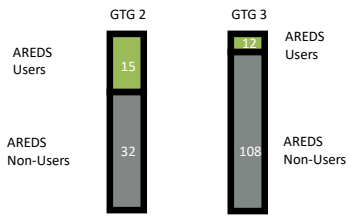
The **odds** of AREDS Formula use in GTG 2 vs GTG 3: **4.22** (p = 0.00126)



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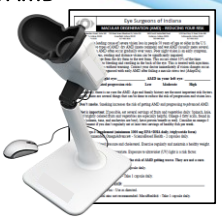
Risk Reduction – Intermediate AMD

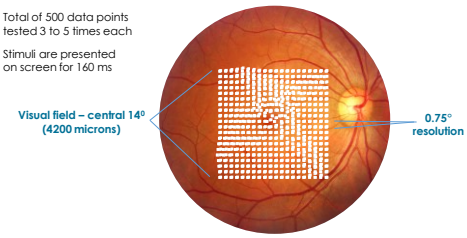
- Smoking cessation
- Diet
- Nutritional supplements
- HTN/cholesterol control
- Exercise/weight control
- UV/blue light protection



Addition #2 - Consider home monitoring

90

The ForeseeHome test



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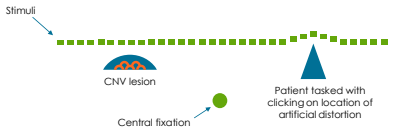
ForeseeHome Test Procedure



When the elevation caused by CNV is larger than the Artificial Distortion, the patient will preferentially pick this spot of true distortion

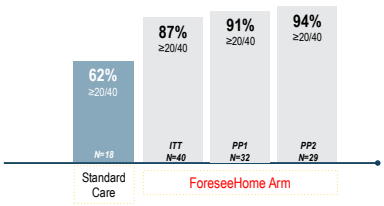
92

The HOME Study

Chew EY, et al. Ophthalmology 2014;121(2):535-544.

93

Proportion of Eyes Maintaining ≥20/40 at CNV Detection



50% INCREASE
in patients in ForeseeHome arm compared to standard care alone

Chew EY, et al. Ophthalmology 2014;121(2):535-544.

94

One of the very few studies in Ophthalmology that has been stopped due to POSITIVE EFFICACY

DSMC RECOMMENDATION

- On April 30, 2013, the DSMC reviewed the study results and concluded that study eyes at risk of AMD progression presented to their study sites with SIGNIFICANTLY BETTER VISION WHEN THEIR NEOVASCULAR AMD DEVELOPMENT WAS DETECTED BY THE FORESEEHOME DEVICE as compared to standard monitoring.
- Therefore, the DSMC UNANIMOUSLY RECOMMENDED EARLY TERMINATION OF THE STUDY AS THEY WERE CONFIDENT THAT THE STUDY HAD MET ITS PRIMARY OBJECTIVE; namely, demonstrating that eyes at high risk of progression to neovascular AMD can be identified with better levels of vision when they are detected by use of the home monitoring device as compared to standard methods.

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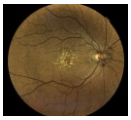

Journal of Clinical Medicine — MDPI

Article

Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular Age-Related Macular Degeneration

Allen C. Ho [1], Jeffrey S. Heier [2], Nancy M. Holekamp [3], Richard A. Garfinkel [4], Byron Ladd [5], Carl C. Awh [6], Rishi P. Singh [7], George E. Sanborn [8], Jennifer H. Jacobs [9], Michael J. Elman [9], Anat Loewenstein [10,11,*] and David A. Eichenbaum [12]

- Large scale retrospective analysis of 3.2 million tests using ForeseeHome
- Identified 306 eyes that converted to wet AMD
- Functional vision (20/40 or better) at conversion was 81%
- "The home telemonitoring system can markedly increase early detection of conversion to wet AMD"

Ho AC, Heier JS, Holekamp NM, Garfinkel RA, Ladd B, Awh CC, Singh RP, Sanborn GE, Jacobs JH, Elman MJ, Loewenstein A, Eichenbaum DA. Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular Age-Related Macular Degeneration. J Clin Med. 2021 Mar 25;10(7):1355.

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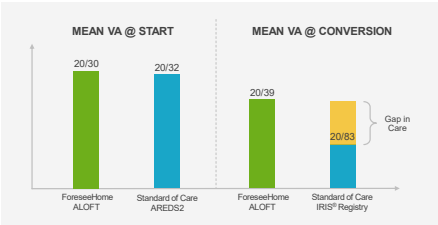
Visual Acuity Results: Comparing ALOFT w/ Standard of Care



[1] Chew EY, et. al. The AREDS2 Randomized Clinical Trial. JAMA. 2015.
[2] Ho, AC, et al. Ophthalmic Surg Lasers Imaging Retina. 2020

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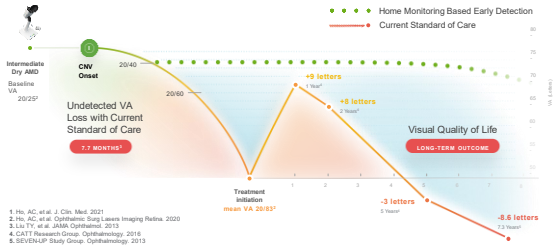
Summary: Average nAMD Patient Journey



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What Else Can Potentially Be Done SOON to Improve Outcomes in Intermediate AMD?

99

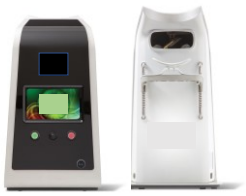
Photobiomodulation (PBM)

Photobiomodulation, also known as low-level light therapy, is the medical application of low-level light wavelengths to stimulate cellular function leading to beneficial clinical effects.

100

Valeda® Light Delivery System

Parameter	Specification
Size	530 mm height x 300 mm width x 330 mm depth (20.8" x 11.8" x 13")
Weight	10.8 Kg (23.8 lbs.)
Light sources	Light Emitting Diodes (LEDs)
Light emission	590 nm output: 5 mW/cm^2 660 nm output: 65 mW/cm^2 850 nm output: 8 mW/cm^2
Beam diameter	30 mm (nominal) at treatment plane
Treatment exposure time	A total of 250 seconds (4 minutes 10 seconds). There are 4 phases: • Phase 1: 590 nm pulsed: 35 seconds • Phase 2: 660 and 850 nm continuous waveform: 90 seconds • Phase 3: 590 nm pulsed: 35 seconds • Phase 4: 660 and 850 nm continuous waveform: 90 seconds



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Valeda® Multiwavelength Photobiomodulation Approach

Wavelengths were selected based on cellular targets and importance in AMD

Wavelength 590	Wavelength 660	Wavelength 850
Stimulates CCO activity, increases NO synthesis	Promotes O_2 binding (Cu_A), stimulates metabolic activity (ATP), and inhibits inflammation and cell death	Drives electron transfer (Cu_A), stimulates metabolic activity (ATP), and inhibits inflammation and cell death

CCO – Cytochrome C Oxidase
NO – Nitric Oxide
ATP – Adenosine Triphosphate

Wong-Riley MTT, et al. J Biol Chem. 2005; 280: 4761-71; Ball KA, et al. J Photochem Photobiol B Biol, 2012; 102: 182-91.

102

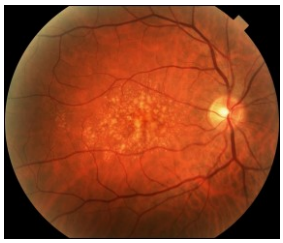
Valeda® Light Delivery System

Valeda Overview

- Valeda treatment delivery very similar to many ophthalmology office diagnostic and treatment devices
- Treatment typically administered by trained staff under doctor supervision
- <5 min treatment per eye
- No pupil dilation required
- 9 flexible treatment sessions delivered over 3–4 weeks
- 2-3 treatment cycles per annum

103

Potential Breakthrough Therapeutic for Dry AMD



Valeda Light Delivery System

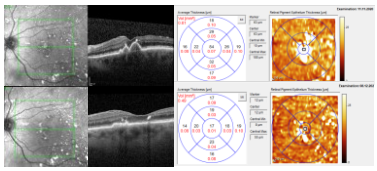
- Five successful clinical studies
- ~200 patients across multiple completed and enrolled trials
- Non–invasive, safe therapy for patient
- Approved in Europe and other OUS markets
- First CE-approved therapy for Dry AMD
- US LIGHTSITE III pivotal trial top line data met primary endpoint
- Data from the two-year LIGHTSITE III trial will be used to support Valeda FDA submission

104

Macular Drusen Reduction Following PBM Treatment

Reduction of anatomical deficits observed in a subject in the LIGHTSITE III study at 13 months.

Age: 77 years
Sex: Female
Eye: OS
Baseline BCVA: 75
13-Month BCVA: 79 letters



- A significant reduction in macular drusen volume was observed following four series of PBM treatment without loss of PR or retinal pigment epithelium visible. A 4-letter increase in BCVA was observed from 75 letters to 79 letters.

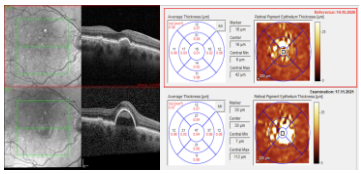
Munk MR, et al. Invest Ophthalmol Vis Sci. 2022; 63:ARVO E-Abstract F0210.

105

Macular Drusen Increase Following Sham Treatment

Progression of anatomical deficits observed in a subject in the LIGHTSITE III study at 13 months.

Age: 73 years
Sex: Male
Eye: OD
Baseline BCVA: 72 letters
13-Month BCVA: 69 letters



- A significant increase in macular drusen volume was observed following four series of Sham treatment with confluent drusen that further developed into large retinal pigment epithelial detachments. A 3-letter loss was observed at Month 13.

Munk MR, et al. Invest Ophthalmol Vis Sci. 2022; 63:ARVO E-Abstract F0210.

106

LIGHTSITE III: U.S. Pivotal Study - 13 Month Results

The LIGHTSITE III study is an FDA, IDE-approved prospective, double-masked, randomized, sham-controlled, parallel group, multi-center study to assess the safety and efficacy of photobiomodulation in subjects with dry AMD

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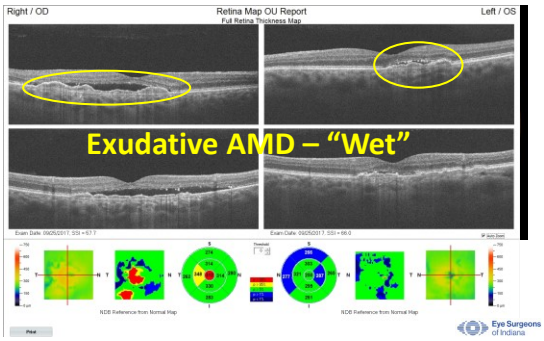
LIGHTSITE III: Study Summary

- LIGHTSITE III met the predetermined primary efficacy BCVA endpoint with a statistically significant difference between the PBM group versus the Sham treatment group ($p = 0.0204$) at Month 13
- An improved BCVA with a mean 5.4 letter gain in PBM eyes from Baseline at Month 13 was observed ($p < 0.0001$)
  - 55% of PBM eyes showed >5 letter gain (mean letter gain of 9.7 letters)
  - 26.4% of PBM eyes showed >10 letter gain (mean letter gain of 12.8 letters)
  - 5.5% of PBM eyes showed >15 letter gain
- Approximate 2x decrease in patients with lost BCVA letter scores in the PBM eyes versus the Sham-treated eyes
- Non-study control eyes (no PBM or Sham treatment) that showed >75 letters in BCVA at baseline (n=12) show a mean BCVA loss of 2.3 letters in comparison to Sham-treated eyes (Active PBM control) which show a mean BCVA gain of 3.0 letters
- A non-significant numerical increase in central drusen volume was observed in Sham group, whereas no increase in central drusen volume was seen in the PBM group
- A statistically significant correlation was observed for improvements in BCVA and reductions in macular drusen volume in PBM eyes
- Occurrence of new geographic atrophy (GA) was observed in 5/51 (9.8%) of Sham subjects and 1 of 88 (1.1%) of PBM subjects. The occurrence of new GA in subjects with intermediate dry AMD was significantly higher in the Sham group than in the PBM group ($p = 0.025$, Fisher exact test, odds ratio 9.3). * $p < 0.05$.
- PBM treatment with Valeda shows an excellent safety profile with high compliance and no signs of phototoxicity

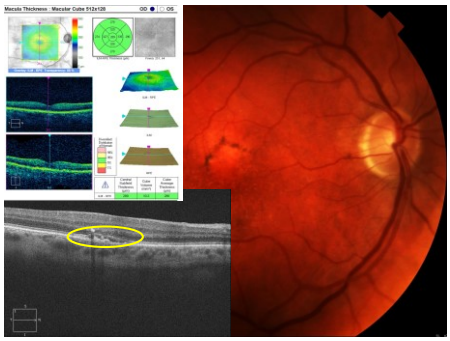
Munk MR, et al. Invest Ophthalmol Vis Sci. 2022; 63:ARVO E-Abstract F0210.

108



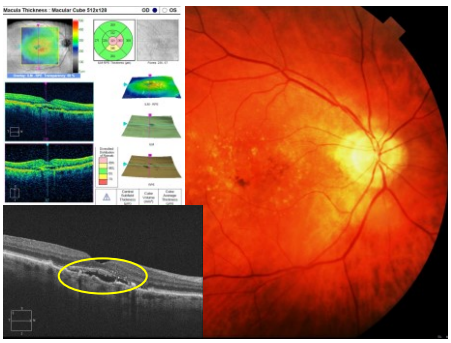
109

Wet AMD
20/20
asymptomatic



110

Wet AMD
20/25
asymptomatic



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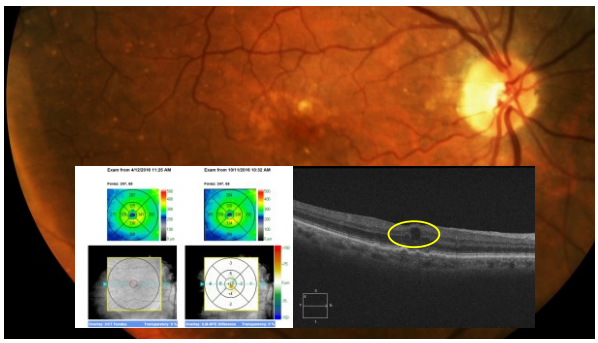
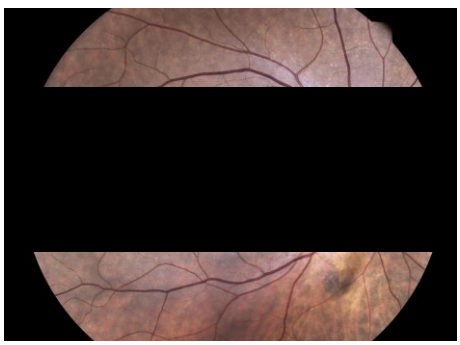


112

Advanced AMD

CNV



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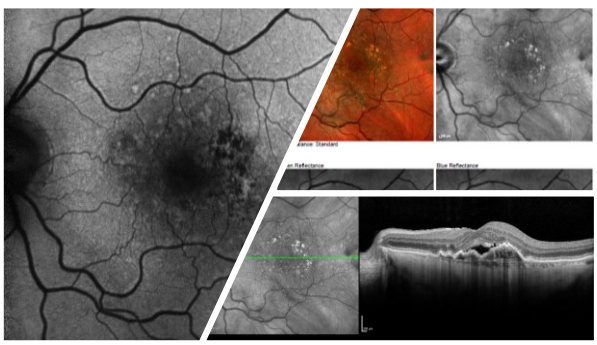
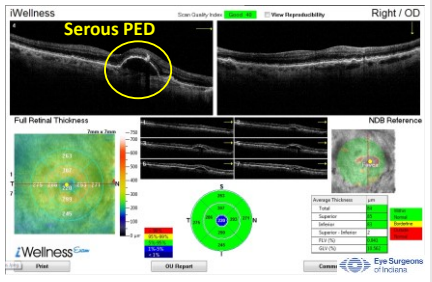


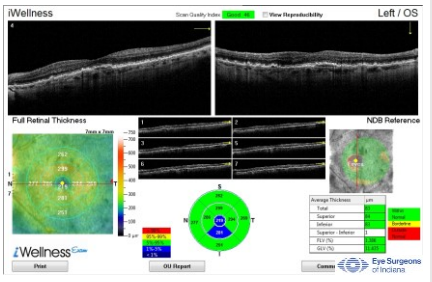
114

76yo WF
Cat eval
20/50
2+ NS



115

76yo WF
Cat eval
20/40
2+ NS



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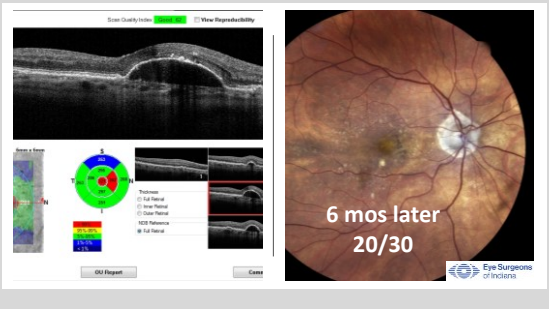

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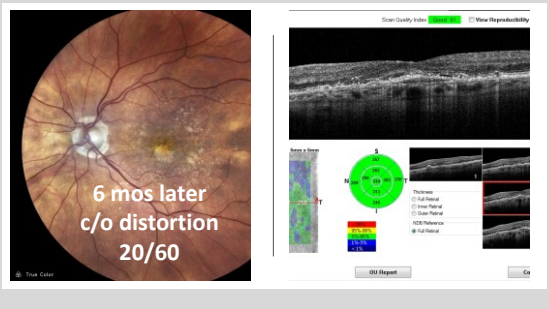

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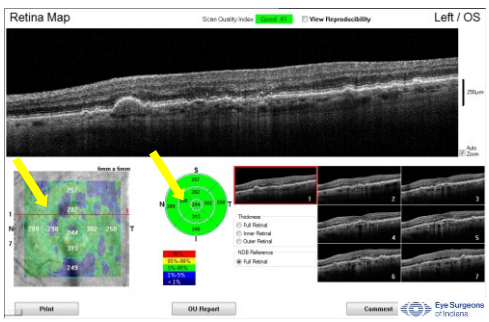

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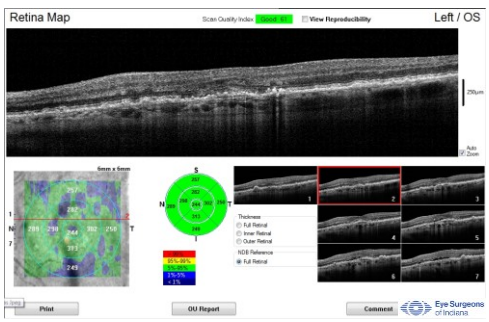

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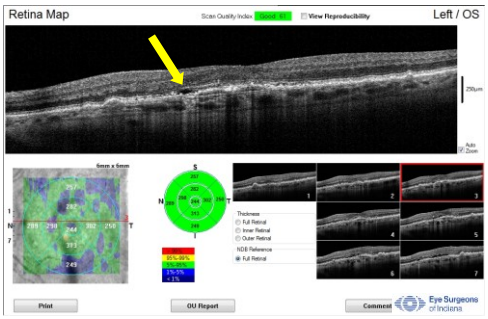

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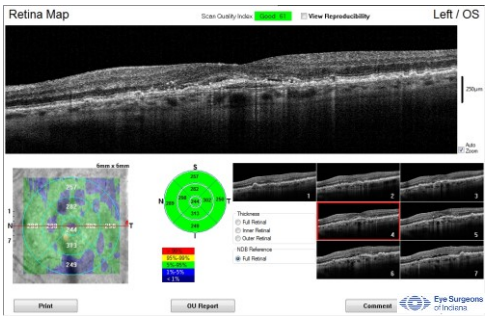

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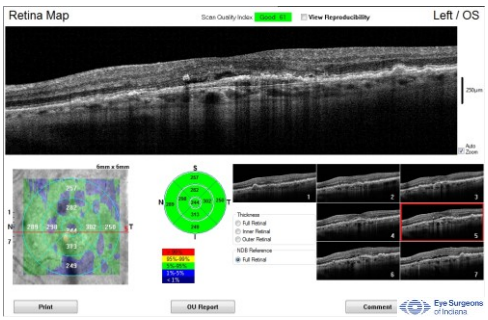

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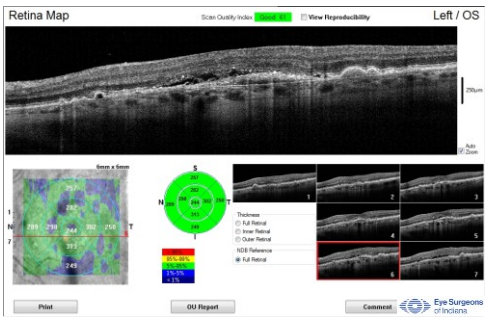

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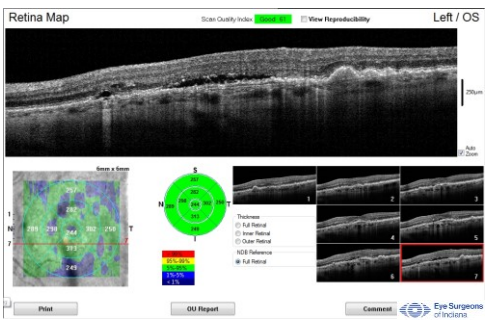
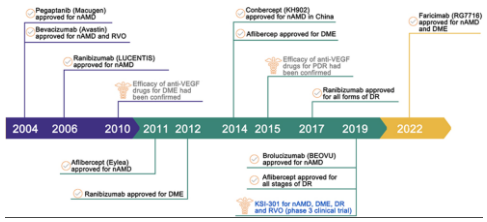


125

Anti-VEGF Evolution



Xu M, Fan R, Fan X, Shao Y, Li X. Progress and Challenges of Anti-VEGF Agents and Their Sustained-Release Strategies for Retinal Angiogenesis. *Drug Des Devel Ther*. 2022;16:3241-3262

126

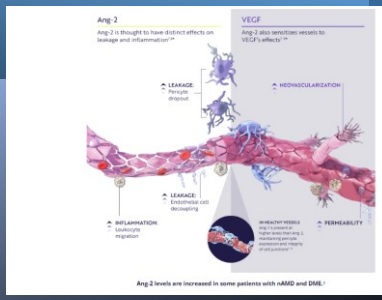
Friday, Jan 28, 2022

FDA Approves Genentech's Vabysmo, the First Bispecific Antibody for the Eye, to Treat Two Leading Causes of Vision Loss

Vabysmo (faricimab-svoa) targets and inhibits two disease pathways that drive wet age-related macular degeneration (AMD) and diabetic macular edema (DME)

Vabysmo is the only injectable eye medicine approved simultaneously in the US for wet AMD and DME, with flexible dosing regimens based on patient need

127



128

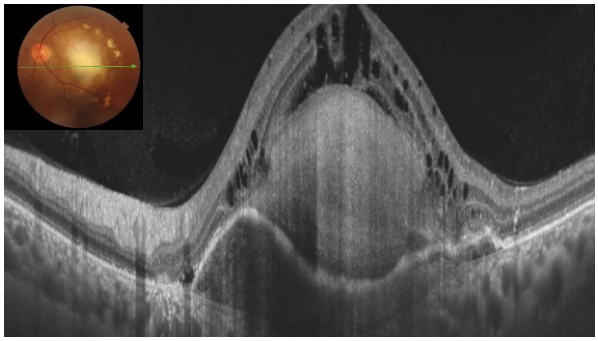
August 18, 2023

EYLEA HD (AFLIBERCEPT) INJECTION 8 MG APPROVED BY FDA FOR TREATMENT OF WET AGE-RELATED MACULAR DEGENERATION (WAMD), DIABETIC MACULAR EDEMA (DME) AND DIABETIC RETINOPATHY (DR)

Approval based on the pivotal PULSAR and PHOTON trials in which EYLEA® HD demonstrated clinically equivalent vision gains to EYLEA (aflibercept) Injection 2 mg that were maintained with fewer injections

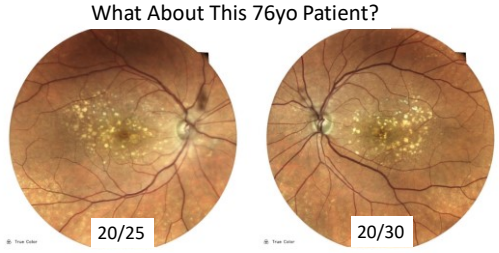
First and only treatment approved in wAMD and DME for immediate dosing at 8-week and up to 16-week intervals following three initial monthly doses

129



130

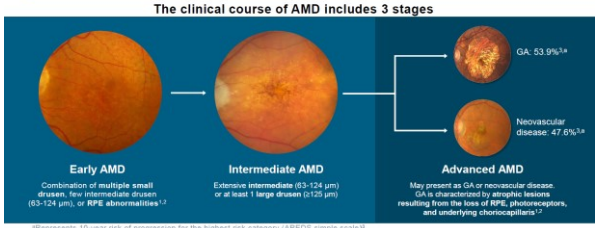
What About This 76yo Patient?



131

GA Is Characterized by Atrophic Lesions Resulting From the Loss of RPE, Photoreceptors, and Underlying Choriocapillaris

The clinical course of AMD includes 3 stages



[a]Represents 10-year risk of progression for the highest risk category (AREDS simple scale)[2]

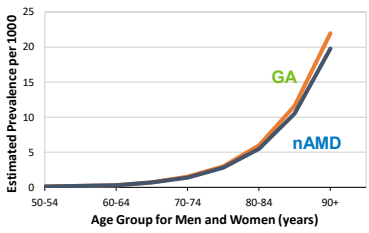
AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; GA, geographic atrophy; RPE, retinal pigment epithelium.

1. Ambati et al. *Nat Rev Immunol*. 2013;13(6):438-451. 2. Fleckenstein et al. *Ophthalmology*. 2018;125(3):369-390. 3. Chew et al. *JAMA Ophthalmol*. 2014;132(3):272-277.

15

132

Estimated Prevalence Rates of GA and Wet AMD Are Similar



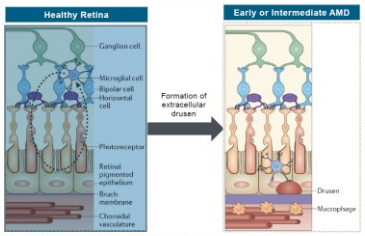
- Geographic Atrophy (GA) is as common as wet AMD[1,2]
- GA and wet AMD prevalence rates both rise **exponentially** with age[1]
- Approximately 1.5 million Americans are estimated to have GA[3]

- nAMD, neovascular age-related macular degeneration. Graph data source: Rudnicka AR et al. 2015;[1] incidence for the US white population aged ≥50 years.
- 1. Rudnicka AR, et al. Am J Ophthalmol 2015;160:85-93.e3; 2. Wong WL, et al. Lancet Glob Health 2014;2:e106-16; 3. Jaffe GJ, Westby K, Csaky KG, et al. Ophthalmology. 2021;128(4):574-586.

133

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.
Bowes et al. Retina. 2017;37(5):819-835.
Image reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Nature Reviews Immunology*, Immunology of Age-related Macular Degeneration, Ambati et al. © 2013.

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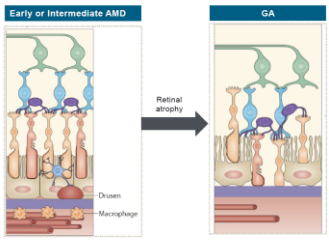
Cumulative Retinal Damage Can Trigger Inflammation and Lead to Widespread Retinal Atrophy

- 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. Bowes et al. Retina. 2017;37(5):819-835. 2. van Lookeren Campagne et al. Immunology. 2018;221(6):733-739. 3. Fleckenstein et al. Ophthalmology. 2018;125(3):369-390.
Image reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Nature Reviews Immunology*, Immunology of Age-related Macular Degeneration, Ambati et al. © 2013.

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Geographic Atrophy May Be Suspected by Symptoms of Impaired Visual Function

Symptoms of impaired visual function in GA can include

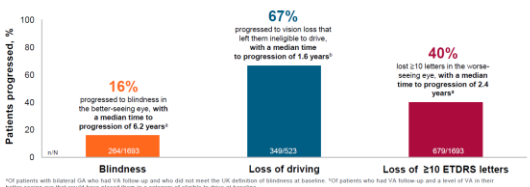
- **Parafoveal scotomas**
  Dark spots or blind spots in the visual field
- **Difficulty reading**
  May only be able to see parts of words with a decrease in reading rate
- **Impaired facial recognition**
  Parafoveal scotomas may result in difficulty recognizing familiar faces
- **Reduced dark adaptation and contrast sensitivity**
  Having trouble seeing in dim light and at night, including difficulty with driving

GA, geographic atrophy.
Saccani et al. Ophthalmol Ther. 2017;6:69-77.

136

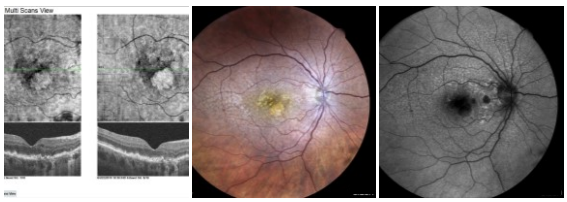
Vision Loss in GA Can Progress Quickly and Can Have Profound Impacts

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



[2]Of patients with bilateral GA who had VA follow-up and who did not meet the UK definition of blindness at baseline. [4]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.

137



GA - Multimodal Imaging

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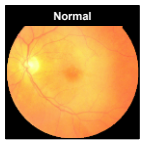
Color Fundus Photography (CFP) Imaging

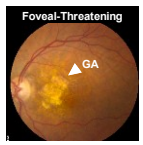
GA lesions are identified on CFP by:

- Depigmentation compared with adjacent healthy retina
- Sharply demarcated borders
- Visibility of choroidal vessels

Limitations of CFP:

- Can be difficult to differentiate lesions from drusen
- Can sometimes be difficult to discern lesions in lightly pigmented eyes





Normal CFP image courtesy of SriniVas Sadda, MD, Doheny Eye Institute.
AREDS Research Group. Am J Ophthalmol 2001;132:668-81. Sunness JS, et al. Invest Ophthalmol Vis Sci 1999;40:1761-9. Sunness JS, et al. Ophthalmology 2007;114:271-7. Schmitz-Valckenberg S, et al. Invest Ophthalmol Vis Sci 2011;52:1-6.

139

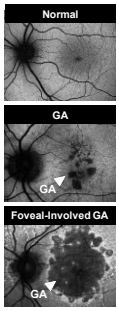
Fundus Autofluorescence (FAF)

FAF is a non-invasive test used to monitor the health of the RPE by visualizing fluorescence

FAF indicates the integrity of the RPE:

- No autofluorescence = RPE loss
- Increased autofluorescence = lipofuscin accumulation or RPE migration into neurosensory retina

- FAF is the current gold standard for GA clinical trials
- Lipofuscin is the main pathological autofluorescent component of the RPE
- Patterns of hyperautofluorescence correlate with rate of GA progression
- Atrophic RPE typically shows as clear dark patches as a result of lost lipofuscin where RPE cells are absent or have died



FAF images courtesy of James Gilman, CRA, FOPS, Moran Eye Center. RPE, retinal pigment epithelium.
Ruiz-Moreno JM, et al. Chapter 9. Fundus autofluorescence in age-related macular degeneration. Silva R, Bandello F, eds. AMD Handbook, 1st Edition 2010, GER Retina Study Group. http://www.amdbook.org/ Last accessed February 2017; Holz FG, et al. Am J Ophthalmol 2007;143:463-72.

140

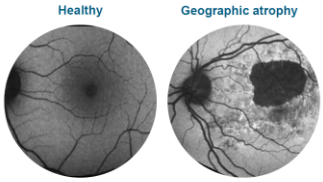
FAF Shows Characteristic Hypoautofluorescence Corresponding To GA Lesions

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 5;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]



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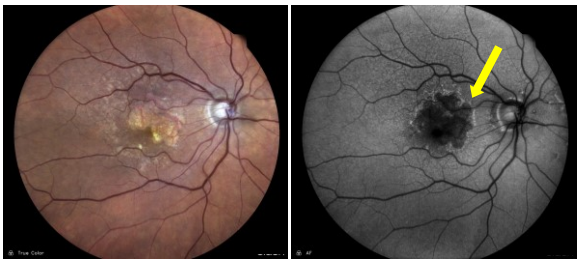

Hyperautofluorescent borders = high risk of progression

Holz FG, et al. *Am J Ophthalmol.* 2007;143:463-72.

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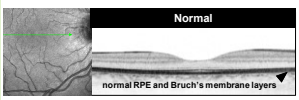
Spectral-Domain Optical Coherence Tomography (SD-OCT) Imaging

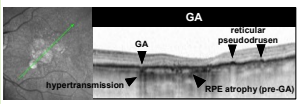
GA lesions are identified by:

- Hyperreflective signal below Bruch's membrane (hypertransmission or visualization of the choroid and choriocapillaris)
- Loss of RPE, photoreceptor, or choriocapillaris layers and/or absence or descent of the external limiting membrane

Limitations of SD-OCT:

- Interpretation/grading not yet standardized for use in GA clinical trials
- Not an FDA-recognized endpoint





SD-OCT images courtesy of Mohammed Rafieetary, OD, Charles Retina Institute.
Schmitz-Valckenberg S, et al. Invest Ophthalmol Vis Sci 2011;52:1-6. Holz FG, et al. Ophthalmology 2014;121:1079-91. Sadda S, et al. Retina 2016;36:1805-22. Holz FG, et al. Ophthalmology. 2018; epub Jan 18, 2017. Csaky KG, et al. Invest Ophthalmol Vis Sci 2008;49:479-89.

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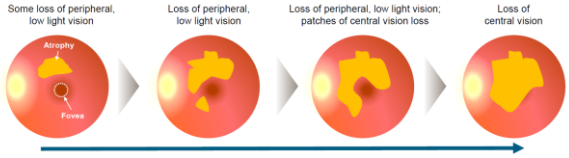
Atrophic Lesion Growth Is Associated With Progressive, Irreversible Vision Loss

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.

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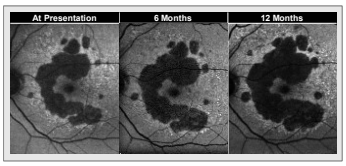
GA Progression Is Marked by Increased Lesion Size



- On average, GA lesions enlarge by 1.5 to 2.1 mm²/year (0.6 to 0.8 MPS disc areas)[1,2]
- Median time to evolution of GA:[3]
  - **2.5 years:** median time to develop central GA (after GA diagnosis)
  - **7 years:** median time to develop bilateral GA (i.e., GA in both eyes) after development of GA in the first eye
- Previous lesion involvement predicts subsequent enlargement[2]

FAF images courtesy of James Gilman, CRA, FOPS, Moran Eye Center. FAF, fundus autofluorescence; MPS, Macular Photocoagulation Study.
1. Holz FG, et al. *Am J Ophthalmol* 2007;143:463-72. 2. Sunness JS, et al. *Ophthalmology* 2007;114:271-7. 3. Lindblad AS, et al. *Arch Ophthalmol* 2009;127:1168-74.

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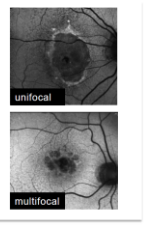
Several Risk Factors Identifiable on FAF Can Predict a Greater GA Progression Rate

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 Rev*. 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.

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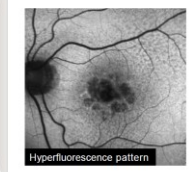

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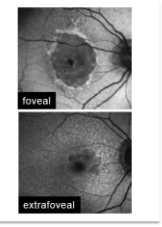

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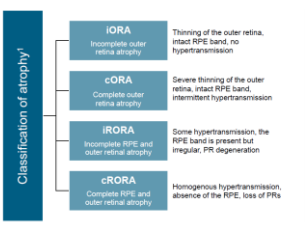
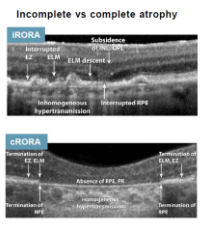
A Classification System of OCT-Defined Atrophy in AMD Based on an International Consensus Has Been Proposed





AMD, age-related macular degeneration; ELM, external limiting membrane; EZ, ellipsoid zone; INL, inner nuclear layer; OCT, optical coherence tomography; OPL, outer plexiform layer; PR, photoreceptor; RPE, retinal pigment epithelium.
Saddia et al. *Ophthalmology*. 2018;125(4):537-548.

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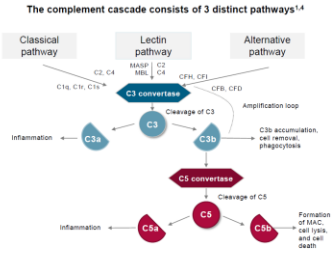
A Leading Contributor to Inflammation in GA Pathogenesis Is Dysregulation of the Complement System

- 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):13805. 3. Smailhodzic et al. *Ophthalmology*. 2012;119(2):339-346. 4. Mastellos et al. *Trends Immunol*. 2017;38(6):383-394.

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



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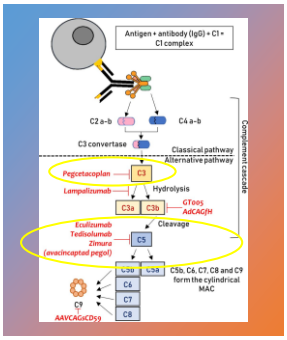

Newly Approved Complement Inhibition Therapy for GA

- **Pegcetacoplan (SYFOVRE®)**
  - Approved February 2023
  - Indication: GA secondary to AMD
  - MOA/Target: C3
  - Clinical Trials: OAKS/DERBY
  - 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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Thank You!

damon.dierker@esi-in.com

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