

FINANCIAL DISCLOSURES

- Speaker-Carl Zeiss Meditec, Bausch and Lomb, Oyster Point
- Advisory Board-Bausch and Lomb, Santen, Peripherex, Ocuphire, Ocuterra
- Shareholder-Clearside Biomedical (<0.01% ownership)
- All relevant relationships have been mitigated

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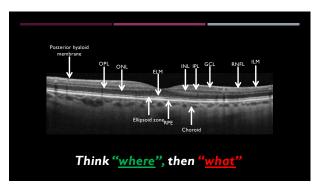


OCT BACKGROUND

- Provides submillimeter detection of retinal tissue
- BIO = $50\mu m$ discrimination
- Ultrasonography = $50-200\mu m$
- SD-OCT = $5-7\mu m$
- Currently the most valuable test to evaluate re-treatment criteria with anti-VEGF

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OCT ANGIOGRAPHY

- The only thing that moves in the retina over time are red blood cells
- Take the 'difference' between multiple B scans at the same location to produce a 'decorrelation signal'

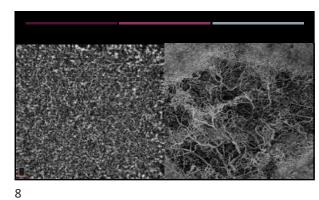
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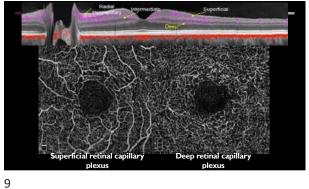
OCTANGIOGRAPHY

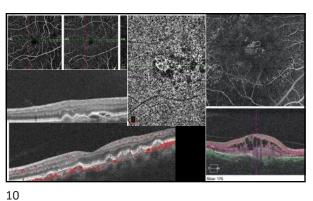
- En face flow formation and cross sectional structural information
- Not a replacement for FA/OCT
- Provides new information

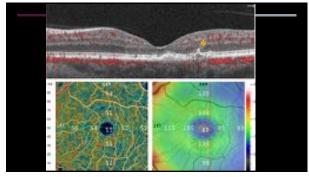
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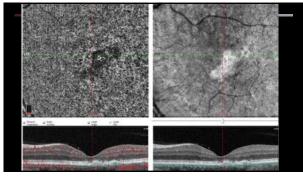
Valuable for detection of choroidal and retinal neovascularization, macular ischemia, segmentation of the deep and superficial capillary plexi—and maybe early glaucoma?

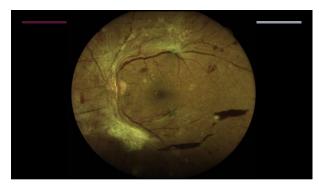


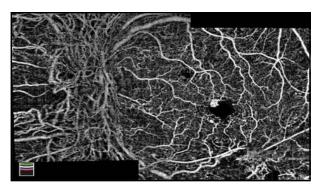












Challenges in OCTA

Static blood flow information
No leakage, pooling or staining

Small field of view 3x3mm; 6x6mm;
8x8mm (or 12x12mm) with current
systems

Motion artifacts are a big deal

Sensitivity is a challenge in eyes with
pathology

Quantification of blood flow-not yet

VASCULAR RESPONSE TO DISEASE

- I) Exudation
- Loss of blood retinal barrier
- Accumulation of plasma fluid and lipid
- Hard exudate and intraretinal edema
- 2) Ischemia
 - Capillary drop out leads to hypoxia
 - Microaneurysms, capillary drop out, neovascularization
- 3) Both

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MICROANEURYSMS

Weakening of capillary wall

Large MAs visible clinically

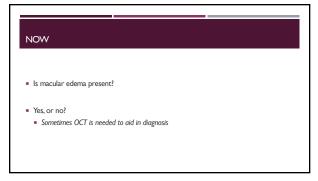
Leak

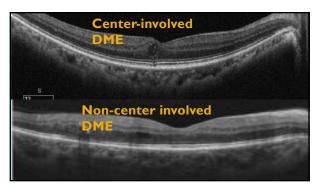
Cause intraretinal edema

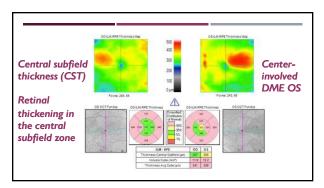
May be visible on OCT, OCTA, and FA



17 19







How do we manage these patients?

22 24

Anti-VEGF in DME & DR

DRCRnet Protocol S (2016): Ranibizumab (Lucentis) in non-inferior to PDR

Protocol T (2018) Aflibercept vs. bevacizumab vs. ranibizumab in DME: For VA 20/50 or worse, aflibercept (Eylea) better at improving VA

Protocol V (2019): Center-involved DME (20/25+) no difference in vision at 2 years between prompt treatment and initial observation

Anti-VEGF in DME & DR

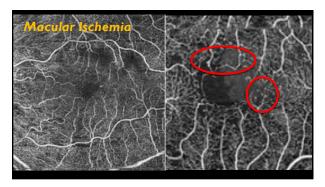
DRCRnet Protocol AC (2022)

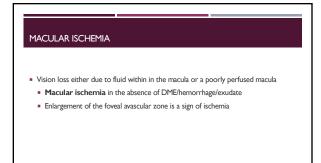
Bevacizumab patients did really well at 2 years-is it reasonable to begin with bevacizumab and switch to aflibercept if "clinically" indicated?

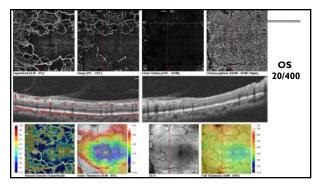
70% of patients met switch criteria; almost all within the first year

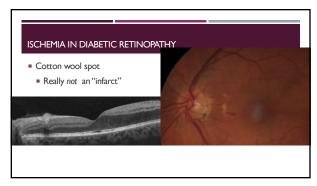
Monotherapy was \$12000 more costly than switch

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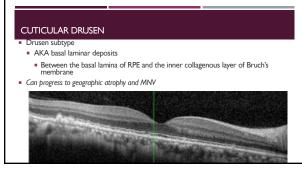








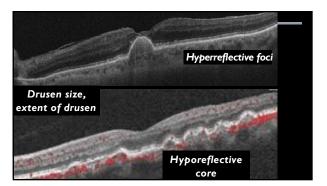
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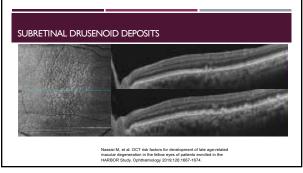




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SUBRETINAL DRUSENOID DEPOSITS

- Distinctive type of drusen aka reticular pseudodrusen
- Subretinal space extending to the outer segments of photoreceptors
- Not just drusen above the RPE
- Include immune-reactive cells (macrophages, microglia)
- Impact dark adaptation; choriocapillaris flow impairment
- Increased risk of progression to late stage AMD
 Finger et al. 2014

36 37

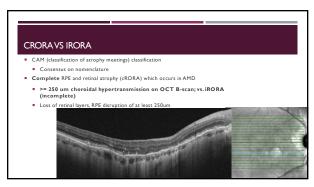
OCT BIOMARKERS FOR PROGRESSION TO NAMD

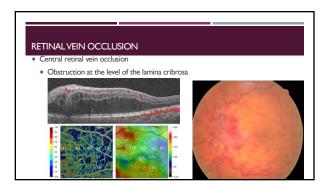
Thick double layer sign, intraretinal hyperreflective foci, fellow eye exudative macular neovascularization

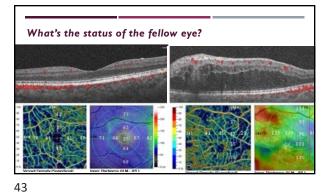
Wakasaki', et al. Opical Coherence Tomography Biomarkers for Coherence to Equations
Neovascular Age-reliated Miscular Degenerationels of Optibules 2023.247:171-144

OCT is the most valuable tool to determine retreatment criteria in nAMD

38 39







SCORE2

5 year data (April 2022)

No significant difference between Avastin and Eylea

66% had at least one treatment between year 4 and 5

RVO is a chronic disease

45

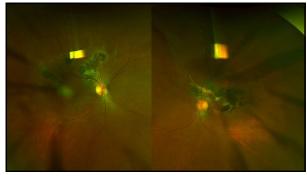
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60 year old Black female

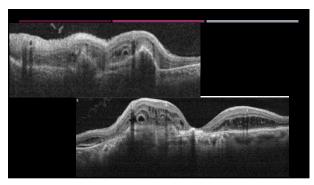
History of insulin dependent diabetes mellitus with retinopathy, hypertension, asthma, cervical cancer, autoimmune thyroid disease, Vogt Koyanagi Harada Syndrome

BCVA 20/20 OD LP OS

No APD OS



46 48





CLINICAL DIAGNOSTIC CHALLENGE

- Uncertain diagnosis follow clinical examination
- Differential diagnosis
- Choroidal melanoma
- Choroidal nevus
- Epiretinal membrane
-something else?

IN OTHER WORDS...

- Bottom line:
- Melanoma or not?
- Urgent referral to ocular oncology...or not?

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DOCTOR GASS (based on 1977 data)

TFSOM (2002)

TFSOM-UHHD (2009)

TFSOM-DI (2019)

TFSOM"DOING IMAGING"

Finally incorporates multimodal imaging

Thickness > 2mm (US)

Fluid (OCT)

(Subretinal fluid) overlying lesion or 3mm or less from lesion margin

Symptoms

Vision loss (<20/50)

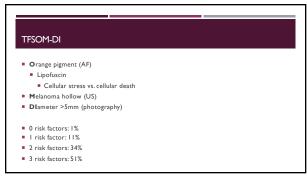
Differ based on location-iris melanoma vs choroid

Typically flashes, floaters/vision loss

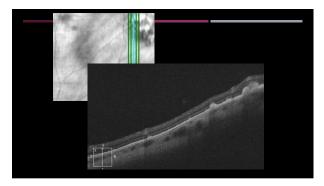
Eye pain/red eye secondary to tumor-related inflammation or secondary glaucoma

25% of choroidal melanoma are asymptomatic

54 55







Article

The MOLES System for Planning Management of Melanocytic Choroidal Tumors: Is It Safe?

Kelsey A. Roelofs ¹, Roderick O'Day ^{1,2}, Lamis Al Harby ¹, Amit K. Arora ^{1,3}, Victoria M.L. Cohen ^{1,3}, Mandeep S. Sagoo ^{1,3} and Bertil Damato ^{1,4,*}

MOLES Score

0 = Common naevus

1 = Low-rish. naevus

2 = High-rish naevus

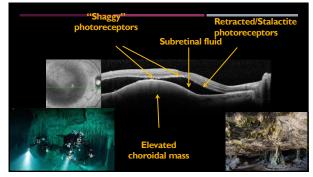
2 = High-rish naevus

3 = Probable melanoma

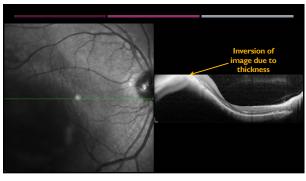
Management Superited Managem

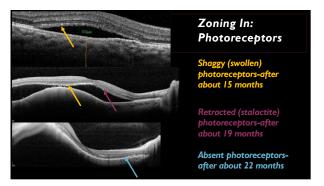
58 59

Indicator	Finding	Score	Bertil Damato, PhD,
Mushroom shape	0 = Absent		FRCOphth University of Oxfore
	1 = Incipient (erosion through RPE) / uncertain) 2 = Present (i.e. definitive mushroom shape with overhang)		
Orange pigment	0 = Absent		
	1 = Dusting / unsure 2 = Confluent (i.e. easily visible clumps of grange pigment)		
	0 = Flat (<1mm thick) and less than 3 disc diameters (DD) wide		
Large size	1 = Subtle dome shape (1-2mm thick) AND/OR 3-4DD wide		
	2 = Significant thickening (>2mm) AND/OR more than 4DD wide		-
Enlargement	0 = None (or no baseline photography)		
	1 = Suspected change on comparing photographs 2 = Definite growth confirmed by sequential imaging		
Subretinal fluid	0 = Nil		1
	1 = Trace (limited retinal detachment seen only with OCT)		
	2 = Definite subretinal fluid visible with ophthalmoscopy		
	Moles total score =		1
MOLES Score 0 = Common naevus	Suggested Management Monitoring in community with color photography every 1–2 yrs.		
1 = Lowerisk paevus	Non-urgent referral for specialist investigation comprising wide-field photography,		
1 - 1011 (1011 1111 1111	autofluorescence imaging, optical coherence tomography and, in selected cases, ultrasonography. Subsequent surveillance to be undertaken at a specialist clinic or in the		
2 = High-risk naevus	community according to risk of malignancy.		
= Probable melanoma	Urgent referral to ophthalmologist with urgent onward referral to ocular encologist if suspicion of malignancy is confirmed.		

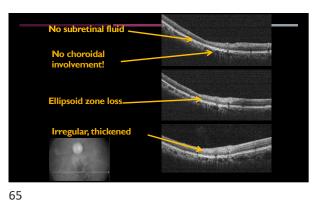


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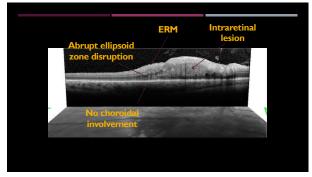


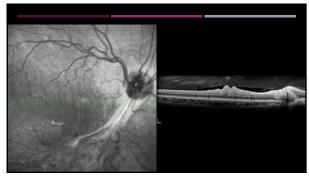






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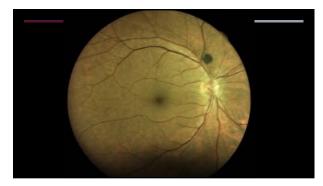
BY DEFINITION

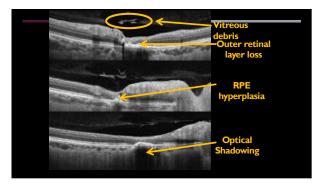
- Retina & RPE disorganization with overlying ERM
- Combined hamartoma of retina and retinal pigment epithelium

"PIGMENTED RETINAL LESION"

- 63 year old African American female
- 12 year history of a 'pigmented retinal lesion'...CHRPE...choroidal nevus...

68 69





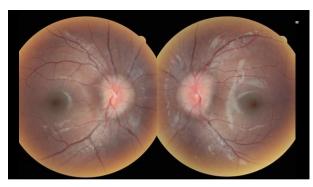
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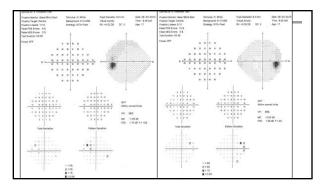


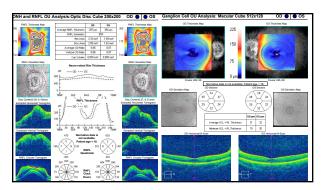
CASE

- 17 year old female presented for comprehensive eye examination
 - No history of headache, no neurological symptoms
 - (-) TVO, (-) pulsatile tinnitus, (-) whooshing in head
 BCVA 20/20 OD and OS
- Trace APD OS?
- Alert, oriented, and awake
- No systemic medications
- Blood pressure I 10/85mmHg
- BMI 36.6kg/m²
- 5'2", 200ll

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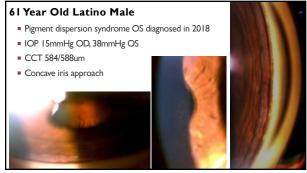


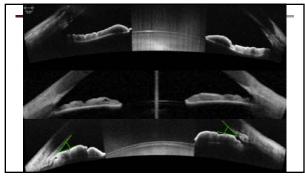


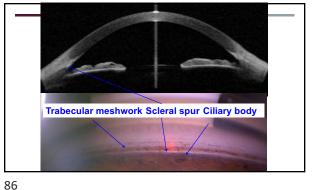




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OCT Evaluation of the Anterior Chamber No inadvertent compression May be performed in complete darkness Most valuable to determine if the angle is open or closed

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There is no one test for detection of glaucoma, or to determine if and when disease progression occurs

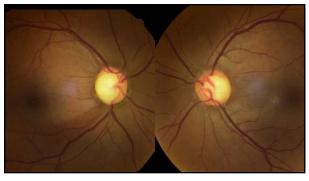
OCT: RNFL AND GCC ANALYSIS • Objective structural (anatomic) assessment · Used as an adjunct to clinical examination and automated perimetry Normative database provides comparative information

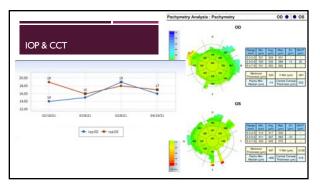
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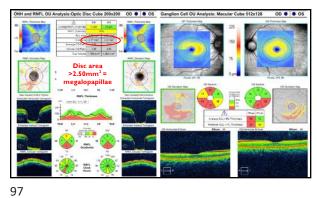
RETINAL NERVE FIBER LAYER VS. GANGLION CELL COMPLEX

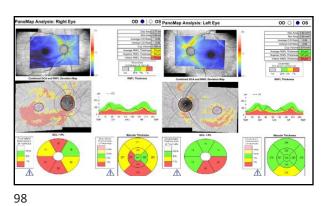
- We use both
- Ganglion cell complex (not just the cell layer-usually IPL-may also include RNFL)
- Difficult to segment ganglion cell layer ONLY
- Retinal ganglion cells most dense at the macula
- More than 30%: 2% of retinal area
- Lack of retinal blood vessels and support cells
- Retinal nerve fiber layer contains non-neuronal elements
- Thickness impacted by blood vessels, glial elements
- BUT-contains all (100% of) retinal ganglion cell axons

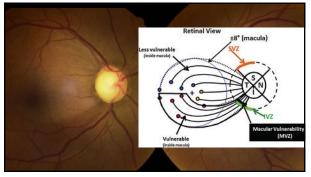
56 YEAR OLD AFRICAN AMERICAN FEMALE • 56 year old African American female referred for evaluation due to suspicion of glaucoma secondary to optic disc appearance No family history of glaucoma ■ No systemic diagnoses; no systemic medications

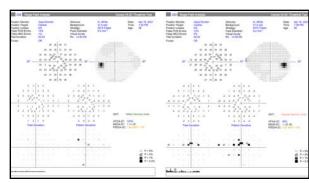


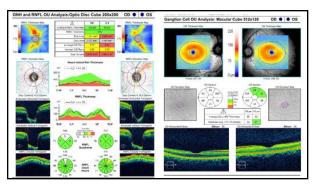


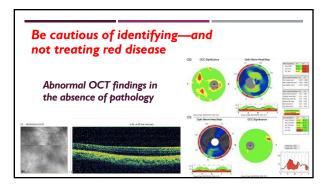


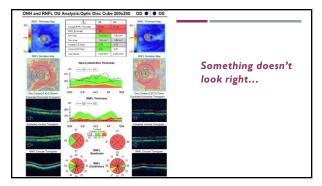












Do normative databases help--or hurt us?

Group of normal individuals to which your images (and therefore patient) are compared to

"Healthy" patients can be labeled as abnormal and vice versa if they don't "fit the mold"

Heidelberg Spectralis: 330 eyes
218 non-Hispanic white, 45 Hispanic white, 41 Black, 23 Asian, 3 American Indian
Age 18-78
Zeiss Cirrus: 282 eyes
Age 19-84; 6 US sites, 1 in China
133 males, 149 females, 43% Caucasian, 24% Asian, 18% African American, 12% Hispanic, 1% Indian, percentile
4% mixed ethnicity

RF-Vue: 600 eyes
19-84 years of age; 11 sites, USA, Japan, India, England

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Sequence

Temporals

Temporals

Sequence

Temporals

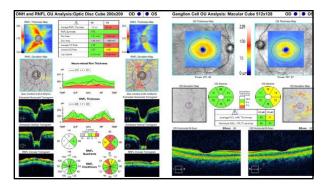
Sequence

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| Column | C

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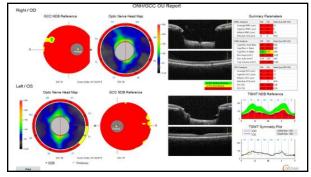
27 YEAR OLD MALE

- 27 year old black male presents for evaluation of blurred vision in the right eye for about a year; he reports 'good' vision in the left eye
 Thinks it has been a gradual change the visual reduction in the right eye
- First eye examination
- 3+ APD OD
- BCVA:
- 20/400 OD
- 20/30 OS
- Unremarkable anterior segmentIOP 41/36mmHg
- Now what?!

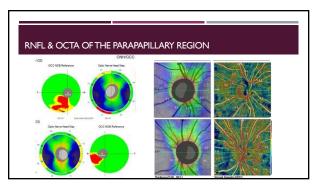
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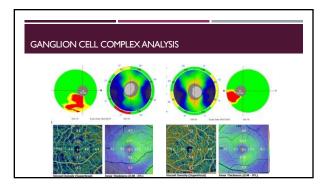


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FLOOR EFFECT When RNFL reaches approximately 50μm, even with further disease progression, thickness measurement will not change Blood vessels and glial support cells





WHAT HAPPENS FIRST?

- · Glaucomatous eyes have reduced ocular blood flow
- Reduced peripapillary capillary density may be observed in glaucomatous eyes
- Does decreased ocular blood flow cause optic neuropathy--or does optic disc damage cause decreased blood flow?
 - A) Ischemia leads to ganglion cell death
 - B) GC loss results in reduced metabolic demand



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CHICKEN OR EGG?

- Metaphysical questions have metaphysical answers
- We're clinicians.



IT'S NOT ACTUALLY THAT SIMPLE

- Neurons, glial cells, cerebral microvascular endothelium function together = neurovascular unit
- Remember, we are limited in a clinical environment by the parameters that we are given
- Velocity of blood flow
- Variation of interscan time
- Research parameters are developed into clinical parameters-eventually

BOTTOM LINE

- No device is better than the human eye and common sense
- $\,\blacksquare\,$ No device is better than a skilled and experienced clinician
- Know the limitations of the technology
- $\,\blacksquare\,$ Technology is only as good as the clinician using it.

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