Posterior Segment Rounds: From Landmarks to the latest

#86346-TD

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Southern College of Optometry

1

- No Financial Disclosures

2

Objectives

- Discuss a variety of posterior segment cases
- Reinforce the necessity of multimodal imaging in the diagnostic sequence
- Provide updates on changing nomenclature and management in conditions seen commonly

3

Imaging Terminology

- IVFA-Hyper/Hypo Fluorescent
- ICG-Hyper/Hypo Cyanescence
- OCT structural-Hyper/Hypo-reflective
- OCT-A-Depends…..
- FAF-Hyper/Hypo auto-fluorescent
- B scan-Hyper/Hypo echoic
- CT-High/Low density
- MRI-High/Low intensity
- Near IR-Hyper/Hypo-reflective
- En Face Slab-Bright/Dark

4

Case CB

5

5

CB

- 44 yo WF c/o reduced vision OS
- Slowly worsening over past 8-10 months
- CL examination on outside revealed reduced VA ~20/40
- Covered up OD 1 week ago and couldn't see cars in front of her through OS but could see trees around it
- Tinnitus has worsened recently
- Hx of Migraines, no worsening of these
- Meds: Loratadine, methocarbamol, naproxen, promethazine

6

6

CB Ocular findings/Ocular Hx

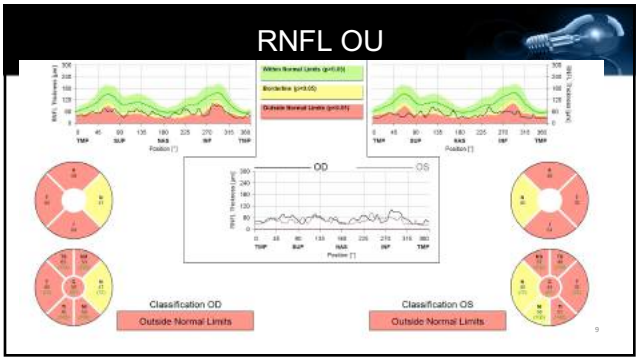
- BCVA: 20/20 OD, 20/150 OS
- Pupils: 1+ APD OS ???
- Amsler: normal OD, +metamorphopsia of entire grid OS
- Color vision: Unremarkable
- Oc Hx: ONH drusen OU c RNFL thinning and VF defect
- Previous Photos/OCTs/VF to follow….
- OCTs unchanged at that visit
- VF from this visit attached

7

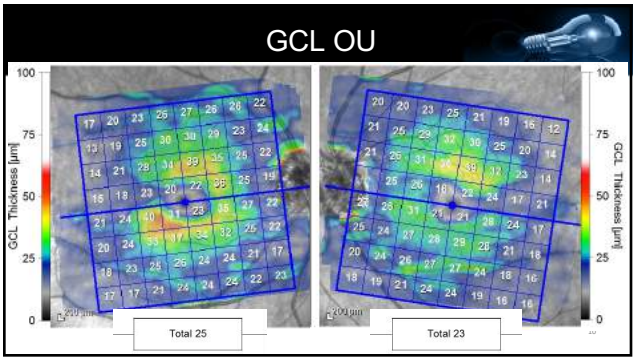
7

Disc Photos

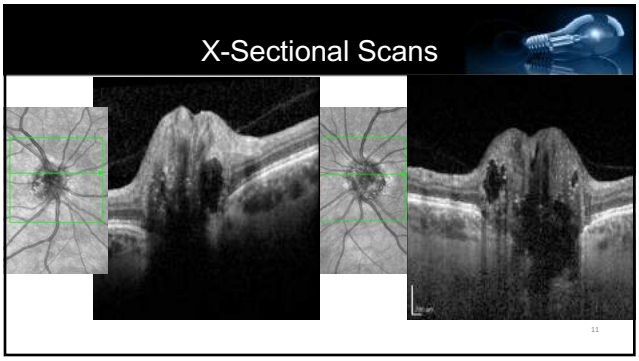
8


RNFL OU
OD
OS
Classification OD
Outside Normal Limits
Classification OS
Outside Normal Limits

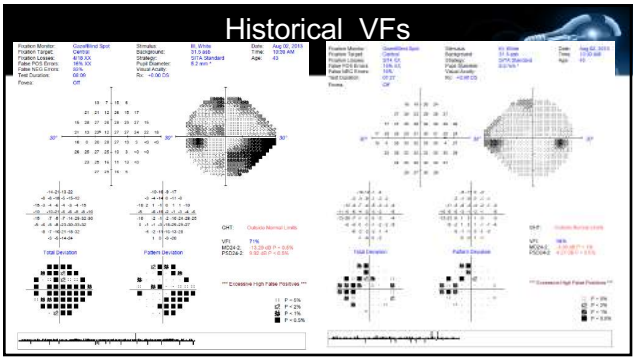
9


GCL OU
GCL Thickness [µm]
Total 25
Total 23

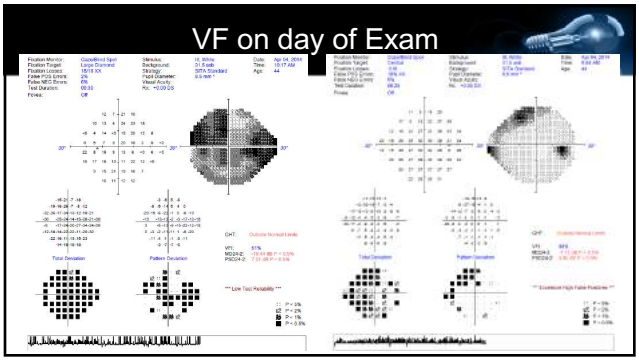
10


X-Sectional Scans

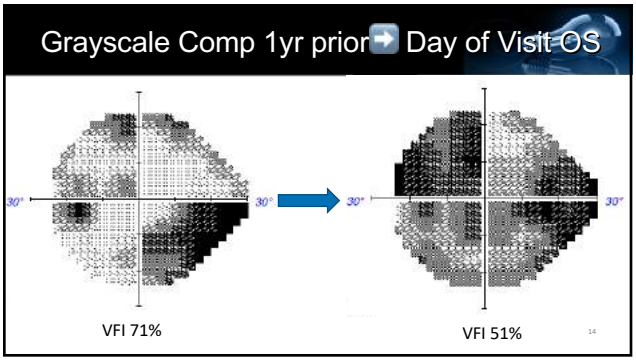
11


Historical VFs

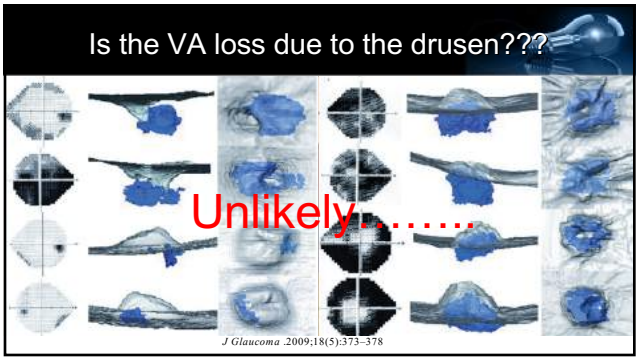
12


VF on day of Exam

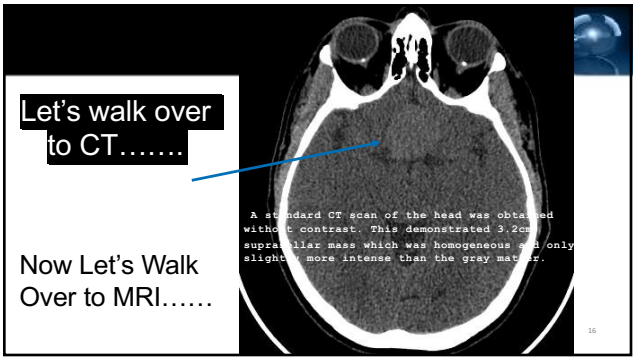
13


Grayscale Comp 1yr prior ➡ Day of Visit OS
30°
30°
30°
30°
VFI 71%
VFI 51%

14


Is the VA loss due to the drusen???
Unlikely……
J Glaucoma 2009;18(5):373–378

15


Let's walk over to CT…….
Now Let's Walk Over to MRI……
A standard CT scan of the head was obtained without contrast. This demonstrated 3.2cm supracellar mass which was homogeneous and only slightly more intense than the gray matter.

16

Quick Differentiation

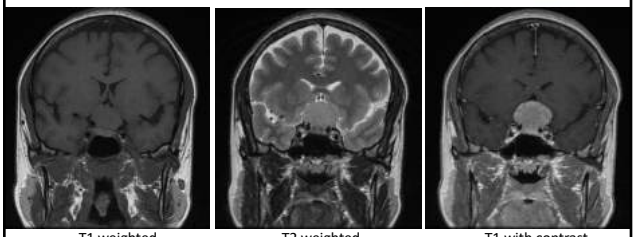
Tissue	T1-Weighted	T2-Weighted	Flair
CSF	Dark	Bright	Dark
White Matter	Light	Dark Gray	Dark Gray
Cortex	Gray	Light Gray	Light Gray
Fat (within bone marrow)	Bright	Light	Light
Inflammation (infection, demyelination)	Dark	Bright	Bright

http://casemed.case.edu/clerkships/neurology/web%20neurorad/mri%20basics.htm

9/30/23 17

17

CB's MRIs



T1 weighted | T2 weighted | T1 with contrast

Slide Courtesy of Jessica Haynes OD, FAAO

18

18

c Contrast

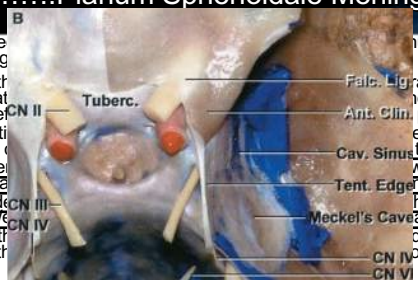
20

20

Dx…….Planum Sphenoidale Meningioma

- Tx: Ele… mening…

"Once th… the ipsilat… was caref… We identi… carefully … side, atte… somewha… surrounde… canal. We… opened th… release th…



…num

…ral side until …e tumor … planum. …ese were …the other …was …mpletely …he optic …al. We also …der to …or"

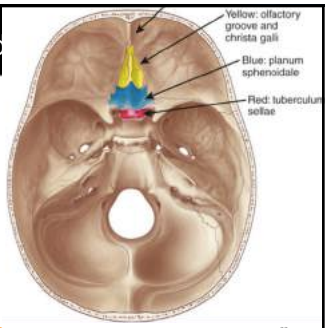
https://vimeo.com/176620437

21

21

Planum Sphenoid

- Account for 5-10% of all intracranial meningiomas
- Constitute 2% of all primary intra-cranial tumors
- F>M predilection
- Benign/Typically slow-growing
- Most patients remain asymptomatic until >4cm
- ~66-77% of pts have monocular reduced vision as 1st symptoms



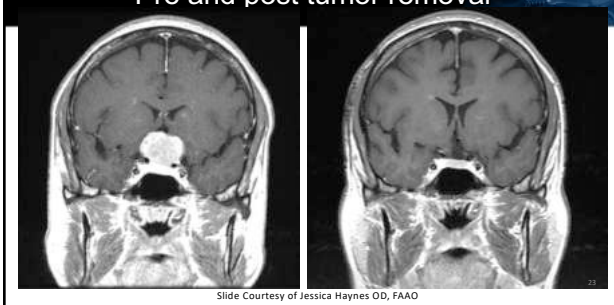
Can Fam Physician 2017;63:288-9, 291
BMJ Case Reports 2011; doi:10.1136/bcr.07.2011.4511
https://radiopaedia.org/cases/planum-sphenoidale-meningioma-9
Romanian Neurosurgery (2013) XX 1: 92 - 99

https://neupsykey.com/surgical-management-of-midline-anterior-skull-base-meningiomas/

22

22

Pre and post tumor removal

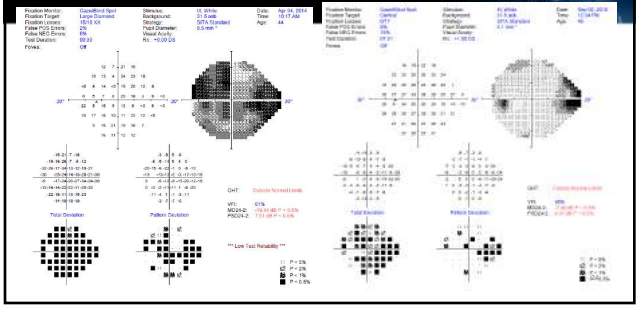


Slide Courtesy of Jessica Haynes OD, FAAO

23

23

VF Pre and Post Tumor Removal



24

24

Food for thought

- Published radiological error rates vary widely[1]
- 70% of errors are perceptual i.e. they fail to "see" something
- 30% are cognitive i.e. attaching the wrong significance to what is seen
- Be very specific in the information you provide to the radiologist on what you are looking for
- American College of Radiology survey revealed 25% of[2] respondents involved in "failed-communication" lawsuits
- Ultimately if you order the test, joint responsibility applies

Berlin L. *Diagnosis* 2014; 1(1): 79–84 Berlin L. *Appl Radiol. 2010 Feb*
Kushner DC, Lucey LL, *J Am Coll Radiol.* 2005;2:15–21.

25

25

OMIC Claims 2008-2014

- **Oncology claims.** There were 27 claims. Failu to diagnose melanoma resulted in six claims an two payments. Pituitary tumors were allegedly missed in four claims but no payments were made. A delay in diagnosing glioma led to three claims and two payments, including a settlemer of $2,000,000, the largest one in the study. The were three lacrimal cancer claims with one payment, three optic nerve tumors with no payments, and one trigeminal schwannoma claim, which settled for $1,000,000.

OMIC DIAGNOSTIC ERROR INDEMNITY PAYMENT ANALYSIS (PART I)

Clinical Category	Patients/ Claims	Settled #/%	Payment
Cataract	3/3	1/33	$250,000
Cornea	18/26	11/44	$1,480,943
Endophthalmitis	11/17	4/24	$1,610,000
Glaucoma	24/27	10/37	$1,628,806
Medical	21/27	10/37	$3,529,000
Neuro	5/7	0	
Orbit	2/3	0	
Oncology	17/27	7/26	$5,341,500
Retina	57/84	21/25	$7,457,900
Uveitis	1/2	0	

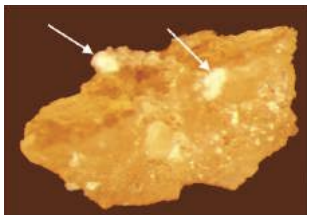
https://www.omic.com/diagnostic-error-types-and-causes/

26

26

Optic Disc Drusen Diagnostics

- CT
- FAF
- Ultrasound
- OCT-EDI

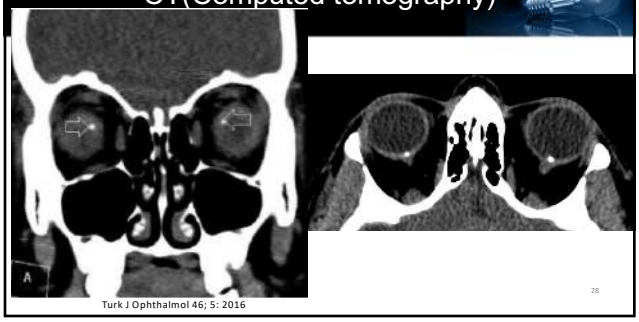


Retina 2008 Jan;28(1):143-6.

27

27

CT(Computed tomography)

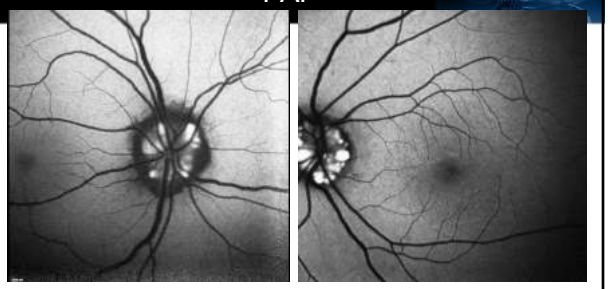


Turk J Ophthalmol 46; 5: 2016

28

28

FAF



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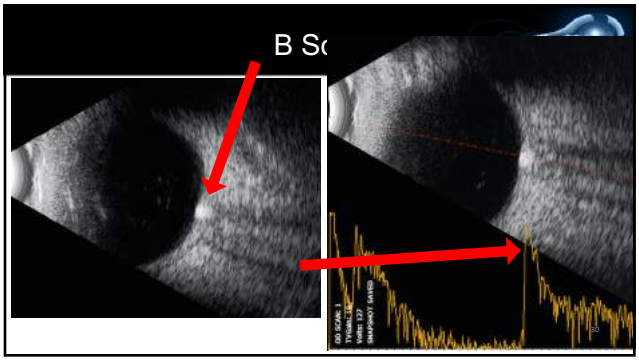
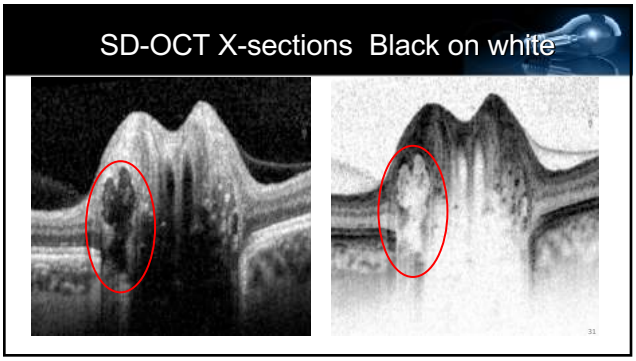
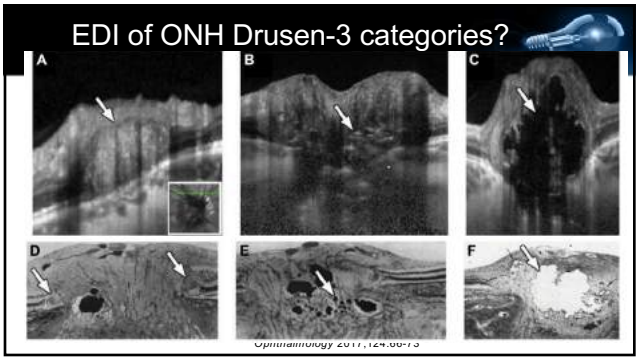

B Sc

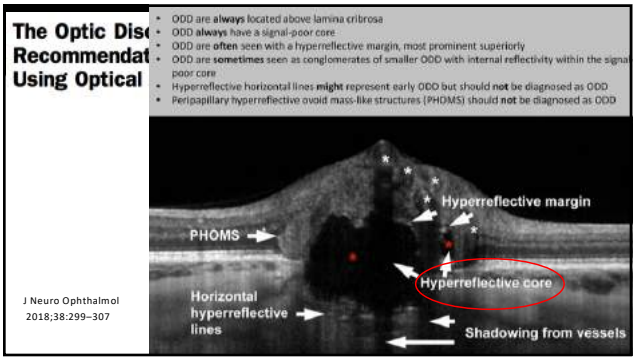
30


SD-OCT X-sections Black on white

31


EDI of ONH Drusen-3 categories?
A
B
C
D
E
F

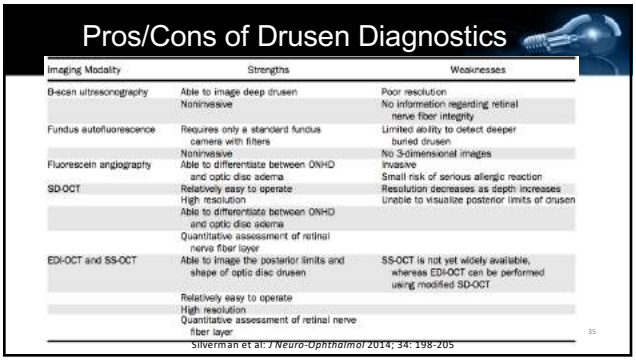
32


The Optic Disc
Recommendat
Using Optical
ODD are always located above lamina cribrosa
ODD always have a signal-poor core
ODD are often seen with a hyperreflective margin, most prominent superiorly
ODD are sometimes seen as conglomerates of smaller ODD with internal reflectivity within the signal-poor core
Hyperreflective horizontal lines might represent early ODD but should not be diagnosed as ODD
Peripapillary hyperreflective ovoid mass-like structures (PHOMS) should not be diagnosed as ODD
Hyperreflective margin
PHOMS
Hyperreflective core
Horizontal hyperreflective lines
Shadowing from vessels
J Neuro Ophthalmol 2018;38:299–307

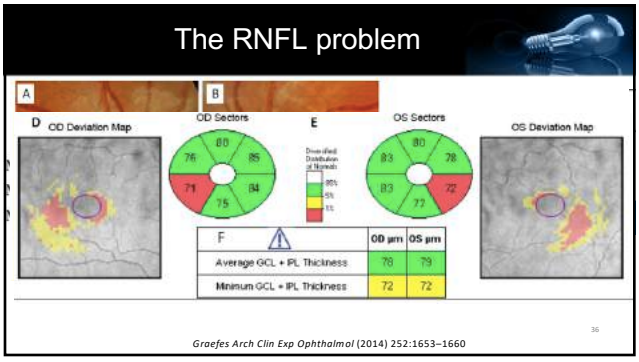
33


Imaging Evolution
Johnson L, et al. Arch Ophthalmol. 2009;127(1):45-49.
Slotnick, S, OVS. 2012;89(5): 1-5.
Silverman A, et al. J Neuro Ophthalmol 2014;34: 198-205.
Slide courtesy of Catherine Hogan OD, FAAO

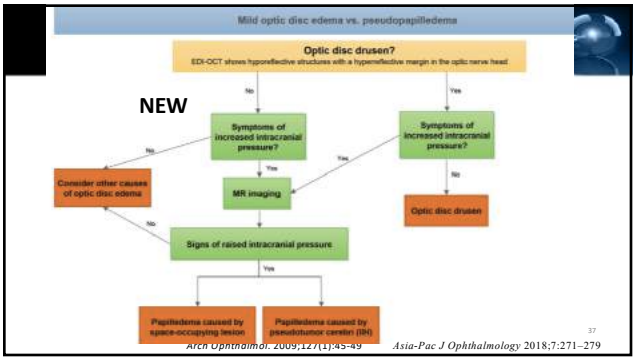
34


Pros/Cons of Drusen Diagnostics
Imaging Modality | Strengths | Weaknesses
B-scan ultrasonography | Able to image deep drusen | Poor resolution
Noninvasive | No information regarding retinal nerve fiber integrity
Fundus autofluorescence | Requires only a standard fundus camera with filters | Limited ability to detect deeper buried drusen
Noninvasive | No 3-dimensional images
Fluorescein angiography | Able to differentiate between ONHD and optic disc edema | Invasive
Small risk of serious allergic reaction
SD-OCT | Relatively easy to operate | Resolution decreases as depth increases
High resolution | Unable to visualize posterior limits of drusen
Able to differentiate between ONHD and optic disc edema
Quantitative assessment of retinal nerve fiber layer
EDI-OCT and SS-OCT | Able to image the posterior limits and shape of optic disc drusen | SS-OCT is not yet widely available, whereas EDI-OCT can be performed using modified SD-OCT
Relatively easy to operate
High resolution
Quantitative assessment of retinal nerve fiber layer
Silverman et al. J Neuro-Ophthalmol 2014; 34: 198-205

35

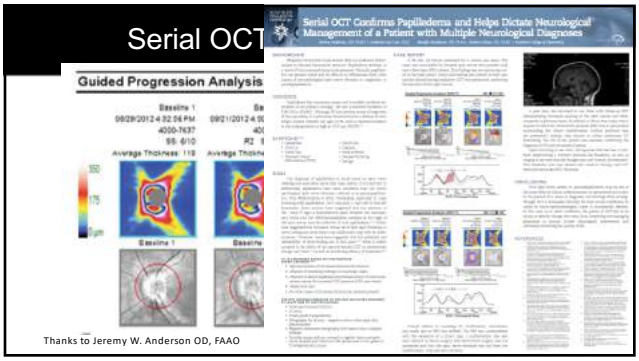

The RNFL problem
A
B
D OD Deviation Map
OD Sectors
E
OS Sectors
OS Deviation Map
F
OD µm
OS µm
Average GCL + IPL Thickness
78
79
Minimum GCL + IPL Thickness
72
72
Graefes Arch Clin Exp Ophthalmol (2014) 252:1653–1660

36


Mild optic disc edema vs. pseudopapilledema
Optic disc drusen?
EDI-OCT shows hyporeflective structures with a hyperreflective margin in the optic nerve head
NEW
Symptoms of increased intracranial pressure?
Symptoms of increased intracranial pressure?
Consider other causes of optic disc edema
MR imaging
Optic disc drusen
Signs of raised intracranial pressure
Papilledema caused by space-occupying lesion
Papilledema caused by pseudotumor cerebri (IIH)
Arch Ophthalmol. 2009;127(1):45-49
Asia-Pac J Ophthalmology 2018;7:271–279

37

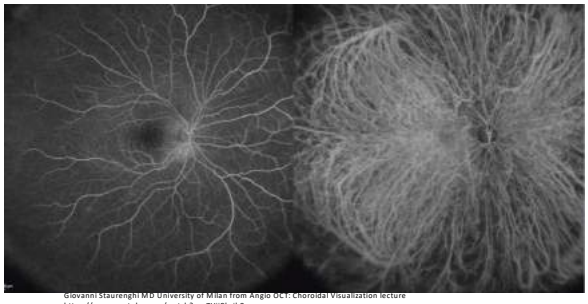
Serial OCT



Thanks to Jeremy W. Anderson OD, FAAO

38

Retina vs. Choroid



Giovanni Staurenghi MD University of Milan from Angio OCT: Choroidal Visualization lecture
https://www.youtube.com/watch?v=s7VjiCbrih8

39

Pachychoroid

https://blog.goodaudience.com/the-eos-elephant-in-the-room-35fb9bd1e94

40

40

Anatomy

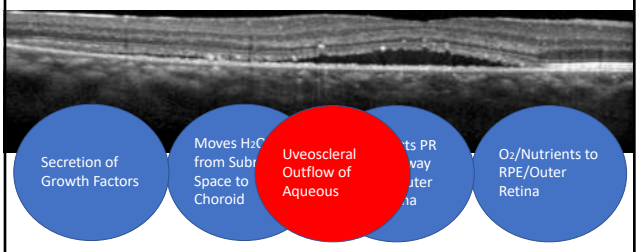
- Highly vascularized tissue between the RPE and sclera
  - Uvea receives 95% of ophthalmic artery blood, retina 5%
    - Choroid 65-85% of uveal flow
  - *Only kidney is comparable

Nickla DL, Wallman J. The multifunctional choroid. *Prog Retin Eye Res.* 2010; 29(2): 144-168.

Wei W, Xu L, Jonas J et al. Subfoveal choroidal thickness: The Beijing Eye Study. Ophthalmology. 2013;120:175-80.

41

Choroidal Physiology



Slide Courtesy Meagan Williams OD, FAAO

42

Choroidal Thickness[1,3]

- Affected by a multitude of factors

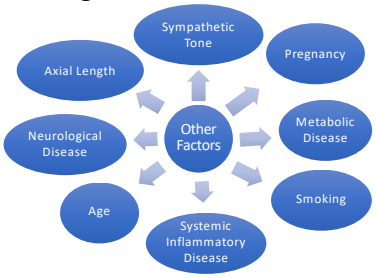
At Birth	Age 90	Subfoveal Thickness	What is thick?
200 um	80 um	~250um in 65yo	No cutoff exists

Twa M, et al. *Optom Vis Sci* 2016;93:1387-1398
Wei W, Jonas J, et al. *Ophthalmology* 2013;120:175-80

43

43

Factors Affecting Choroidal Thickness[2,4,5]



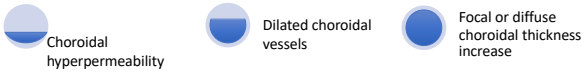
Slide Courtesy Meagan Williams OD, FAAO

44

44

Increased Choroidal Thickness

- Pachychoroid "phenotype"



- Pachychoroid vascular changes cause focal disruptions in RPE and Bruch's membrane

Akkaya S. Spectrum of pachychoroid disease. *Int Ophthalmol.* 2017; 1-8

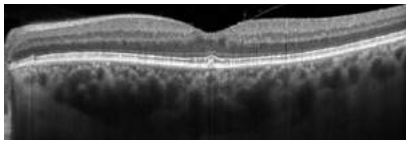
Slide Courtesy Meagan Williams OD, FAAO

46

46

Pachychoroid Disease

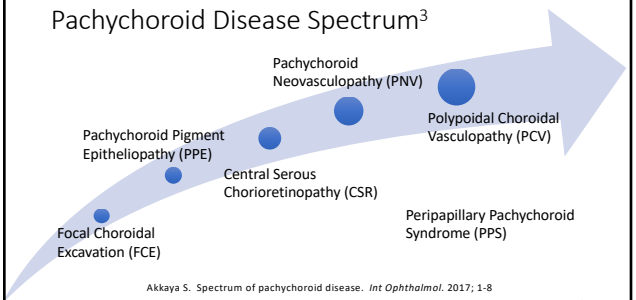
- Was initially based just on thickness
- Now accepted requires qualitative features concurrent with choroidal thickening
- No strict definition with no strict cutoff
- 18 unique definitions, 39 with no definitions in meta analysis



Spaide R. *Retina.* 2021;41(2):231-237

47

Pachychoroid Disease Spectrum[3]



Akkaya S. Spectrum of pachychoroid disease. *Int Ophthalmol.* 2017; 1-8

Slide Courtesy Meagan Williams OD, FAAO

48

JG Case

51

51

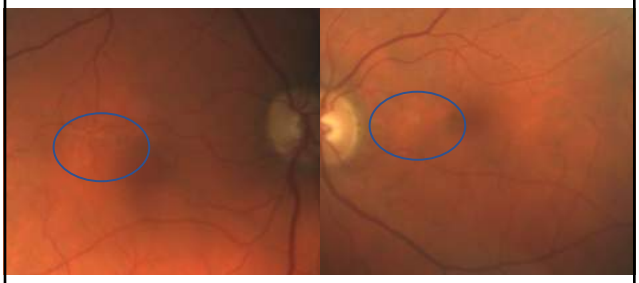
JG Case details-Hint, he is an old white guy!

- 82yo **WM** for Dr directed f/u of Dry AMD, unspecified stage
- Dx AMD in 2008 in our clinic-DUH, He's an old white guy!!!!
- Uses AREDS2 x2yrs (inconsistent recommendations)
- Sys Hx: DM Type II, Htn, Chronic Ischemic Heart Disease,
- Smokes rare cigar, no Hx of cigarette smoking
- OcHx: Amarosis fugax 5mo previous, CT, CTA, Carotid, EKG unremarkable, 1+ NS OU
- (-)metamorphopsia

52

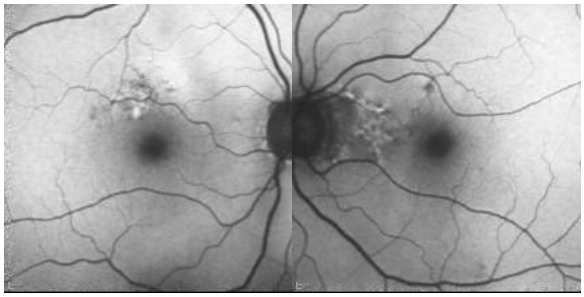
52

Color Fundus Photos



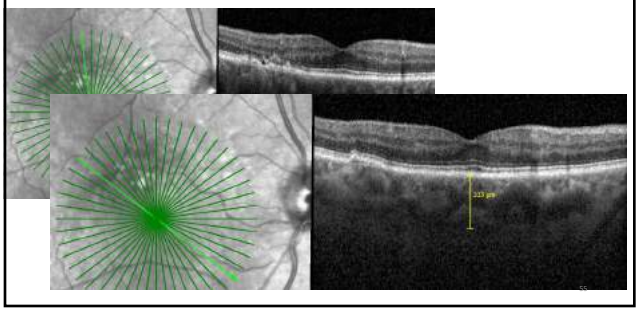
53

FAF



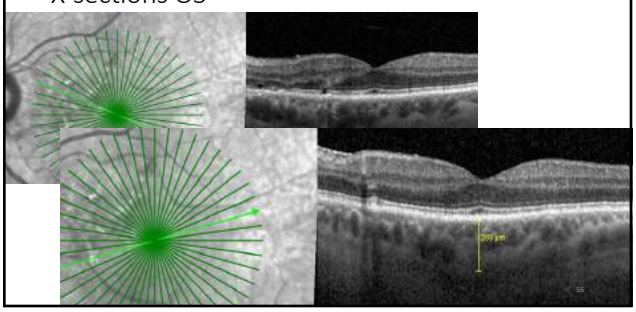
54

X-sections OD



55

X-sections OS



56

Pachychoroid Pigment Epitheliopathy[6,7]

- "Form fruste" or incomplete version of CSR
  - No SRF
- Pachychoroid phenotype
- Reduced fundus tessellation
- Unilateral or bilateral
- RPE abnormalities
  - Small RPE detachments
  - Absence of SRF and drusen
- **Commonly confused with ARMD, macular dystrophies, choroiditis**

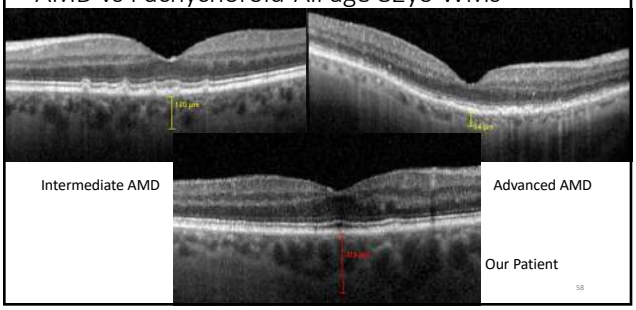
Retina 2013;33:1659-1672
Retina 2016;36(3);499-516

Slide Courtesy Meagan Williams OD, FAAO

57

57

AMD vs Pachychoroid-All age 82yo WMs



Intermediate AMD

Advanced AMD

Our Patient

58

58

Choroidal Thickness and AMD???

- Proposal that choroidal thinning and insufficiency contributes to outer retinal ischemia
- If choroid cannot supply oxygen and remove waste from photoreceptors and RPE it may contribute to AMD worsening
- Although physiologic aging diminishes choroidal thickness, further decrease is observed in dry and wet AMD independent of controls
- RPD associated with choroidal thinning
- Choroidal thickness change associated with resultant GA
- Debate in the literature continues…..

Graefe's Archive for Clinical and Experimental Ophthalmology (2018) 256:511–518
Am J Ophthalmol. 2018;191:23-33 *Surv Ophthalmol* 2016; **61**: 521–37
Am J Ophthalmol 2015;159:617-626

59

59

Editorial

The Ambiguity of Pachychoroid

- "Pachychoroid," and the broader category "pachychoroid spectrum," seem to be both incompletely defined and overly broad in their inclusion. There does not seem to be a published study examining a normal population to determine how many would be considered to have a pachychoroid spectrum disorder.

  -Richard Spaide

Spaide RF. *Retina*. 2021;41(2):231-237

60

60

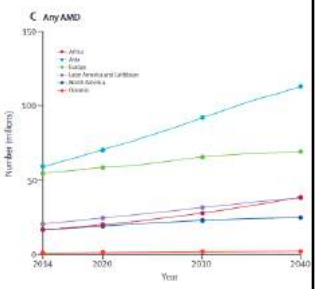
AMD

What is Macular Degeneration? - AMDF

61

AMD Current/Future

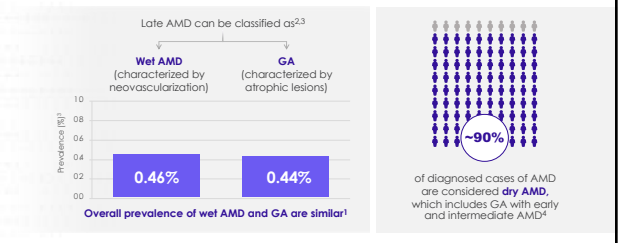
- Most common cause of blindness in developed countries
- Specifically in age >60
- Account for 8.7% of all blindness worldwide
- 50% of blindness in the U.S.
- Expected to affect 300 million by 2040
- 2004 8 million with bilateral intermediate, 2 million with advanced



Wong WL, et al. *Lancet Glob Health* 2014;2:e106-16
AREDS2 writing team. JAMA. 2013;309(19)

62

Prevalence of late AMD forms of wet AMD and GA are similar[1]



of diagnosed cases of AMD are considered **dry AMD**, which includes GA with early and intermediate AMD[4]

AMD, age-related macular degeneration; GA, geographic atrophy.
1. Wong WL, et al. *Lancet Glob Health*. 2014;2:e106-e116. 2. Holz FG, et al. *Ophthalmology*. 2017;124:464-478. 3. Gehrs KM, et al. *Ann Med*. 2006;38:450-471. 4. Taylor DJ, et al. *Ophthalmic Physiol Opt*. 2018;38:95-105.

63

How is it defined?

	Definition
Epidemiological classification (Wisconsin grading)*	
Early AMD	Large (≥125 μm) drusen or retinal pseudodrusen, or pigmentary abnormalities
Late AMD	Neovascular AMD or geographic atrophy
Basic clinical classification*	
No ageing changes	No drusen and no pigment abnormalities
Normal ageing changes	Only small drusen ≤63 μm and no pigment abnormalities
Early AMD	Medium drusen >63 μm and ≤125 μm, and no pigment abnormalities
Intermediate AMD	Large drusen >125 μm or any pigment abnormalities
Late AMD	Neovascular AMD or geographic atrophy
AREDS simplified severity scale points†‡	
0	No large drusen (>125 μm) or pigment changes in either eye
1	Large drusen or pigment changes in one eye only
2	Large drusen and pigment changes in one eye only; or large drusen or pigment changes in both eyes; or neovascular AMD or geographic atrophy in one eye
3	Large drusen and pigment changes in one eye; and large drusen or pigment changes in the fellow eye
4	Large drusen and pigment changes in both eyes

AMD=age-related macular degeneration. AREDS=Age-Related Eye Disease Study. *Definition is based on the worse eye. †An eye with late AMD has a score of 2.

Table 1: Definitions and classification scales for AMD

Mitchell P, et al. *Lancet* 2018;392:1147-59

64

Enrollment into 4 AMD categories

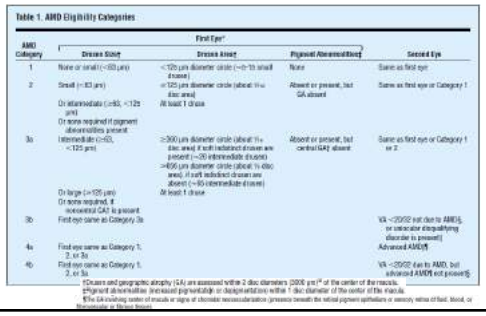


Table 1. AMD Eligibility Categories

AMD Category	First Eye* Drusen Size†	First Eye* Drusen Area†	First Eye* Pigment Abnormalities‡	Second Eye
1	None or small (<63 µm)	<125 µm diameter circle (~0.15 disc area) of small drusen	None	Same as first eye
2	Small (<63 µm)	<125 µm diameter circle (about ½ disc area) of small drusen	Absent or present, but GA absent	Same as first eye or Category 1
	Or intermediate (≥63, <125 µm)	At least 1 druse		
	Or some required if pigment abnormalities present			
3a	Intermediate (≥63, <125 µm)	≥360 µm diameter circle (about ½ disc area) if soft indistinct drusen are present (~20 intermediate drusen) ≥406 µm diameter circle (about ½ disc area), if soft indistinct drusen are absent (~10 intermediate drusen)	Absent or present, but central GA§ absent	Same as first eye or Category 1 or 2
	Or large (≥125 µm)	At least 1 druse		
	Or some required, if noncentral GA§ is present			
3b	First eye same as Category 3a			VA <20/32 not due to AMD§, or vascular disqualifying disorder is present‖
4a	First eye same as Category 1, 2, or 3a			Advanced AMD¶#
4b	First eye same as Category 1, 2, or 3a			VA <20/32 due to AMD, but advanced AMD¶ not present§

†Drusen and geographic atrophy (GA) are assessed within 2 disc diameters (3000 µm)² of the center of the macula.
‡Pigment abnormalities (increased pigmentation or depigmentation) within 1 disc diameter of the center of the macula.
§The GA involving center of macula or signs of choroidal neovascularization (presence beneath the retinal pigment epithelium or sensory retina of fluid, blood, or fibrovascular or fibrous tissue).

65

Categories

AREDS Research Group. *Arch Ophthalmol*. 2001;119:1417-1436

66

Case RG

67

67

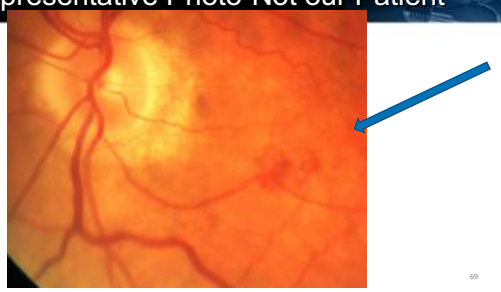
Case History/Exam details

- 74yo WM presents for annual doctor directed Diabetic exam
- No ocular complaints
- Last HbA1c=6.9%
- Systemic Hx: Type II DM x 15yrs, Hld
- Smoker x 20yrs ago
- Meds: Glipizide, Metformin, Simvastatin, Omega-3s
- OcHx: Non visually significant cataracts (-)retinopathy
- BCVA OD: 20/20, OS: 20/25
- SLE: 2+ NS, 2+ Cortical
- Images to Follow……

68

68

Representative Photo-Not our Patient



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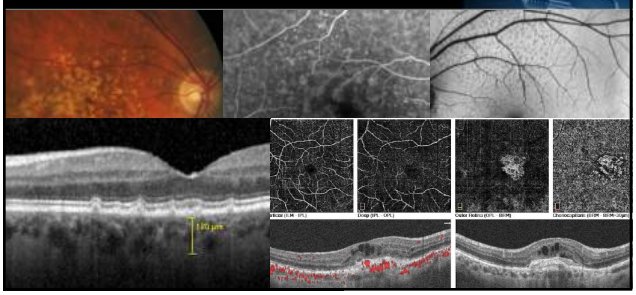
Major Imaging Modalities…..



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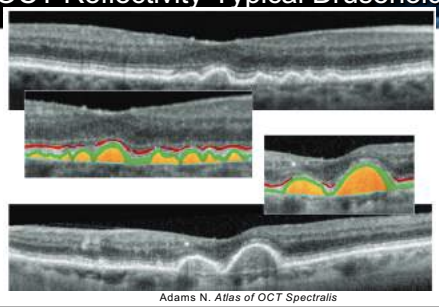
Reflectivity Review

9/30/23 71

71

71

OCT Reflectivity-Typical Drusenoid PED

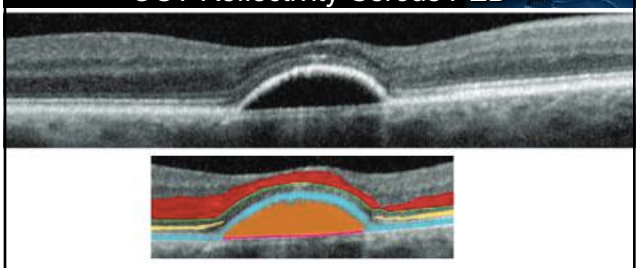


Adams N. *Atlas of OCT Spectralis*

72

72

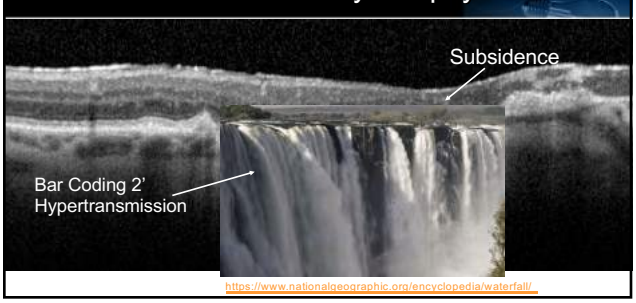
OCT Reflectivity-Serous PED



Adams N. *Atlas of OCT Spectralis*

73

OCT Reflectivity-Atrophy



https://www.nationalgeographic.org/encyclopedia/waterfall/

76

What's a biomarker?

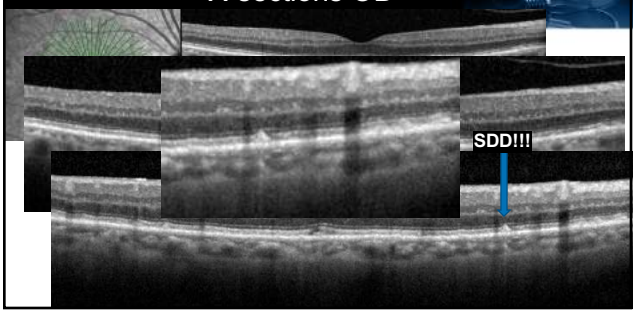
"a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers but a biomarker is not an assessment of how an individual feels, functions, or survives"

-FDA/NIH Biomarker Working Group

9/30/23 Daniel N Cagney, et al. *Neuro-Oncology. 2018;20(9):1162-1172* 79

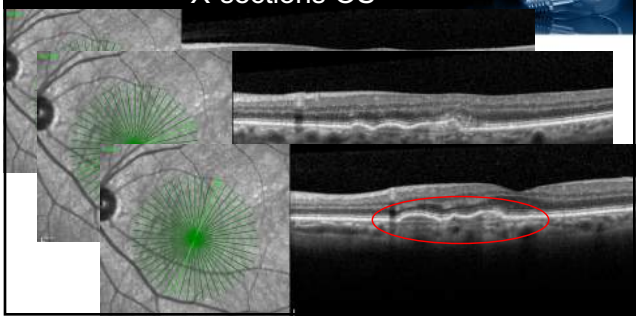
79

X-sections OD



80

X-sections OS



81

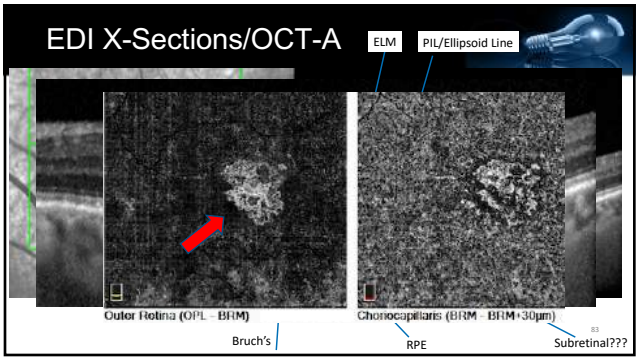
OCT Angiography

- Employs motion contrast imaging to high resolution volumetric blood flow information
- Compares differences in the backscattered signal intensity or amplitude between sequential B-scans at exactly the same cross-section
- This difference is used to construct a map of blood flow
- Remaining captured movement presumed due to erythrocyte movement
- Detects flow at the machines threshold which is the SLOWEST the machine can detect

9/30/23 de Carlo et al. International Journal of Retina and Vitreous (2015) 1:5

82

EDI X-Sections/OCT-A



83

Update!!!!

- CNVM is now MNV
- Macular Neovascularization
- MNV denotes that neovascular disease in the macula is not always derived from the choroid
- Now Type 1, 2, 3 MNV instead of CNV

Consensus Nomenclature for Reporting Neovascular Age-Related Macular Degeneration Data

Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group

9/30/23 *Ophthalmology* 2020;127:616-636 84

84

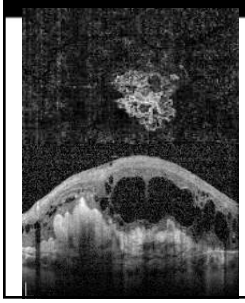
Quick Note on SIREs and NE-MNVs

- Previously used term “double-layer sign”
- Shallow, irregular RPE elevation (SIRE)
  - -Greatest transverse linear dimension of 1000um or more
  - -Irregular RPE layer with a height of predominantly less than 100um
  - -Non-homogenous internal reflectivity as characteristic features of the DLS
- Pt’s with SIRE are at a higher risk of

Narita C, et al. *Ophthalmology* 2020;127:637-647

85

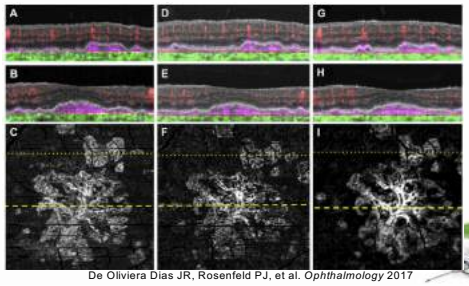
Wet AMD treatment Options



- Aflicbercept
- Ranibizumab
- Faricimab-SVOA
- Brolucizimab
- Bevacizumab
- Port Delivery System

86

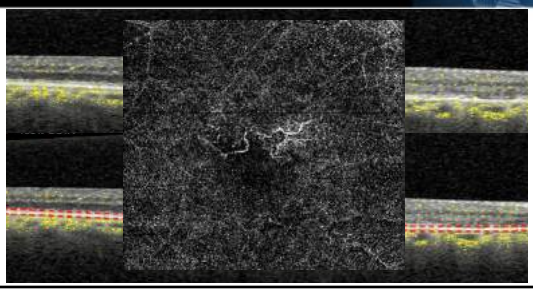
That was Wet, what about Neo in NE-AMD???



De Oliviera Dias JR, Rosenfeld PJ, et al. *Ophthalmology* 2017

87

Last Thursday



88

Fundus Autofluorescence (FAF)

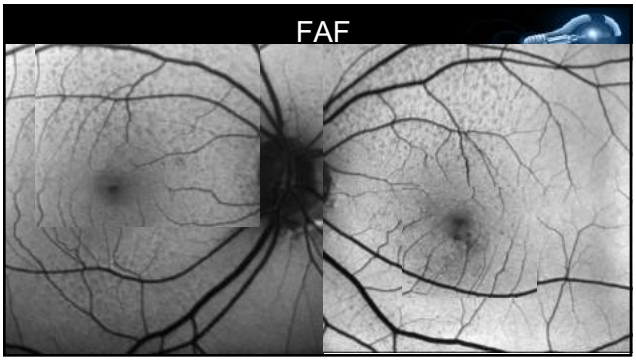
- Lipofuscin is the primary ocular fluorophore found in RPE
- Fluorophores absorb and emit light of specific wavelengths
- Autofluorescence is produced when a fluorophore absorbs a photon of the excitation wavelength, causing electron to be excited
- The electron dissipates energy, emits a quantum of light at a lower energy and longer wavelength as it returns to its ground state
- Typically FAF uses blue-light excitation, then collects emissions within a preset spectra to form a **brightness map reflecting the distribution of lipofuscin**

Yung, M., Klufas, M.A. & Sarraf, D. *Int J Retin Vitr* **2,** 12 (2016)

89

89

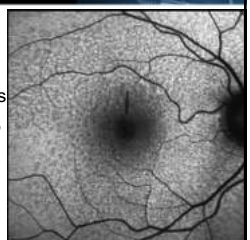
FAF



90

Reticular Pseudodrusen (RPD)

- 1st described in 1990 as yellowish and ill-defined interlacing network on clinical examination and/or fundus photography
- Now known as Subretinal Drusenoid Deposits
- Appear as an orderly array of relatively white, dot-like accumulations
- RPD give a 4-8x increased risk of 5yr progression to late AMD
- Riskier early/moderate, less risk advanced
- Risk independent of druse/pigment

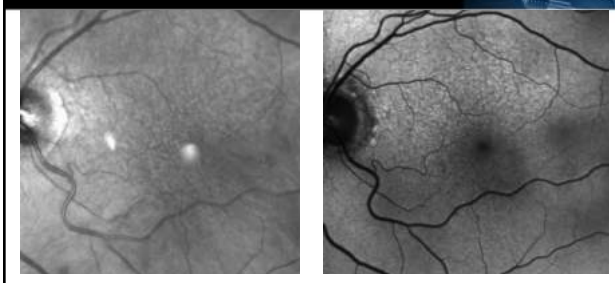


1) *IOVS.* 2016;57:1310–1316 2) *Surv Ophthalmol* 61 (2016) 521e537
3) *Clin Exp Optom* 2019; 102: 455–462 4) AREDS2 Report 30 Ophthalmology 2022 May 31

Surv Ophthalmol 61 (2016) 521e537

91

RPD/SDD Case 2017



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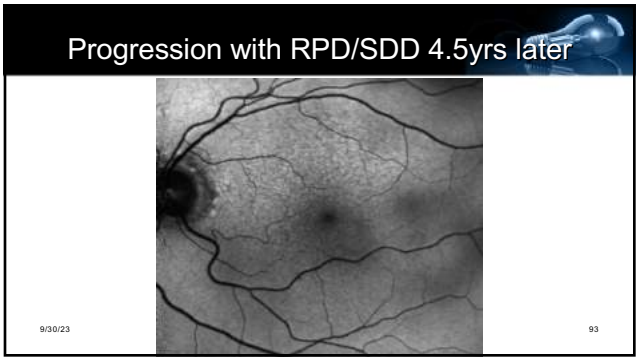
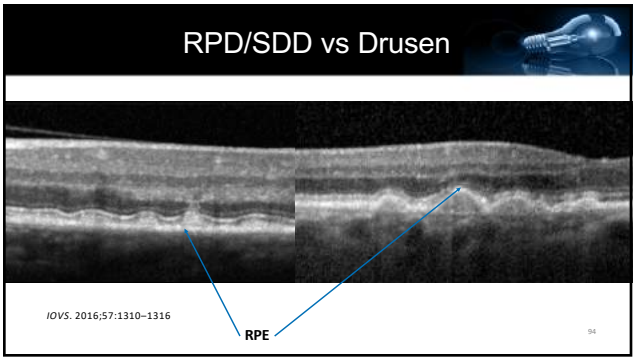
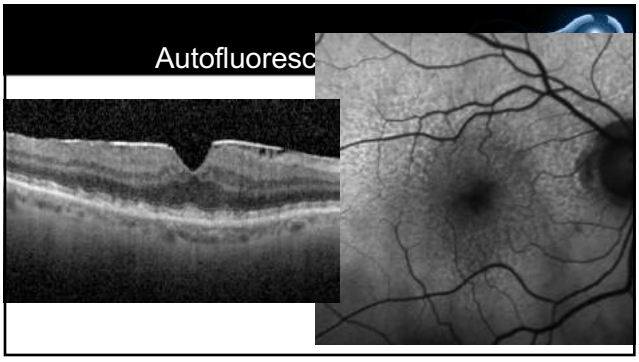

Progression with RPD/SDD 4.5yrs later
9/30/23
93

93


RPD/SDD vs Drusen
IOVS. 2016;57:1310–1316
RPE
94

94


Autofluoresc

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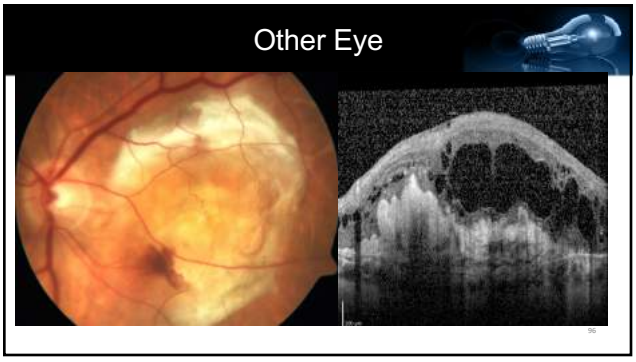
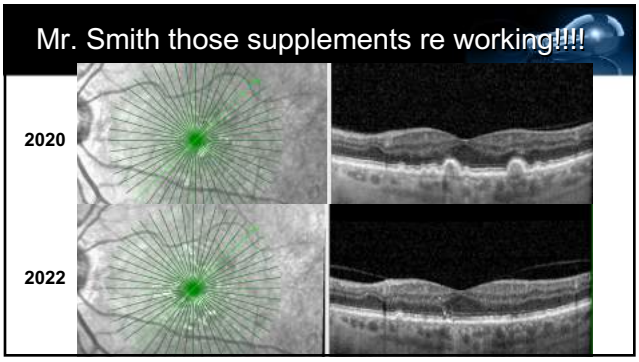
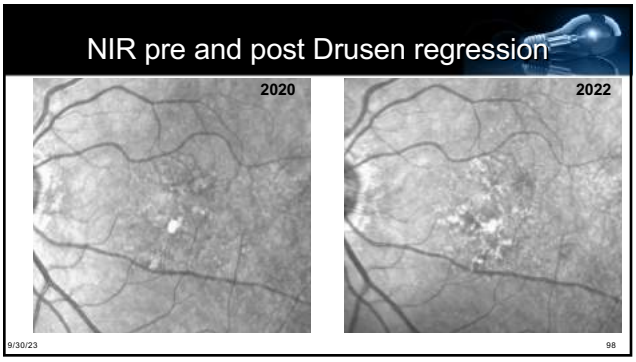

Other Eye
96

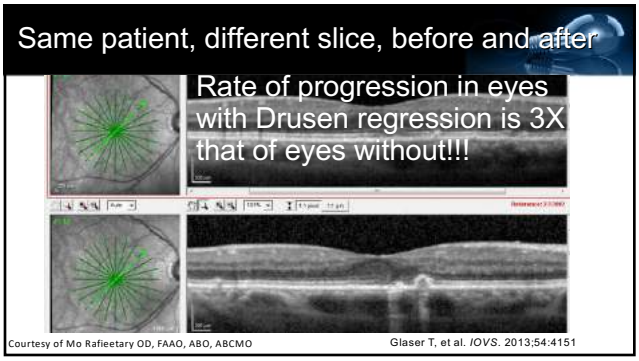
96


Mr. Smith those supplements re working!!!!
2020
2022

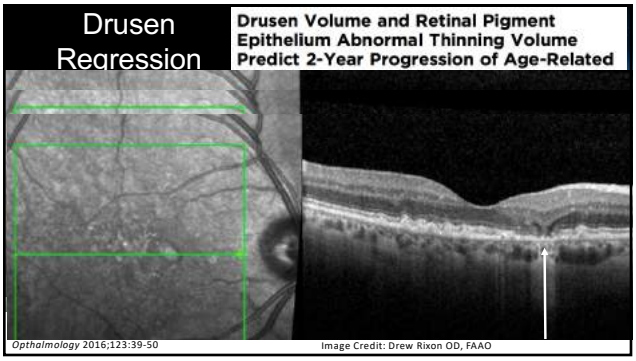
97


NIR pre and post Drusen regression
2020
2022
9/30/23
98

98


Same patient, different slice, before and after
Rate of progression in eyes with Drusen regression is 3X that of eyes without!!!
Courtesy of Mo Rafieetary OD, FAAO, ABO, ABCMO
Glaser T, et al. IOVS. 2013;54:4151

99


Drusen Regression
Drusen Volume and Retinal Pigment Epithelium Abnormal Thinning Volume Predict 2-Year Progression of Age-Related
Opthalmology 2016;123:39-50
Image Credit: Drew Rixon OD, FAAO

100

Classification of Atrophy Meeting (CAM)

- To develop consensus terminology and criteria for defining atrophy based on OCT findings in the setting of age-related macular degeneration (AMD).
- Panel of retina specialists, image reading center experts, retinal histologists, and optics engineers.
- Enlargement of atrophy as determined by CFP or FAF is only regulatory agency approved main anatomic end point in therapeutic trials
- Use of OCT proposed to identify precursor end points and achieve earlier and more precise estimation of tissue loss

9/30/23

Sadda S, et al. *Ophthalmology* 2018;125:537-548

101

101

GA can move quick!!!!!

102

cRORA

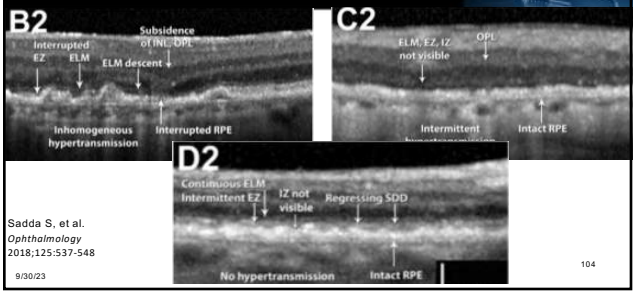
- Complete RPE and outer retinal atrophy (cRORA)

9/30/23

Sadda S, et al. *Ophthalmology* 2018;125:537-548

103

iRORA, cORA, iORA



Sadda S, et al. *Ophthalmology* 2018;125:537-548

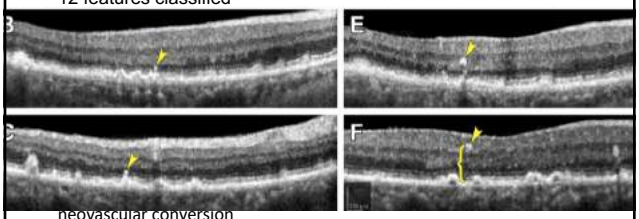
9/30/23

104

104

Imaging Features Associated with Progression to GA

- 12 features classified

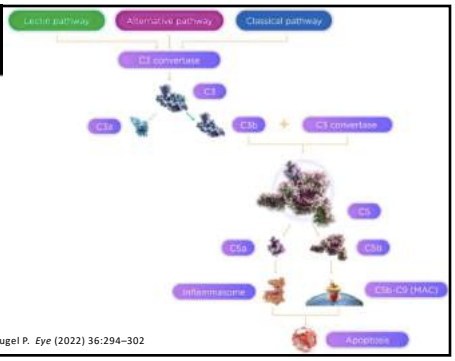


neovascular conversion

Jaffe GJ, et al. *Ophthalmology Retina* 2021;5:855-867
Fragiotta S, et al. *J Ophthalmol.* 2021. Article ID 6096017

105

The Complement Cascade



Desai D, Dugel P. *Eye* (2022) 36:294–302

107

Complement Cascade and GA

- Multiple studies have implicated complement activation as a key component in development and progression of GA
- Complement proteins, age-dependent increases in the upregulation of complement genes and related accumulation of MAC, and inflammatory cytokines/chemokines found in the retina support this
- Abnormalities in the function of the proteins associated with the complement system lead to an imbalance in homeostasis, often resulting in damage to healthy tissue
- Insufficient data into which specific locations in the complement cascade that affect development/progression of GA
- Overactivity of complement also leads to drusen

Desai D, Dugel P. *Eye* (2022) 36:294–302

108

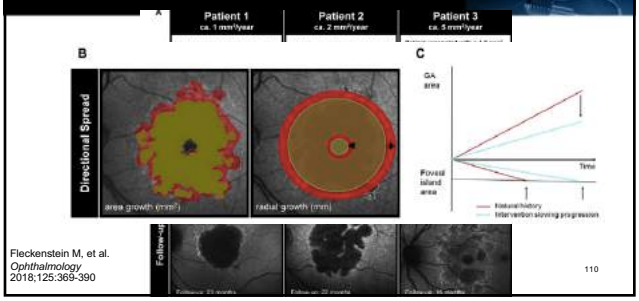
Potential Targets for Dry AMD

Target	Molecule(s)	Company	Type/MOA	Pathway	Comments
Complement factor B	IONIS-FB-L_{Rx}	Ionis/Bayer	Subcutaneous ligand-conjugated (LICA) antisense therapy	Alternative pathway	Phase II GOLDEN trial ongoing
Complement factor I	GT005	Gyroscope	Subretinal AMD vector; gene therapy designed to induce expression of CFI	Alternative pathway	Phase I/II FOCUS trial showed GT005 to be well tolerated; phase II DERI,ORE and HORIZON studies are ongoing
Complement factor H	GEM103	Gemini	IVT recombinant human CFH	Alternative pathway	Phase 2a ReGAIN trial enrollment complete
Complement factor I	GEM104	Gemini	IVT full length recombinant human CFI	Alternative pathway	In preclinical development
Complement factor D	ALXN2000	Alexion/ AstraZeneca	Oral factor D inhibitor	Alternative pathway	IND application submitted; phase II study planned
Complement C2	INCB9221	NGM Bio	IVT humanized IgG1 monoclonal antibody	Classical pathway	Phase II CANALINA study currently recruiting
Complement C3	Pegcetacoplan	Apellis	IVT cyclic peptide-based polyethylene glycol polymer	Classical pathway	Phase II FILLY trial showed reduction of GA growth; phase III DERBY and OAKS trials ongoing
Complement C5	Avacincaptad pegol	Iveric Bio	IVT pegylated RNA aptamer	Classical pathway	Phase II GATHER2 trial showed decrease in GA lesion size; phase III GATHER2 trial ongoing

Desai D, Dugel P. *Eye* (2022) 36:294–302

109

How is Progression of GA captured?



Fleckenstein M, et al. *Ophthalmology* 2018;125:369-390

110

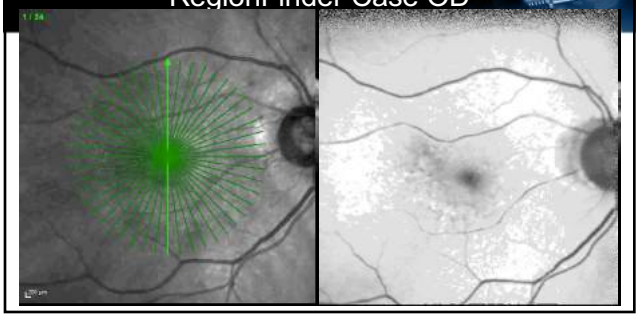
110

FAF for Progression

Rixon A, Haynes J. *Rev Optom* Jan 2017

111

RegionFinder Case OD



112

Is BCVA/Snellen the best way to assess vision?

- BCVA often incompletely captures visual status
- Low Luminance visual acuity
- Reading speed assessment
- Microperimetry
- Patient reported outcomes (NEI-VFQ-25)

Fujita K, et al. *Clin Exper Op* 105.

Eye Movement Exercises Im Related Macular Degeneration

Validation and Test Characteristics of a 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25

Roh M, *et al. BJO. 2019;103:1769-1776*

1) Chung STL. *Ophthalmic Physiol Opt.* 2020 Mar;40(2):171-186.
2) Fleckenstein M, et al. *Ophthalmology* 2018;125:369-390
3) Qasim, A., et al. *Eye* **36**, 1339–1341 (2022)
4) Raphael BA, et al. *Am J Ophthalmol* 2006;142:1026 –103
5) Cassels NK, et al. *Surv Ophthalmol* Jan-Feb;63(1):40-55

113

Near IR (NIR)

- Non-inva
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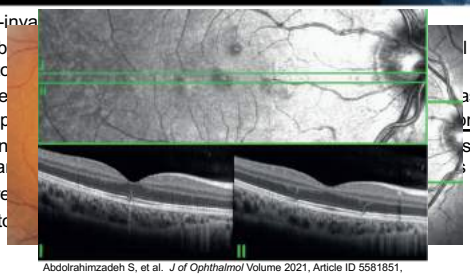

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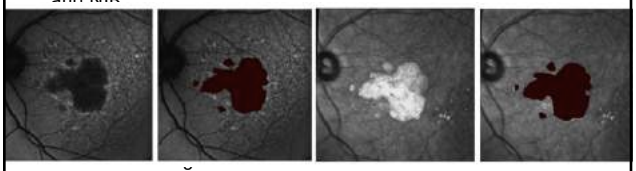
Abdolrahimzadeh S, et al. *J of Ophthalmol* Volume 2021, Article ID 5581851,

114

Near IR (NIR) vs FAF in GA

- Group compared measurements of GA area obtained by FAF and NIR



Abdelfattah NS, et al. *AJO*. 2020;212:169–174.

115

Pegcetacoplan-Derby/Oaks

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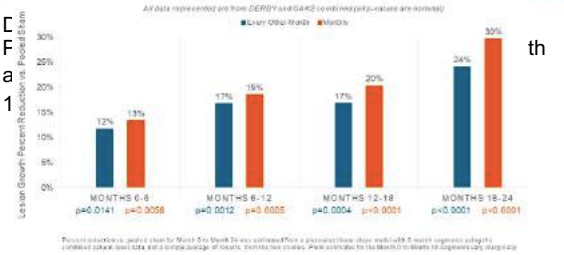


https://investors.apellis.com/news-releases/news-release-details/apellis-announces-24-month-results-showing-increased-effects

116

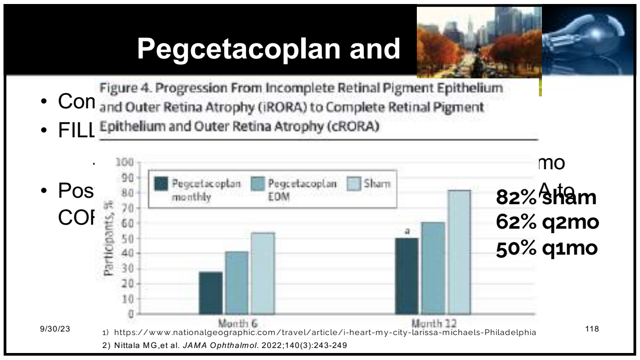
FDA approves Apellis' pegcetacoplan for geographic atrophy therapy

Published on: February 17, 2023
Lynda Charters

Apellis has received FDA approval for intravitreal pegcetacoplan (SYFOVRE) to treat geographic atrophy secondary to AMD. This news follows the submission of the 24-month phase 3 data in November 2022.

The FDA has approved intravitreal pegcetacoplan (SYFOVRE, Apellis) to treat geographic atrophy (GA) secondary to age-related macular degeneration (AMD). The approval is based on the results of the 24-month phase 3 data submitted in its New Drug Application in November 2022.

117



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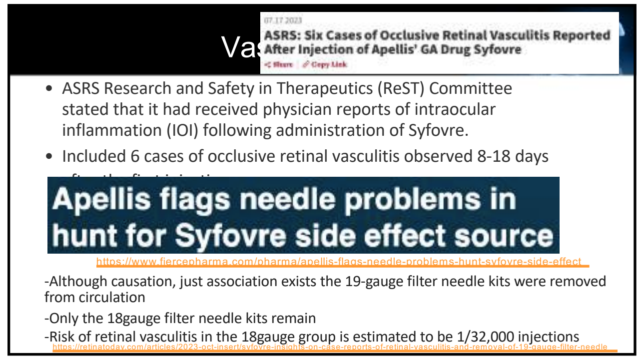

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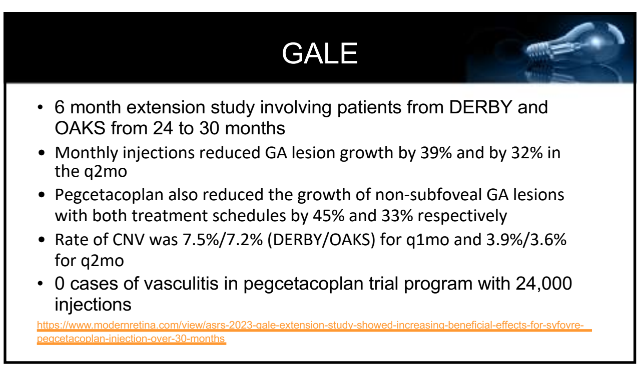

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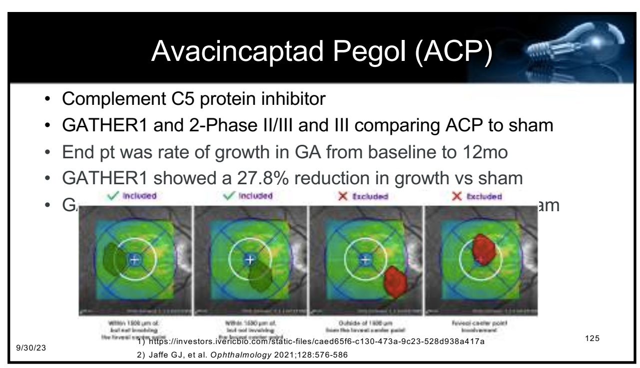


125

Iveric Bio Announces Positive 24-Month Topline Results from Phase 3 Study of IZERVAY™ (avacincaptad pegol intravitreal solution) for Geographic Atrophy

- Monthly ACP significantly slow GA compared to sham at 24mo
- Q2mo dosing showed similar reduction rate to qmo versus sham
- 12% of patients with ACP developed CNV, 9% of sham did
- One case of culture positive endophthalmitis, one non-seirous ocular inflammation
- No occlusive retinal vasculitis or ischemic neuropathy.

https://www.ophthalmologytimes.com/view/iveric-bio-releases-24-month-topline-results-from-phase-3-study-of-avacincaptad-pegol-intravitreal-solution-izervay-for-geographic-atrophy

126

Big Heart Case/Quick Review of when the flow does not go

130

9/2014

- 46yo AAM who presents with the loss of vision to his left eye over the last 24 hours.
- Denies any pain.
- Patient states that he was in an MVA 3 days ago and had some soreness to the left side of his body that brought him into the ER yesterday.
- Patient left the ER before his encounter was complete. Patient states that progressively over the night he lost his eyesight at 11:08 PM.
- Denies any other complaints

131

131

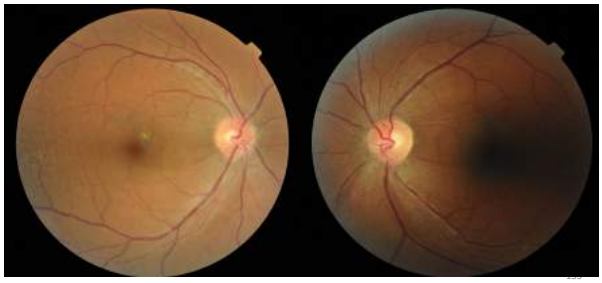
Past Hx

- 5'6" 228lbs
- Ischemic Cardiomyopathy Dx as 30yo
- Htn x 16 yrs (BP on first exam at age 33 was 175/122)
- DM x 15 yrs Avg HbA1C 9%
- Hyperlipidemia
- (-) cocaine
- CABG at 41yo 2' to 80% stenosis
- TIA c R sided numbness and weakness 2013
- MRI 2013 Left thalamic infarct noted, old CVA

132

132

3/2014 Photos



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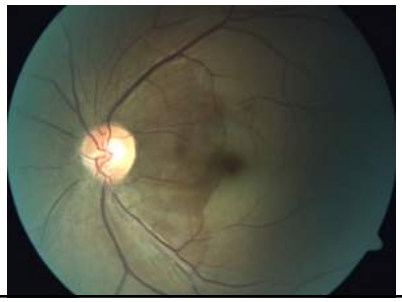
9/2014 Photo OS



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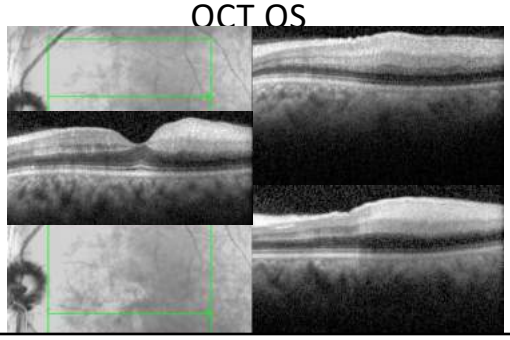
IVFA/OCT OD

Image credit: Jim Williamson OD, FAAO

135

135

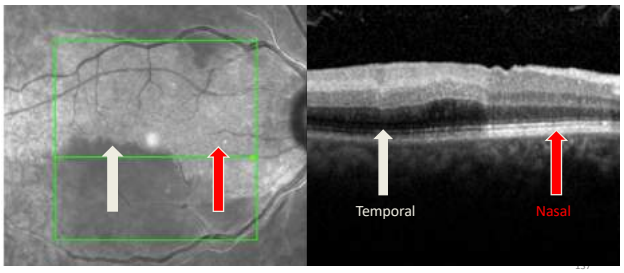
OCT OS



136

136

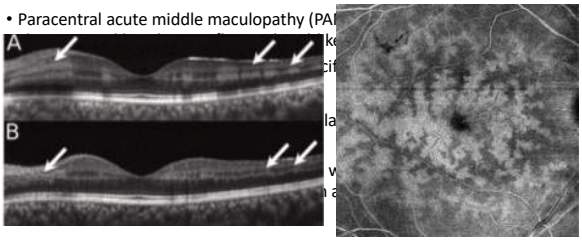
Middle Maculopathy Example



137

Was that really a PAMM? RAO?

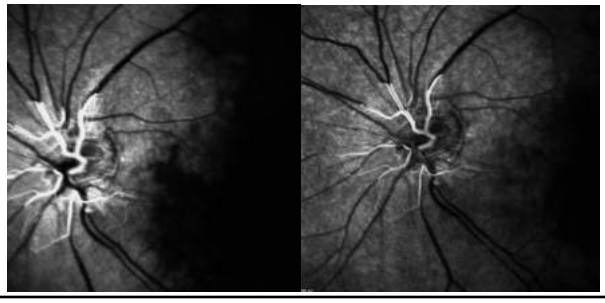
- Paracentral acute middle maculopathy (PA



Abtahi SH, et al. *Surv Ophthalmol.* 2022. https://doi.org/10.1016/j.survophthal.2022.11.009
Scharf J, et al. *Prog Retin Eye Res.* 2021 Mar;81:100884.

138

What does the IVFAs show?



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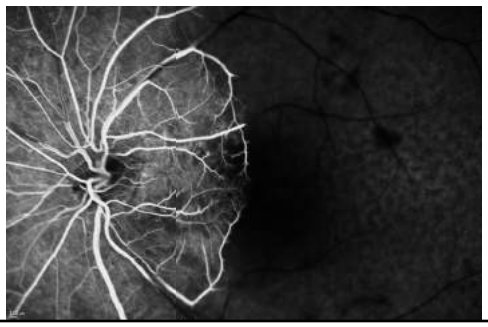
38 sec



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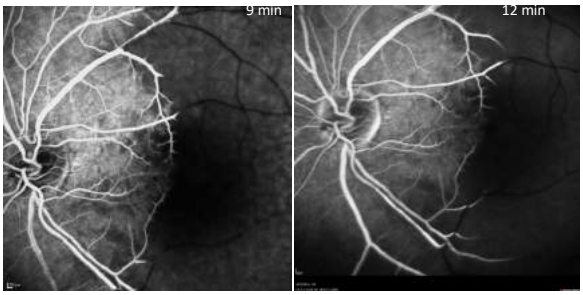
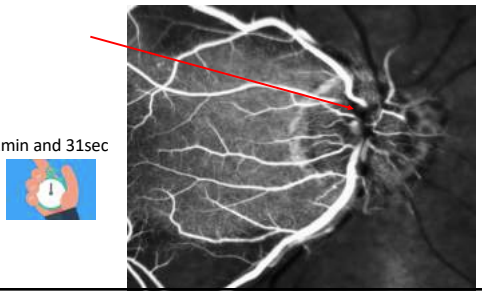
OS cont…..



142

Case 2 Attention CRA!!!

1min and 31sec



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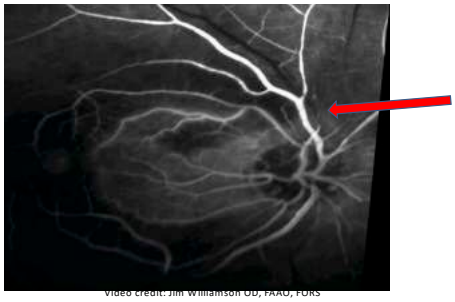
IVFA advice? Ask Dr.Williamson

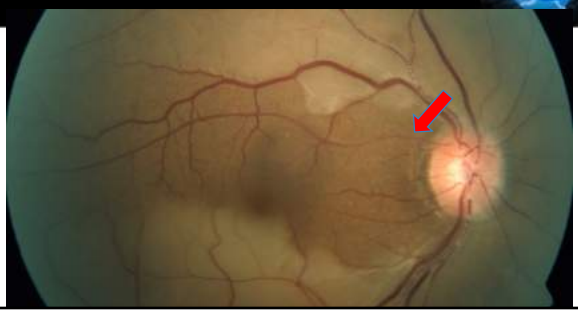


Video credit: Jim Williamson OD, FAAO, FORS

144

144

What about Case 3?



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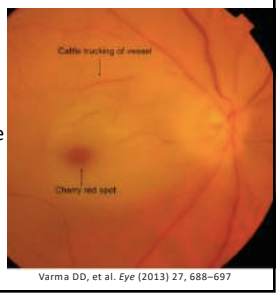
145

CRAO Review

- Causes infarction of the inner retina
- Acute, painless, catastrophic VA loss
- 80% >20/400
- Cherry red spot in fovea
- RGC infarction followed by progressive axonal degeneration with pale optic atrophy evident after some weeks
- Non-arteritic and arteritic forms
- Cause for 1 in 10,000 outpatient OMD visits



Tobalem et al. *BMC Ophthalmology*. 2018;18:101
Biousse V, et al *Neurol Clin* 35 (2017) 83–100
Varma DD, et al. *Eye* (2013) 27, 688–697

146

AHA/ASA Defi

- The 2009 revised (and current) definition of a TIA
  - "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or **retinal ischemia,** without acute infarction"
- 2013 (and current) Stroke definition
  - "Central nervous system infarction is defined as brain, spinal cord, or **retinal cell death** attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury"

Easton JD, *Stroke*. 2009;40:2276–2293
Sacco RL, *Stroke*. 2013;44:2064–2089
Stroke. 2021;52: e282-e294

147

147

CRAO and CVA

- 5 year risk of death from cerebral ischemia post CRAO is 11.7%[1]
- Rate of CVA upwards of **70x greater in 1st week after CRAO[2]**
- Acute ischemic stroke detected in 24% of subjects with RAO[3]
- Patients with acute CRAO should be promptly evaluated for stroke and stroke prevention[4]
- Patients with MVL; TMVL, CRAO, BRAO may have up to 19.5% risk of concurrent ischemic stroke[5]
  - -No concurrent focal neurological s/s
- Recommended to do DWI on MRI, CT misses

1) Biousse V, et al *Neurol Clin* 35 (2017) 83–100 2)Park SJ, et al. *Ophthalmology* 2015;122:2336-2343
3) Lee J, et al. *Am J Ophthalmol* 2014;157:1231–1238 4)French DD, et al. *Ophthalmol Ther*. 2018 Mar 24 5) Zhang LY, et al. *J Neuro-Oph* 2018;0:1–6

148

So what's the recommendation?

- "Based on the currently available literature, the treatment of CRAO should be focused on identifying a concomitant acute cerebral infarction, which is a medical emergency; optimization of all cardiovascular risk factors; and a thorough investigation for undiagnosed cardiovascular risk factors, with the ultimate goal being prevention of subsequent ischemic events, such as an acute MI, vascular death, and acute cerebral ischemia."
- "Optimal management of these patients requires collaboration between ophthalmologists and stroke neurologists"
- Note 65% of programs in a national survey of teaching hospitals routinely referred patients to a general ER

Biousse V, et al *Neurol Clin* 35 (2017) 83–100
Youn TS, *J Neurol*. 2018;265:330-335

149

149

AAO PPP RA

- Acute, symptomatic OAO or CRAO from embolic etiologies should prompt an *immediate* referral to the nearest stroke referral center for prompt assessment for consideration of an acute intervention
- However, the current evidence is limited for a similar referral for patients with an asymptomatic BRAO*

Retinal and Ophthalmic Artery Occlusions Preferred Practice Pattern®

150

Retinal Survival Time/Heroic Measures

- Retinal infarct likely to occur after only 12-15min[1]
- Historically between 90-240 min[1]
- NO strong evidence based therapy exists for CRAO
- If no retinal arterial flow after 15min heroic measures likely futile

Table 1 Common Emergency CRAO Treatment Options

Treatment	Action
Sublingual isosorbide dinitrate	Vasodilation
Oral pentoxifylline	Vasodilation
Carbogen inhalation	Cerebral vasodilation and increased oxygen
Retrobulbar alpha adenergic blocker (tolazoline) or local anesthetic	Vasodilation
Hyperbaric oxygen	Increased oxygen
Ocular massage	Attempt to dislodge emboli or thrombus
Systemic anticoagulation	Limit thrombosis
Intravenous acetazolamine and mannitol	Reduce IOP to increase perfusion pressure
Aqueous humor removal by paracentesis	Reduce IOP to increase perfusion pressure
Thrombolysis, intra-arterial or systemic	Dissolve thrombus

Tobalem et al. *BMC Ophthalmology*. 2018;18:101

151

151

Where do patients go?
Median time to get to tertiary care?

Presentation times from symptom onset to the first provider seen, to the ED and to our institution from 2010–2020.

	Number[a]	2010–2013 (n=44)[b]	2014–2016 (n=47)[b]	2017–2020 (n=87)[b]	F-test[c]
Time to first provider	178/181	24 hours (10–72) [0–672]	24 hours (4–120) [0–13140]	24 hours (3–48) [0–1344]	p = 0.5
Time to ED	125/132	24 hours (10–72) [0.5–840]	11.5 hours (3–48) [1–416]	24.5 hours (6.7–78) [0.33–504]	p = 0.2
Time to our institution	181/181	144 hours (23–442) [0.5–2920]	72 hours (10.5–372) [0–13140]	48 hours (7–180) [0–8030]	p = 0.07

Our institution's ED 36 (20%)

Outside eye care provider 63 (35%)

Flowers AM. *J Neuroophthalmol*. 2021 December 01; 41(4): 480–487

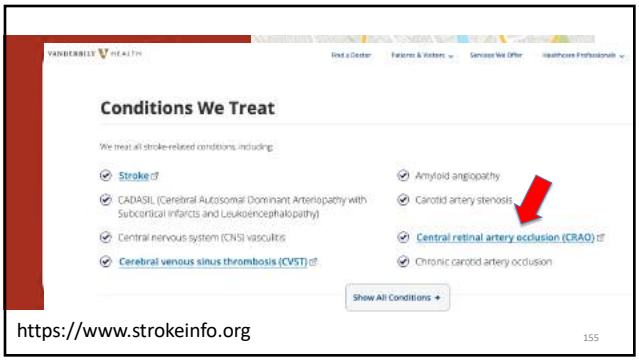
152

What has historically happened at the ER?

- Retrospective review of national emergency department sample from 2006-2014 on patient's presenting with an RAO
- Outcome was proportions of patients undergoing Neuro or carotid imaging and/or cardiac testing
- Of 259,343,582 ER visits, 2,802 had primary dx of RAO
- Brain Imaging was done on 20.3% of RAO
- Carotid imaging on 7.1%
- Cardiac testing on 23.8%
- Reinforce need for multidisciplinary approach on RAO

Yousuf SJ, et al. *Ophthalmol Retina*. 2022 Apr;6(4):318-324

153

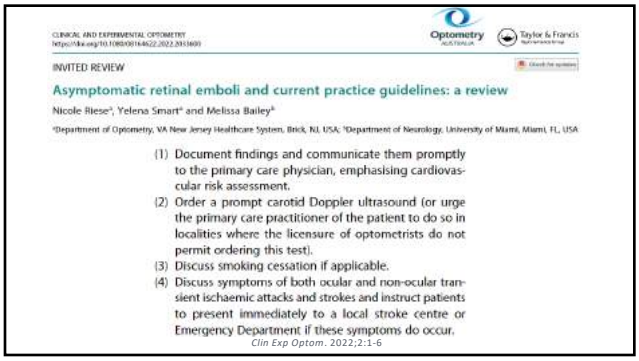


https://www.strokeinfo.org

155

Asymptomatic/What would you do?

156



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158

Diabetic Retinopathy Study (DRS)

- Study Question: Does PRP (argon or xenon arc) prevent severe vision loss in eyes with diabetic retinopathy?
- Population/Eligibility: Patients with PDR in at least one eye or severe NPDR in both eyes, with VA of 20/100 or better in each eye
- Study Design: Randomized, multicenter trial of 1742 subjects
  - -One eye from each subject was randomly assigned to PRP, the other to no PRP
- Primary Outcome Measure: Severe vision loss (SVL), defined as VA <5/200 on two consecutive follow-ups, 4 months apart

Diabetic Retinopathy Study Research Group. *Am J Ophthalmol*. 1976;81:383-396

159

Standard Photographs for Severe NPDR

Standard photograph 2A, the intermediate standard for hemorrhages/microaneurysms

Standard photograph 8A, less severe of two standards for grading CWS and IRMA (TOP)
Bottom more severe-BB

Standard photograph 6A, less severe of two standards for venous beading

161

High Risk PDR Definitions..

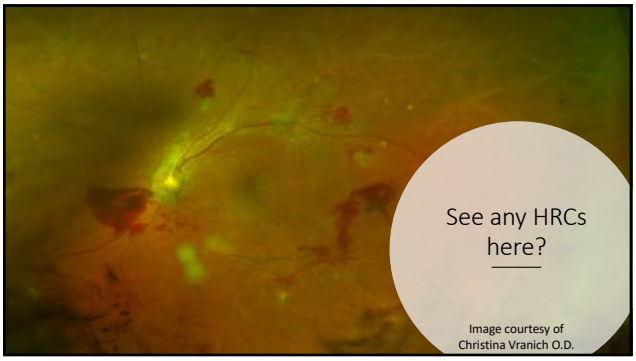
1 of the following;

1) NVD ≥ 1/3 disc area
2) Any NVD with vitreous hemorrhage (VH)
3) NVE ≥ ½ disc area with VH

Standard photograph 10A, lower boundary of moderate NVD ~1/3 Disc Area

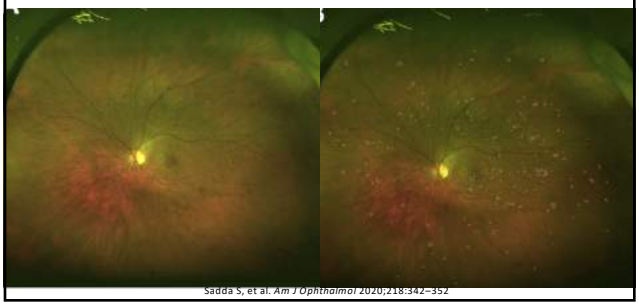
ETDRS Research Group. *Ophthalmology* 1991;98:786-806

162



164

UWF wasn't around……

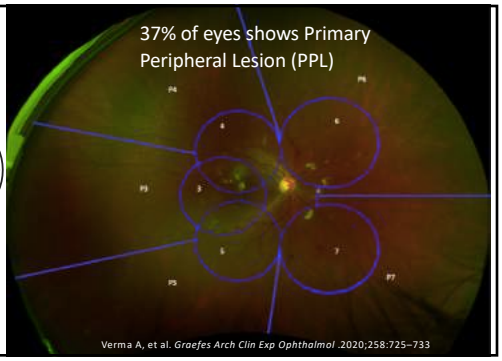


Sadda S, et al. *Am J Ophthalmol* 2020;218:342–352

165

ETDRS didn't cover much real estate…

37% of eyes shows Primary Peripheral Lesion (PPL)



Verma A, et al. *Graefes Arch Clin Exp Ophthalmol* .2020;258:725–733

166

Early Treatment of Diabetic Retinopathy (ETDRS)

- Study Questions:
  1) When in the course of DR is it most effective to initiate photocoagulation
  2) Is photocoagulation effective in the treatment of macular edema
  3) Is aspirin effective in altering the course of DR
- Population/Eligibility: Patients with moderate or severe NPDR or mild proliferative diabetic retinopathy. VA of 20/40 or better if no edema or 20/200 or better if macular edema present.
- Study Design: multi-center, randomized clinical trial designed to evaluate argon laser photocoagulation in the management of patients with moderate to severe NPDR or early PDR. 3711 patients accepted.
- Primary Outcome Measure: BCVA, specifically development of SVL (<5/200)

Early Treatment Diabetic Retinopathy Study Research Group. ETDRS report number 7. *Ophthalmology*. 1991;98:741-56

168

CSME= Thickening, Thickening, Thickening

CSME definition:

1)Retinal edema located at or within 500 µm of the center of the macula

2) Hard exudates at or within 500 µm of the foveal center if associated with thickening of adjacent retina

3) A zone of thickening larger than 1 disc area if located within 1 disc diameter of the center of the macula

Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991 May; 98 (5): 786-806.

169

We interrupt this program…Moving to the 201st

Ophthalmic imaging in diabetic retinopathy: A review

Nanegrungsunk O, et al. *Clin Experiment Ophthalmol* 2022;50:1082–1096.

171

The RESTORE Study

Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema

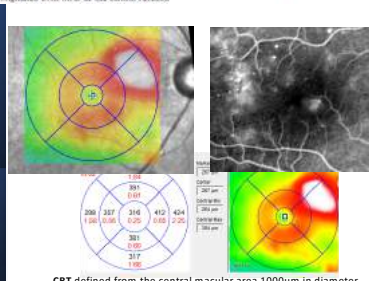
Paul Mitchell, MD, PhD,[1] Francesco Bandello, MD, FEBO,[2] Ursula Schmidt-Erfurth, MD,[3] Gabriele E. Lang, MD,[4] Pascale Massin, MD, PhD,[5] Reinier O. Schlingemann, MD, PhD,[6] Florian Sutter, MD,[7] Christian Simader, MD,[8] Gabriela Burian, MD, MPH,[9] Ortrud Gerstner, MSc,[9] Andreas Weichselberger, PhD,[9] on behalf of the RESTORE study group*

Mitchell P, et al. *Ophthalmology* 2011;118:615-625

172

*Focal DME: More than 67% of leakage originated from leaking microaneurysms (MAs) in the whole edema area or 30%–67% leakage from MAs in the whole edema area, but >67% of the leakage originated from MAs in the central subfield.
Diffuse DME: Less than 33% of leakage originated from leaking MAs the rest from diffuse leaking capillaries in the whole edema area or 30%–67% leakage comes from MAs, but <33% of the leakage originated from MAs in the central subfield.

How did they define DME? CRT?



CRT defined from the central macular area 1000um in diameter

174

Results/Conclusions

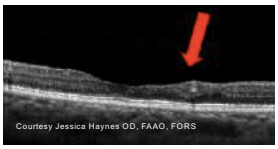
- Ranibizumab alone or in combo with laser was superior to laser monotherapy in improving mean BCVA at 12mo
- CRT significantly reduced with Ranibizumab (R) and Ranibizumab+Laser (R + L) when compared to laser monotherapy (L)
- No outcome difference between R alone vs R+L
- HRQoL (NEI VFQ-25) improved significantly over baseline in R and R+L when compared to L
- 7 injections on average over 12mo

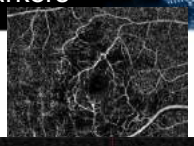
Mitchell P, et al. *Ophthalmology* 2011;118:615-625

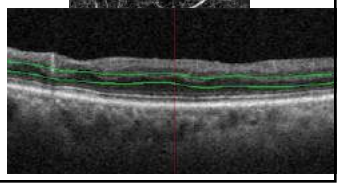
175

Diabetic Biomarkers

- Enlarged FAZ
- Loss of deep capillary plexi thickness
- Inner macular thickness

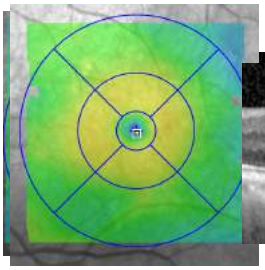


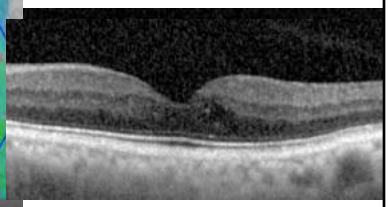




176

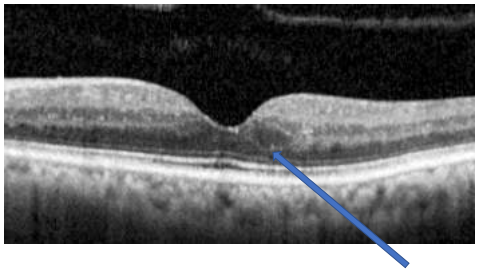
What do we do in 2023?….OD History





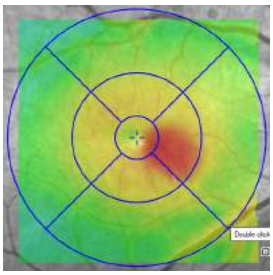
177

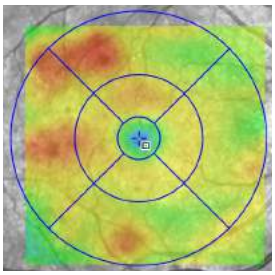
Should I send this for Injection/What to inject?



178

Center Involved vs Non-CI





179

DME facts

- Presence of good vision in an eye with CI-DME is common
- Starting in 2010 anti-VEGF was demonstrated to be superior to laser photocoagulation in patients with CI-DME and VA worse than 20/32
- 84% of patients with DME have 20/40 or better vision
- ETDRS showed 40% of DME eyes had VA of 20/20 or better
- Up to 60% of eyes with CI-DME left untreated do not experience visual decline (≥3 lines on an eye chart) over 5 years

180

Protocol T

https://public.jaeb.org/drcrnet/pubs

- Comparative effectiveness of aflibercept, bevacizumab, and ranibizumab for center-involved diabetic macular edema (DME) associated with vision impairment (20/32-20/320).

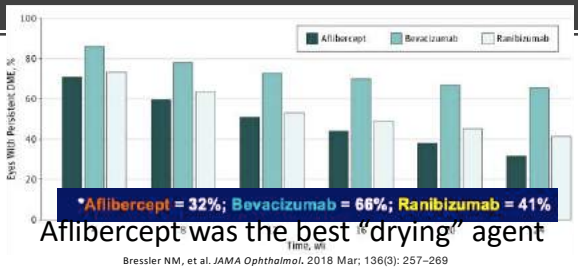
Main Outcome

Change in visual acuity at 1 Yr (primary outcome) and 2 Yrs
- Adjusted for baseline visual acuity and multiple comparisons
- Multiple imputation for missing values, intent-to-treat principle
- Truncated to 3 SD from the mean

Aflibercept vs. Bevacizumab | Aflibercept vs. Ranibizumab | Bevacizumab vs. Ranibizumab

181

Persistence of DME at 2 years



Aflibercept was the best "drying" agent

Bressler NM, et al. *JAMA Ophthalmol*. 2018 Mar; 136(3): 257–269

183

DRCR Retina Network

Treatment for Center-Involved DME in Eyes with Good Visual Acuity (Protocol V)

DRCR Retina Network - Public Site (jaeb.org)

NIH National Eye Institute | NIH National Institute of Diabetes and Digestive and Kidney Diseases

184

Anti-VEGF Has Not Been Evaluated In Eyes That Have Center-Involved DME with Good VA (20/25 Or Better)

How should we treat eyes with center-involved DME and visual acuity 20/25 or better?

- Anti-VEGF?
- Focal/Grid Laser (Add Anti-VEGF if VA drops)?
- Observation (Add anti-VEGF if VA drops)?

185

185

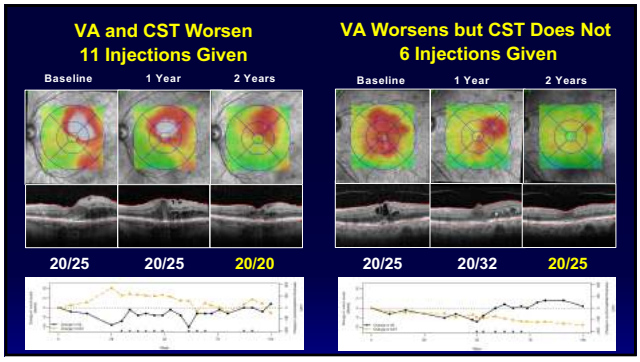
Protocol V (CI-DME* and Good VA)

- All three strategies resulted in mean VA at 2 years of 20/20
- Based on these results, many clinicians and patients might choose initial observation for eyes with CI-DME and good VA, withholding anti-VEGF treatment unless vision worsens.

* Defined by OCT machine and sex: Heidelberg Spectralis CST ≥ 305 µm in women and ≥ 320 µm in men; Zeiss Cirrus CST ≥ 290 µm in women and ≥ 305 µm in men.

188

188



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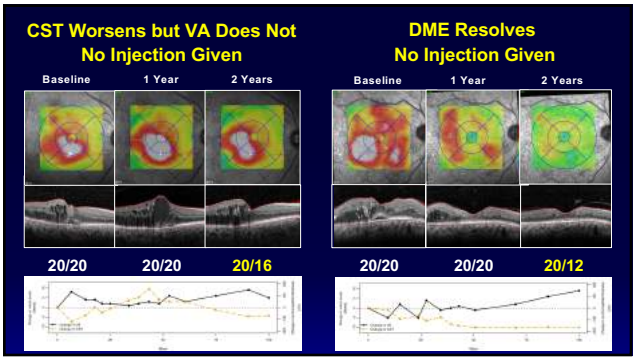

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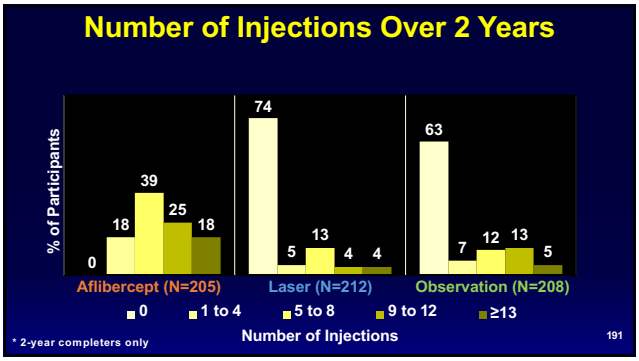


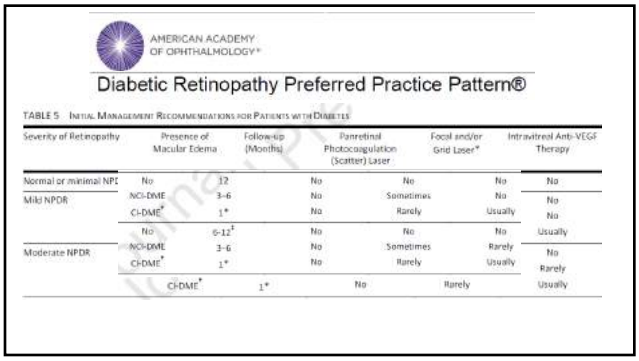
191

Number of Injection Needed vs Real World

- DME management is ”front loaded”
- ~1:1 ratio of injection to letter gained
- Average in some studies 9-10 in 1st year
- Intensity of treatment difficult to capture in clinical practice
- Real world practice studies range of 3 to 7 injections in first 12mo and then substantial drop off per year out to 5 years
- Results in worse outcomes when compared to RCTs

Van Aken E, et al. *Clin Ophthalmol*. 2020;14:4173–4185.
Ciulla TA, et al. *Br J Ophthalmol*. 2021;105(2):216-221

192



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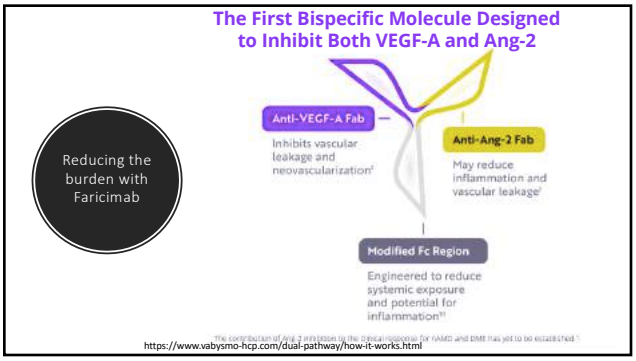


194

But what about the NCI-DME? Is laser dead?

- Pro laser;
  - -Macular laser still needed p Anti-VEGF in Protocol T
  - -CI Leakage caused by capillaries outside in 33% of cases
  - -Loss to f/u reality/Need to be practive
- Against laser
  - -Macular laser less effective for diffuse edema
  - -True effectiveness of lasers not shown
  - -Anti-VEGF is good with diffuse and focal and reduces severity of retinopathy
  - -Low risk of VA loss with observation

https://sn4.scholastic.com/issues/2019-20/111819/the-day-the-dinosaurs-died.html

1) Zur, D., Loewenstein, A.. *Eye* 2022;**36**:483–484
2) Mueller, I., Talks, J.S.. *Eye. 2022*;**36**:485–486

195

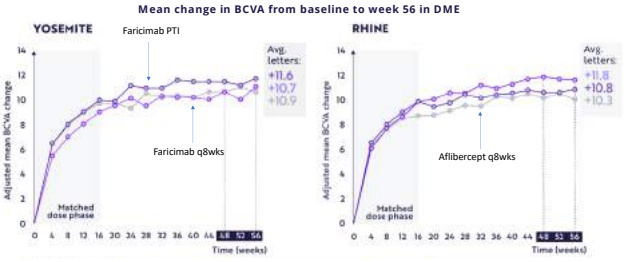
Yosemite/Rhine Trials

- Phase 3 non-inferiority trial
- Faricimab 6mg q8wks vs. Faricimab 6mg PTI vs. Aflibercept 2mg q8wks out to 100wks
- After 4 monthly loading doses
- PTI dosing intervals were extended, maintained, or reduced (q4wks up to q16wks) based on disease activity at each visit
- End point was VA at 12mo

Wycoff CC, et al. *Lancet*. 2022.19;399(10326):741-755

196

Faricimab was non-inferior to aflibercept



https://www.vabysmo-hcp.com/dme-data/efficacy-in-dme.html

197

PTI is promising

Proportion of VABYSMO Variable arm patients on a Q4W, Q8W, Q12W, or Q16W treatment interval at week 52 (pooled)[12]	
Q16W	51.9%
Q12W	20.5%
Q8W	15.5%
Q4W	12.1%

https://www.vabysmo-hcp.com/dme-data/efficacy-in-dme.html

- PTI simulates more real-world
- Treat and Extend
- Allows clinical durability to be tested
- >70% of patients on the faricimab PTI regimen were able to have 3 months or longer Tx intervals at the end of the first year.
- Drawback is PTI is variable and might undermine true potential efficacy of the drug

Sharma A, et al. *Eye* (2022) 36:679–680

198

PHOTON

- Higher dose Aflibercept-8mg
- Compared 2mg q8wks to 8mg q12wks vs 8mg q16wks
- 8mg had 3 loading doses
- 93% of patients receiving 8mg were able to maintain dosing regimens >12wks
- FDA approved on August 31, 2023 for wet AMD, DME, and diabetic retinopathy

https://investor.regeneron.com/static-files/da20405e-b843-402e-855b-d824a15dec60

https://investor.regeneron.com/static-files/da20405e-b843-402e-855b-d824a15dec60

199

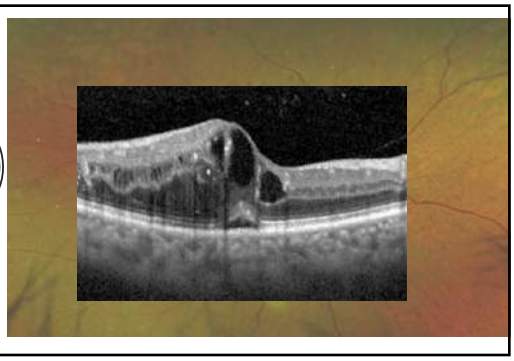
Applying W and PANORAMA

Support For Observing until VTCs occur	Support for Anti-VEGF prevention before VTC occur
VA no different between tx and sham	Eyes with moderate and severe have a greater lifetime risk of vision loss
Unknown cost-effectiveness	Patient may prefer to be proactive if side effect profile is low long term
Endophthalmitis risk	
Visit burden-Avg 15 in 24 mo	
Long term outcome of early Tx unknown	
Pregnancy-Unknown effect to fetus	

Nanegrungsunka O, Bressler NM. *Curr Opin Ophthalmol* 2021, 32:590-598

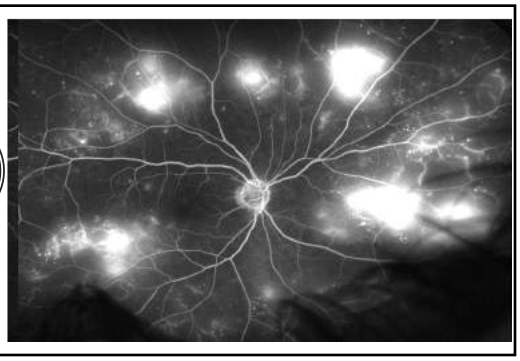
216

UWF PDR c CI-DME



217

UWF PDR

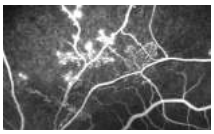


218

PDR Perspectives

Estimated to affect 7.5% of patients with DM → Left untreated is a leading cause of blindness worldwide → Without treatment ~50% of patients with high-risk PDR experience severe vision loss within 5 years

Progression is rule rather than exception ~40% progress in 4-6yrs → PRP has been standard of care since DRS in 1981



Lee R, et al. *Eye Vis (Lond)*. 2015;2:17

219

Protocol S and CLARITY

- Compared Anti-VEGF to PRP in patients with PDR, with and without DME
- Protocol S found that[1];
  - -Tx with Ranibizumab was superior to PRP in VA and development of CI-DME at 2yrs
  - -"Ranibizumab may be a reasonable treatment alternative, at least through 2 years."
- CLARITY found that[2];
  - -Tx with aflibercept showed superior VA outcomes when compared to PRP over 12mo

Bressler S, et al. *Retina*. 2019;39(9):1646-1654
Sivaprasad S, et al. *Lancet*. 2017;3;389(10085):2193-2203

220

How many injections?

- CLARITY was week 4,8, and 12 afterwards watched q4wks and injections were customized to individual
- Protocol S was 6 initial injections q4wks, resume injections if NV worsens
- PRP watch q16wks in S
- PRP reviewed q8wks in CLARITY

Bressler S, et al. *Retina*. 2019;39(9):1646-1654
Sivaprasad S, et al. *Lancet*. 2017;3;389(10085):2193-2203

221

New Paradigm in PDR?

- PRP still an option in some patients as a stand alone and is not always a "1 and done" scenario
- Anti-VEGF now a stand-alone option in some patients
- Combo may be best option in patients as well
- Caveats……
  - -Anti-VEGF are more effective in the short term
  - -PRP is likely more durable
  - -Treatment burden of anti-VEGF may increase the risk of drop out and subsequent worsening

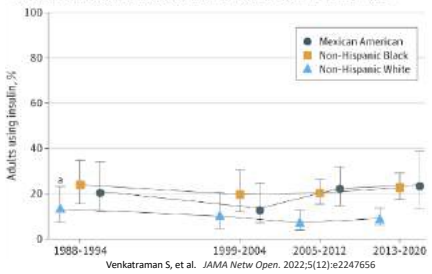
1)Gonzalez V, Wang PW, Ruiz CQ. *Ophthalmology* 2021;128:1448-1457
2)UpToDate Diabetic Retinopathy Last Updated Nov 2022 last accessed 12/26/2022

222

Original Investigation | Diabetes and Endocrinology

Trends and Disparities in Glycemic Control and Severe Hyperglycemia Among US Adults With Diabetes Using Insulin, 1988-2020

Siddharth Venkatraman, BS; Justin B. Echouffo-Tcheugui, MD, PhD; Elizabeth Selvin, PhD, MPH; Michael Fang, PhD, MHS



Venkatraman S, et al. *JAMA Netw Open*. 2022;5(12):e2247656

223

THANK YOU!

9/30/23

224