On behalf of Vision Expo, we sincerely thank you for being with us this year.

Vision Expo Has Gone Green!

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VISION EXPO

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- www.octangio.org

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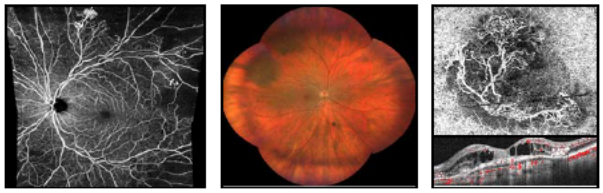
- Majcher@nsuok.edu
- 918-444-4155

Disclosures
- Paid consultant/ speaker for Carl Zeiss Meditec and Regeneron Pharmaceuticals
- Dr. Majcher has received honorarium from Regeneron Pharmaceuticals and Zeiss. She is on the speaker's bureau for Regeneron Pharmaceuticals and Zeiss.

2



21st CENTURY RETINA CARE

Carolyn Majcher, OD, FAAO, FORS
Oklahoma College of Optometry

NSU OCO

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TABLE 5 Initial Management Recommendations for Patients with Diabetes

Severity of Retinopathy	Presence of Macular Edema	Follow-up (Months)	Panretinal Photocoagulation (Scatter) Laser	Focal and/or Grid Laser*	Intravitreal Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No	12	No	No	No
	NCI-DME	3–6	No	Sometimes	No
	CI-DME†	1*	No	Rarely	Usually
Moderate NPDR	No	6–12*	No	No	No
	NCI-DME	3–6	No	Sometimes	Rarely
	CI-DME†	1*	No	Rarely	Usually
Severe NPDR	No	3–4	Sometimes	No	Sometimes
	NCI-DME	2–4	Sometimes	Sometimes	Sometimes
	CI-DME†	1*	Sometimes	Rarely	Usually
Non-high-risk PDR	No	3–4	Sometimes	No	Sometimes
	NCI-DME	2–4	Sometimes	Sometimes	Sometimes
	CI-DME†	1*	Sometimes	Sometimes	Usually
High-risk PDR	No	2–4	Recommended	No	Sometimes[61,188]
	NCI-DME	2–4	Recommended	Sometimes	Sometimes
	CI-DME†	1*	Recommended	Sometimes	Usually

Anti-VEGF = anti-vascular endothelial growth factor; CI-DME = center-involved diabetic macular edema; NCI-DME = noncenter-involved diabetic macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

American Academy of Ophthalmology – Preferred Practice Patterns 2019, p20

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	Referral	FU Frequency	PRP	Focal Laser	Anti-VEGF
Mild/Moderate NPDR					
No ME	communicate with PCP	Mild 12 mo , Moderate 6-9 mo	No	No	No
non-clinically significant DME	Retinal consult in 2-4 wks	4-6 mo	No	No	No
CSME or center-involved DME	Retinal consult in 2-4 wks	1-4 mo	No	Based on clinical judgement	Yes, if vision ↓
Severe or Very Severe NPDR					
No ME	Retinal consult in 2-4 wks	3-4 mo	Sometimes	No	Alternative, Sometimes
non-clinically significant DME	Retinal consult in 2-4 wks	2-3 mo	Sometimes	No	Alternative, Sometimes
CSME or center-involved DME	Retinal consult in 2-4 wks	1-4 mo	Sometimes	Based on clinical judgement	Yes, if vision ↓
Low risk PDR					
No ME	Retinal consult in 2-4 wks	3-4 mo	Sometimes	No	Alternative, Sometimes
non-clinically significant DME	Retinal consult in 2-4 wks	2-3 mo	Sometimes	No	Alternative, Sometimes
CSME or center-involved DME	Retinal consult in 2-4 wks	1-4 mo	Sometimes	Based on clinical judgement	Yes, if vision ↓
High risk PDR					
No ME	Retinal consult in 24-48 hrs	2-3 mo	Yes	No	Alternative
non-clinically significant DME	Retinal consult in 24-48 hrs	2-3 mo	Yes	No	Usually
CSME or center-involved DME	Retinal consult in 24-48 hrs	1-4 mo	Yes	Based on clinical judgement	Usually

American Optometric Association– Clinical Practice Guideline 2019, p61-63

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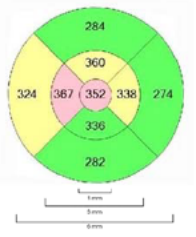
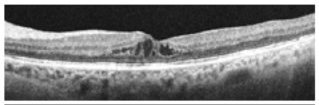
DME STAGING

Macular edema: Retinal thickening within 2 DD of the center of the fovea

- Center involved (CI-DME) vs non-center involved (NCI-DME)

  CI-DME= thickening within the central subfield zone that is 1mm in diameter





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MANAGEMENT OF DME

Management of DME

- Who should be treated?
  - CI-DME with VA 20/32 or worse- referral within 2-4 weeks (AOA-CPG 2019)
- Who can usually be observed?
  - CI-DME with VA 20/25 or better - defer tx until VA is 20/30 or worse (**DRCR.net Protocol V**)
    - Re-examine every 2-4 months
  - NCI-DME with VA 20/25 or better
  - Consider early treatment if:
    - DR stage is severe NPDR or worse
    - Planning PRP or cataract extraction
    - Systemic risk factors for progression exist (HTN, renal failure, pregnancy)
    - Pt is unobservant/uncompliant

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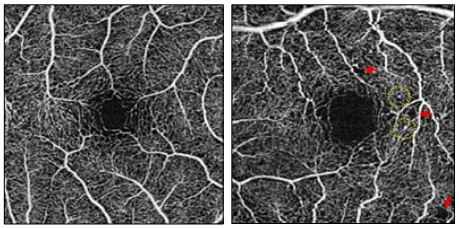
OCTA DETECTION OF SUBCLINICAL DR

NO CINICALLY DETECTABLE DR!!!

Normal **Diabetic without DR**



De Carlo TE, et al. Detection of microvascular changes in eyes of patients with diabetes but not clinical DR using OCTA. Retina 2015.

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PREDOMINANTLY PERIPHERAL DIABETIC RETINOPATHY

Silva PS, et al. UWF Peripheral Lesions Predict DR Progression. Ophthalmology 2015.

- Followed 200 DR eyes for ~ 4 yrs
- Eyes with predominately peripheral DR defined as majority of DR lesions outside the 75° ETDRS standard 7 fields
- Compared to eyes without, eyes with predominately peripheral DR had a 3.2-fold ↑ risk of ≥2-step DR progression (11% vs. 34%), and a 4.7-fold ↑ risk for progression to PDR (6% vs. 25%).

EYES WITH PREDOMINANTLY PERIPHERAL DR HAVE A GREATER RISK FOR DR PROGRESSION AND DEVELOPMENT OF PDR!!

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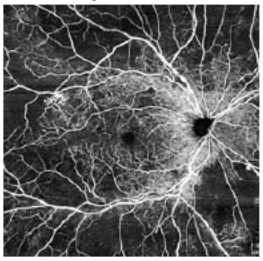
OCTA MONTAGE MIDPERIPHERAL NONPERFUSION IN DR

Very Severe NPDR



- Increased risk for progression to PDR
- Consider early PRP/anti-VEGF treatment

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EARLY ANTI-VEGF TX FOR SEVERE NPDR

- **Strongly consider referring all eyes with severe NPDR regardless of DME status!!!**

TABLE 5 Initial Management Recommendations for Patients with Diabetes

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	CI-DME†	1*	Sometimes	Sometimes	Usually
High-risk PDR	No	2–4	Recommended	No	Sometimes[¶,‖]
	NCI-DME	2–4	Recommended	Sometimes	Sometimes
	CI-DME†	1*	Recommended	Sometimes	Usually

- Start considering anti-VEGF therapy/PRP at the severe NPDR stage <u>even without CI-DME</u> (optional)
  - Anti-VEGF: reverse DR stage/prevent development of vision threatening complications
  - Both ranibizumab and aflibercept FDA approved even if no DME
  - DRCR.net Protocol W

American Academy of Ophthalmology – Preferred Practice Patterns 2019, p20

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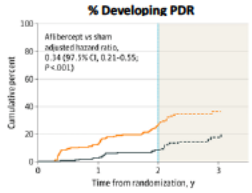
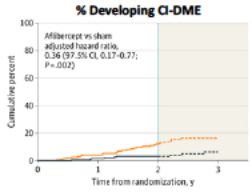
DRCR.net Protocol W- Effect of Intravitreous VEGF vs Sham for Prevention of Vision-Threatening Complications of DR, 2 Year Results

- Randomized eyes with moderate to severe NPDR without CI-DME to sham (tx deferred until CI-DME or high risk PDR developed) vs periodic intravitreal aflibercept
- Lower rates of developing CI-DME with vision loss (4% vs 15%) or PDR (14% vs 33%) in treated eyes vs sham at 2 years
- Change in VA at 2 years: -5.8 letters vs -6.1 letters (not significant)

% Developing PDR



% Developing CI-DME



Maturi, R. , et al. Effect of Intravitreous Anti-VEGF vs Sham Treatment for Prevention of Vision-Threatening Complications of DR. JAMA Ophthalmology, 139 (7), 701-712.

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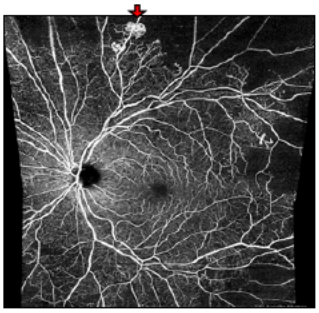
PROLIFERATIVE DIABETIC RETINOPATHY

OCTA – Visualization of peripheral NP (nearly invisible without) and subclinical NVE



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PROLIFERATIVE OR NONPROLIFERATIVE?

You QS et al. Detection of Clinically Unsuspected Retinal Neovascularization with Wide-field OCTA. 2019

- Performed wide-field OCTA on 27 eyes with NPDR via DFE & color fundus photography
- Of the 7 eyes originally graded as severe NPDR, wide field OCTA detected neovascularization in 4 eyes (57%)
  - 2 of these eyes would have been missed with 6x6mm scan alone

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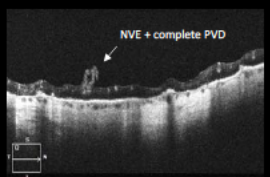
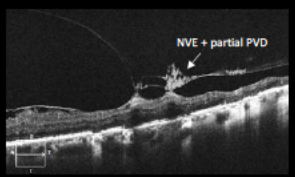
PROLIFERATIVE DIABETIC RETINOPATHY

PVD Status?





COMPLETE PVD IS PROTECTIVE!

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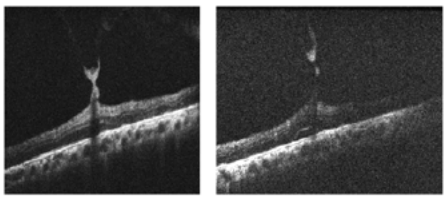
DIABETIC RETINOPATHY

Detecting/monitoring vitreoretinal traction

Early Tractional RD

2 months time, new onset vitreous hemorrhage



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FENOFIBRATE FOR DIABETIC RETINOPATHY

- Safe and inexpensive PO fibric acid derivative conventionally used to treat dyslipidemia, generic in the US and off-label for DR
  - Licensed in Australia and Singapore for the tx of DR
- Experimentally has been shown to decrease vascular leakage, downregulate VEGF, & reduce endothelial cell and pericyte loss
- Dose: 135mg – 200mg per day (67mg qd if mild-moderate renal disease)
- Contraindications: Severe renal disease, liver disease, possibly potentiates warfarin anticoagulation

Stewart S, et al. Fenofibrate for DR. Asia Pac J Ophthalmol (Phila). 2018 Nov-Dec;7(6):422-426.

17

PERSPECTIVE

Fenofibrate – A Potential Systemic Treatment for Diabetic Retinopathy?

TIEN YIN WONG, RAFAEL SIMÓ, AND PAUL MITCHELL

Am J Ophthalmol. 2012

"There are now robust and consistent clinical data to recommend fenofibrate as an adjunctive treatment for early DR in patients with type 2 DM, taking into account the risks vs benefits of therapy."

- Two large RCTs have demonstrated that fenofibrate in pts with Type 2 DM decreased the rate of progression in eyes with preexisting DR:
  1. **FIELD (Fenofibrate Intervention and Event Lowering in DM) 2005**
     - In eyes with preexisting DR, 14.6% on placebo had 2 step worsening vs 3.1% on 200mg/day fenofibrate after ≥2 years FU.
     - Fenofibrate also decreased need for laser treatment for PDR or DME.
  2. **ACCORD (Action to Control Cardiovascular Risk in DM) 2007**
- Does not reduce the risk of new DR development in eyes with DR at baseline

SUBSTANTIAL EVIDENCE EXISTS SHOWING THAT FENOFIBRATE DECREASES DR PROGRESSION IN TYPE 2 DM!!!

Stewart S, et al. Fenofibrate for DR. Asia Pac J Ophthalmol (Phila). 2018 Nov-Dec;7(6):422-426.

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NUTRITIONAL SUPPLEMENTATION FOR DIABETIC RETINOPATHY

Pts with DR have high incidences of vitamin and mineral deficiencies

Supplementation with vitamins, minerals, and nutraceuticals may complement current tx approaches

Goals of supplementation:

- Reduce oxidative stress
- ↓ ischemic injury
- Combat elevated homocysteine
- Support retinal metabolism/function
- Promote microvascular health

THE KEY PLAYERS!!

- L-methylfolate
- Natural vitamin E complex
- Vitamin D
- Vitamin C
- N-acetylcysteine
- Vitamins B1, B2, B6 & B12 (methylcobalamin)
- Lutein & zeaxanthin
- Alpha-lipoic acid

Shi C, Wang P, Airen S, et al. Nutritional and medical food therapies for diabetic retinopathy. Eye Vis (Lond). 2020;7:33.

19

NUTRITIONAL SUPPLEMENTATION FOR DIABETIC RETINOPATHY

CASE EXAMPLE: 67yo with NPDR on Ocufolin® x 3yrs

- Improvement in NPDR appearance and resolution of DME

List of Ingredients:	Quantity per capsule
Vitamin D3	37.5 µg
Vitamin E	5 mg
Vitamin C	45 mg
Vitamin B1	1.5 mg
Vitamin B2	10 mg
Vitamin B6	3 mg
L-methyl folate calcium	900 µg
Vitamin B12	500 µg
Pantothenic acid	5 mg
Zinc	25 mg
Selenium	20 µg
Copper	0.667 mg
Lutein	10 mg
Zeaxanthin	2 mg
N-Acetyl-L-cystein	180 mg

Wang J, et al. Improving DM and hypertensive retinopathy with a medical food containing L-methylfolate: a preliminary report. Eye Vis (Lond) 2019;6:21.

20

NUTRITIONAL SUPPLEMENTATION FOR DIABETIC RETINOPATHY

EyePromise DVS

EyePromise DVS is formulated for:

- Patients at risk of macular edema
- Patients at risk of retinal blood vessel degeneration
- Improved visual performance

Supplement Facts

Serving Size 2 Softgels | Servings Per Container 30

Amount Per Serving		%DV*
Calories	15	
Total Fat	1 g	1%
Vitamin C (as Ascorbic Acid)	60 mg	67%
Vitamin D (as Cholecalciferol)	50 mcg	250%
Vitamin E (as d-Alpha Tocopherol)	40 mg	267%
Vitamin B12 (as Cyanocobalamin)	6 mcg	250%
Zinc (as Zinc Oxide)	15 mg	136%
Fish Oil 70%	320 mg	†
Total Omega-3 Fatty Acids A% (as EE)	240 mg	†
EPA 40% (Eicosapentaenoic Acid) A%	128 mg	†
DHA 30% (Docosahexaenoic Acid) A%	96 mg	†
Alpha Lipoic Acid	150 mg	†
Co-Enzyme Q-10	20 mg	†
Mixed Tocotrienol/Tocopherol	20 mg	†
Zeaxanthin	8 mg	†
Lutein	4 mg	†
Proprietary Blend	530 mg	†

Benfotiamine, N-Acetyl-L-Cysteine, Grape Seed Extract, Resveratrol (Polygonum Cuspidatum), Turmeric Root Extract (Curcuminoids), Green Tea Leaf, Pycnogenol® (French Maritime Pine Bark Extract)

*Percent Daily Values are based on a 2,000 calorie diet.
†Daily Value (DV) not established.

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Clinical science

OPEN ACCESS

The Diabetes Visual Function Supplement Study (*DiVFuSS*)

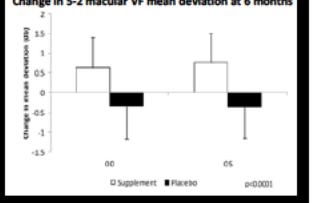
A Paul Chous,[1] Stuart P Richer,[2] Jeffry D Gerson,[3] Renu A Kowluru[4]

67pts with type 1 and type 2 DM with no or mild/moderate NPDR, 6 months of DVS vs Placebo

- Subjects on DVS had significantly better visual function performance
  - Contrast sensitivity
  - Color discrimination
  - 5-2 macular threshold perimetry
- Subjects on DVS also improved peripheral neuropathy symptoms

"This [study] suggests that the DiVFuSS formula positively influences the pathogenesis of diabetes-induced retinal dysfunction with concomitant effects on visual function in a manner independent of tight or improved blood glucose control."

Change in 5-2 macular VF mean deviation at 6 months



Br J Ophthalmol. 2016;100:227-34

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RETINA RISK MOBILE APP

- Co-developed by ophthalmology & endocrinology
- Enables pts to calculate their personalized risk of developing sight-threatening diabetic retinopathy
- Clinically validated in over 25,000 diabetic patients
- Allows users to understand which are the key underlying risk factors for retinopathy and which lifestyle changes can lower the risk
- Can give pts a visual representation of their blood sugar (HbA1c) and blood pressure levels as well as personalized messages based on those levels
- Can help keep track of eye appts

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AUTONOMOUS ARTIFICIAL INTELLIGENCE SYSTEMS FOR DR SCREENING

- AI software program algorithms used to analyze fundus photographs
  - Images are uploaded to cloud-based server for analysis
- Requires two 45° photos per eye, usually does not require dilation unless photos are poor quality
- Target users: PCP and endocrinologist offices esp in areas with poor access to eyecare
- Goal: Increase rates of DR screening/ identify patients at risk of vision loss (moderate NPDR or worse, DME) to expedite and preference referrals for eye exams
- Two systems already FDA-approved

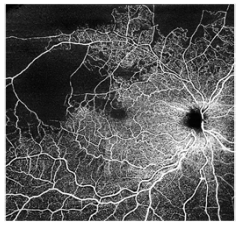
1) IDx-DR (pair with Topcon NW400 retinal camera) - FDA approved Aug 2018
   - Identified more than mild DR with a sensitivity of 88.2% & specificity of 89.0%
2) EyeArt (pair with Canon CR-2 AF) - FDA approved Aug 2020
   - Identified more than mild DR with a sensitivity of 96% & specificity of 88.0%

Gerendas B, et al. FDA-authorized autonomous AI for DR screening in clinical routine. IOVS July 2019, Vol.60, 4776.
Bhaskaranand M, et al. The value of automated DR screening with the EyeArt system: A study of more than 100,000 consecutive encounters from people with DM. Diabetes Technol Ther 2019;21:11:635-43.

24

MONTAGE OCTA IN RVO

Ischemic BRVO



- Estimate the degree of NP and classify as ischemic or nonischemic
  - CRVO → ant seg neo
  - BRVO → post seg neo

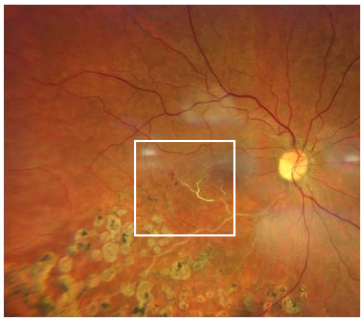
Predictive Value of Retinal NP!!!

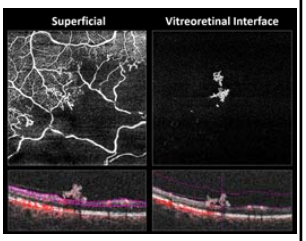
BVOS 50/50/50 rule: ~ 50% of eyes with ischemic BRVO will develop NVD/NVE

Branch Vein Occlusion Study Grp. Argon laser scatter photocoagulation for prevention of neovascularization and vit heme in BVO. A RCT. Arch Ophthalmol. 1986.

25

OCTA DETECTION/MONITORING OF NEO IN RVO





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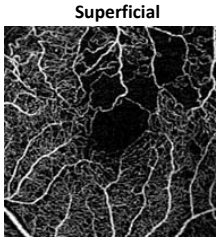
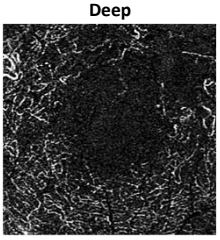
OCT ANGIOGRAPHY– MACULAR ISCHEMIA

OCTA 3mm Macula

Superficial



Deep



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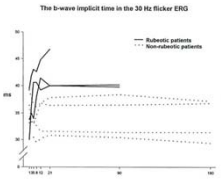
ERG PREDICTORS OF NEO IN CRVO

Full Field ERG

- ↓ b wave amplitude and ↑ b wave implicit time
- b wave/a wave amplitude ratio < 1 suggestive of ischemic CRVO

Photopic 30 Hz Flicker ERG

- Increased b wave implicit time (Lb)
  - Considered to be one of the best predictive parameters
  - In one study, 100% of eyes with b wave implicit times of >35ms developed neo
- Progression of abnormal parameters



Larsson J, et al. The 30 Hz flicker cone ERG for monitoring the early course of CRVO. Acta Ophthalmol Scand. 2000

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NEVUS OR MELANOMA?

Differentiating small choroidal melanoma from choroidal nevus 2019 UPDATE

To **F**ind **S**mall **O**cular **M**elanoma Doing IMaging (TFSOM-DIM)

T- Thickness (>2mm US = ~ 890um OCT)
F- Fluid, SRF
S- Symptomatic VL (VA ≤20/50)
O- Orange pigment (FAF)
M- Melanoma acoustic hollowness
DIM- DIaMeter >5mm

Risk for growth within the next 5 years:

- 0 risk factors = 1.1%
- 1 factor = 11%
- 2 factors = 22%
- 3 factors = 34%
- 4 factors = 51%

Table 1. Risk factors for choroidal nevus transformation into melanoma using multimodal imaging (multivariable analysis)

Variable	Letter	Mnemonic	Testing	Hazard ratio (mean) multivariate analysis	P value
Thickness tumor >2 mm	T	To	US	3.80	<0.0001
Fluid subretinal	F	Find	OCT	3.56	<0.0001 0.0003
Symptoms visual acuity ≤20/50	S	Small	Snellen VA	2.28	0.0030
Orange pigment	O	Ocular	AF	2.07	0.0004
Melanoma acoustic hollowness	M	Melanoma	US	2.10	0.0020
Diameter tumor >5 mm	DIM	Doing IMaging	Photography	1.84	0.0275

AF, autofluorescence; OCT, optical coherence tomography; US, ultrasonography; VA, visual acuity. Adapted from [11••].

Shields CL. Small choroidal melanoma: detection with multimodal imaging and management with plaque radiotherapy or AU-011 nanoparticle therapy. Curr Opin Ophthalmol. 2019

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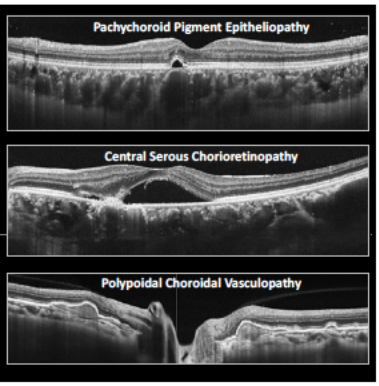
NEVUS OR MELANOMA?

Diameter more than 5mm (by photography)

Shields CL. Small choroidal melanoma: detection with multimodal imaging and management with plaque radiotherapy or AU-011 nanoparticle therapy. Curr Opin Ophthalmol. 2019

30

Pachychoroid Spectrum

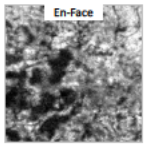


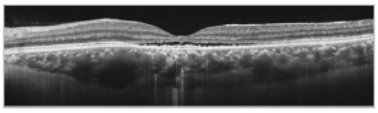
31

PACHYCHOROID SPECTRUM- CSCR

- Associated with bilateral increased choroidal thickness with "boggy" fluid accumulation
- Utilize enhanced depth imaging OCT (EDI-OCT) to measure choroidal thickness
- Utilize en-face OCT to visualize choroidal fluid pockets
- May be complicated by type 1 CNV

EDI OR SS-OCT IS CRITICAL IN DEMOSTRATING ↑ CHOROIDAL THICKNESS IN EYES WITH CSCR!!!

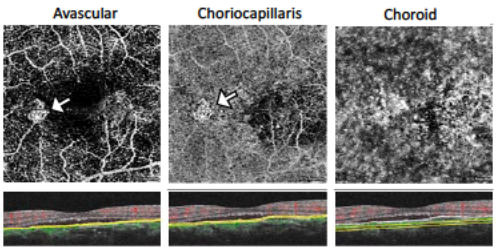




32

OCTA DETECTION OF TYPE 1 CNV IN CSCR

OCTA 3mm Macula



~1/3 of CSCR eyes have abnormal choroidal vessels, of which 2/3rds are confirmed Type 1 CNV membranes.

Costanzo et al. OCTA in CSCR. J Ophthalmol 2015.

33

CHRONIC CSCR TX UPDATES

Oral Mineralocorticoid Antagonism

- Off-label for treatment of CSCR
- Spironolactone- a PO aldosterone receptor antagonist, high binding affinity for mineralocorticoid receptors
  - Dose: 50mg qd x 2-4 months
- Eplerenone- mineralocorticoid receptor antagonist used in the treatment of HTN and CHF, more selective than spironolactone so less SEs but less potent
  - Dose: 25-50mg qd x 3 months
- Monitor electrolyte levels (esp potassium) at baseline, 1 wk after starting TX, and then monthly thereafter
- Contraindications: renal and liver dysfunction, hypotension, hyperkalemia, pregnancy, interacting drug use

Hanumunthadu D, et al. Management of chronic CSCR. Indian J Ophthalmol. 2018;66(12):1704-1714.

34

AGE-RELATED MACULAR DEGENERATION

- Leading cause of blindness in the developed world in persons >50yo
- Characterized by drusen, RPE abnormalities, GA, CNV
- 80% nonexudative/20% exudative
  - Neo accounts for 90% of severe central VA loss from AMD
- OCT is useful in detecting new or recurrent neovascular disease activity and guiding therapy
  - Early detection and prompt treatment of neo improves the visual outcome

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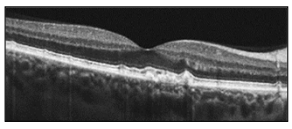
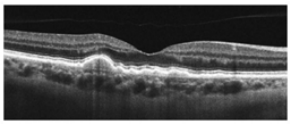
OCT CLASSIFICATION OF DRUSEN – PROGNOSTIC VALUE

Hard/cuticular drusen



Soft drusen

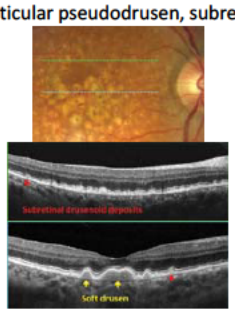


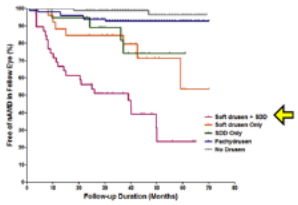
SOFT DRUSEN = GREATER RISK FOR EXUDATIVE CONVERSION!

36

OCT CLASSIFICATION OF DRUSEN – PROGNOSTIC VALUE

Reticular pseudodrusen, subretinal drusenoid deposits (SDDs)





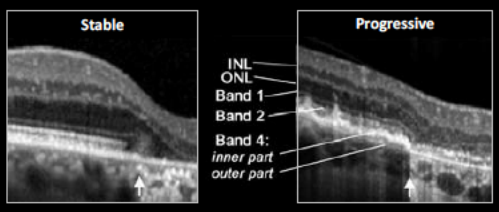
THE COMBINATION OF SOFT DRUSEN AND SDDs POSES THE GREATEST RISK FOR EXUDATIVE CONVERSION!!!

Lee J, et al. Neovascularization in Fellow Eye of Unilateral Neovascular AMD According to Different Drusen Types. Am J Ophthalmol. 2019

37

OCT PREDICTERS OF GA DEVELOPMENT/EXPANSION

RPE/Bruch's membrane complex (band 4) splitting



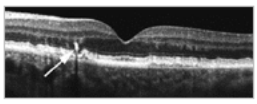
Fleckenstein M, et al. FAF and SD-OCT characteristics in a rapidly progressing form of GA. Invest Ophthalmol Vis Sci. 2011.

38

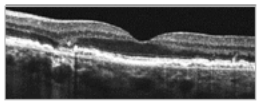
OCT PREDICTERS OF GA DEVELOPMENT/EXPANSION

RPE activation/migration

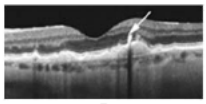
Risk factor for GA and.....



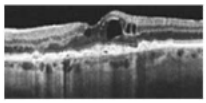
1 year later early GA formation



Risk factor for CNV



2 years later early CNV present



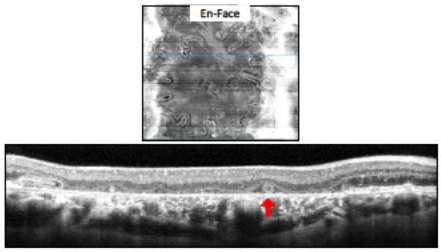
Ferrara D, et al. OCT Features Preceding the Onset of Advanced ARMD. IOVS. 2017.

39

OCT PREDICTERS OF GA STABILITY

Protective Factor!!

Outer Retinal Tubulation



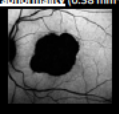
Hariri A, et al. Outer retinal tubulation as a predictor of the enlargement amount of GA ARMD. Ophthalmology. 2015.

40

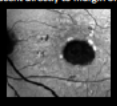
PROGNOSTIC VALUE OF GA PHENOTYPIC FAF PATTERNS

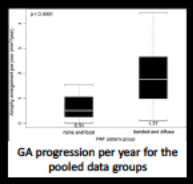
Slow Progression

No abnormality (0.38 mm^2/yr)



Focal (0.81 mm^2/yr)
Single or individual small spots of ↑ FAF adjacent directly to margin of GA

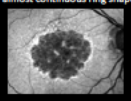




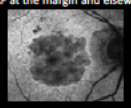
GA progression per year for the pooled data groups

Rapid Progression

Banded (1.81 mm^2/yr)
↑ FAF adjacent directly to margin of GA in an almost continuous ring shape



Diffuse (1.77 mm^2/yr)
↑FAF at the margin and elsewhere



The GAIN Study. Am J Ophthalmol. 2015;160: 345–353.e5.
Holz FG, et al (FAM-Study Group). Progression of GA and Impact of FAF patterns in ARMD. Am J Ophthalmol. 2007 Mar;143(3):463-72.

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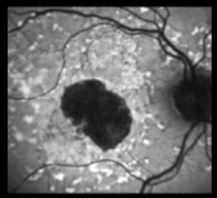
PROGNOSTIC VALUE OF GA PHENOTYPIC FAF PATTERNS

Fastest Rate of Progression!!

Diffuse Trickling (3.02 mm^2/yr)
Diffuse pattern + high intensity at margin that seeping towards the periphery



The GAIN Study. Am J Ophthalmol. 2015;160: 345–353.e5.
Holz FG, et al (FAM-Study Group). Progression of GA and Impact of FAF patterns in ARMD. Am J Ophthalmol. 2007 Mar;143(3):463-72.

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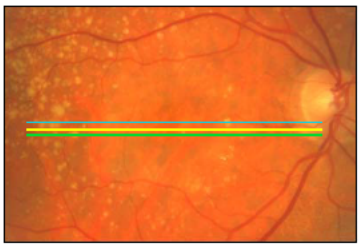
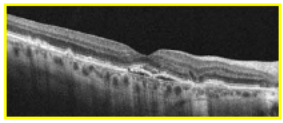
Exudative AMD OCT Features
PED/SRF





EARLY DETECTION AND PROMPT TREATMENT OF NEO IS CRITICAL TO MAXIMIZE VISUAL OUTCOMES!!!

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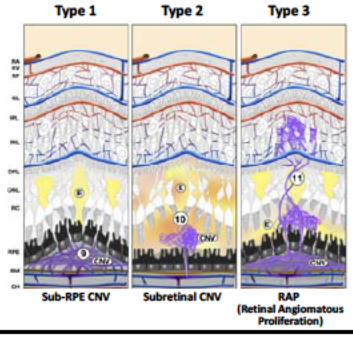
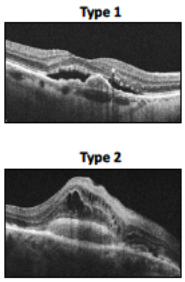
OCT CLASSIFICATION OF CNV





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"DON'T WAKE THE SLEEPING DRAGON"

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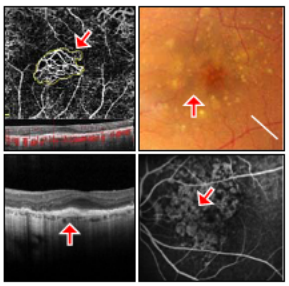
OCTA DETECTION OF NONEXUDATIVE CNV



1. Well-defined neovascular complex via OCTA
2. No signs of exudation via ophthalmoscopy such as exudate or blood
3. No fluid via structural OCT
4. No leakage with IVFA

Present in approx. 10% of high-risk AMD eyes (intermediate AMD, exudative fellow eye)

Or C, et al. Incidence of Vascularized Drusen in Non-Exudative ARMD using SD-OCTA. ARVO 2018.

Carnevali A, et al. OCTA: A Useful Tool for Diagnosis of Treatment-Naïve Quiescent CNV. Am J Ophth. 2016.

46

NONEXUDATIVE CNV

Prognosis

- Rate of future exudation, eyes with nonexudative CNV vs eyes without nonexudative CNV
  - **Bailey S ARVO 2017.** 60% vs 4% (5 months)
  - **De Oliveira Dias J Ophthal 2018.** 21% vs 4% (12 months)
    - 15x greater risk of exudation after detection of nonexudative CNV

EYES WITH NONEXUDATIVE CNV ARE AT HIGH RISK FOR EXUDATIVE CONVERSION!

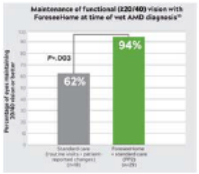
Bailey S et al. Early detection of CNV with OCTA. ARVO 2017.
De Oliveira Dias JR, et al. Natural History of Subclinical Neovascularization in Nonexudative ARMD Using SS-OCTA. Ophthalmol 2018.

47

AMD HOME MONITORING SYSTEMS

Foresee®HOME Monitoring Device

- FDA approved home preferential hyperacuity perimeter (PHP)
  - *Augments* in-office eye exams
- Detects early conversion from intermediate AMD to neovascular
  - BCVA 20/60 or better (stable)
- Covered by Medicare and some private insurances
- Only available by physician order
- Each test results are compared to a normative database and the pt's personal baseline- clinician is alerted if sig change
- Pt clicks where a wave or bump appears in a dotted line
- Research: Foresee Home identified 64% of converters in the AREDS2 HOME study
  - Functional vision (≥20/40) at conversion was maintained in 94% of patients using Foresee Home vs 62% without
- Home OCT device in development



Chew EY, et al. Randomized Trial of the Foreseehome Device for Early Detection of nARMD. Home Study Report Number 1. Contemp Clin Trials 2014.
Ho AC, et al. Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of nARMD. *J Clin Med* 2021.

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AMD MOBILE MONITORING SYSTEMS

myVisionTrack (mVT®) app

- Smartphone and tablet-based app
- Based on shape discrimination hyperacuity testing
- Monitors progression of DME and AMD
- Prescription required
- Clinician is alerted if significant change in test results

MaculaTester app

- Electronic version of the Amsler grid
- Record areas of distortion by touching screen
- Does not automatically detect progression or communicate with doctor
- Can set up reminder notifications

Alleye app

- 2 different app versions:
  1. AlleyeOne: for those at increased risk of retinal disease
  2. Alleye: for those with existing retinal disease (AMD & DME)
- Assesses vernier acuity using an alignment task
- In studies, 52-66% of the pts who came to the clinic bc of a + test result received an intravitreal injection

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NEWLY APPROVED ANTI-VEGF AGENTS

Brolucizumab

- Anti-VEGF agent FDA approved in Oct 2019
- Phase III HAWK and HARRIER clinical trials
  - Demonstrated noninferiority to aflibercept at 1 year
- Dosing monthly x 3 months then once every 2-3 months
  - ~50% are expected to maintain a q 3mo dosing schedule through the first year of tx
- Case reports of occlusive retinal vasculitis
  - 92% were associated with intraocular inflammation (occurs at a mean of 25 days post injection)
  - ~ half of eyes had a > 3-line decrease in VA at final follow-up and a final VA of 20/200 or worse

Faricimab

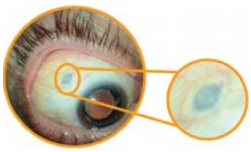
- Anti-VEGF agent FDA approved in Jan 2022 for wet AMD and DME
- Dual mechanism of action: not only a VEGF-A inhibitor but also inhibits angiopoietin-2
- Phase III YOSEMITE and RHINE clinical trials
  - 60% of people eligible for extended dosing could be treated every 4 months at two years
  - Dosing monthly x 4 months then flexible dosing based on pt need

Witkin AJ, et al. Occlusive Retinal Vasculitis Following Intravitreal Brolucizumab. J Vitreoretin Dis. 2020.
Baumal CR, et al. Retinal vasculitis and intraocular inflammation after intravitreal brolucizumab. Ophthalmology. 2020.

50

RANIBIZUMAB PORT DELIVERY SYSTEM (PDS)

- FDA approved Oct 2021
- A permanent refillable drug reservoir eye implant
- Continuously releases ranibizumab over months
- Initial surgical implantation is done in the OR
- Can maintain therapeutic drug concentration levels with in-office refills every 6 months
- Phase III Archway clinical trial underway
  - PDS was non-inferior to monthly ranibizumab injections at 10 months
  - 3-fold higher rate of endophthalmitis compared monthly ranibizumab intravitreal injections (1.7% vs 0.5%), most cases related to conj erosion



May reduce the burden of frequent injections and physician visits associated with standard anti-VEGF therapy

Holekamp NM, et al. Archway Randomized Phase 3 Trial of the PDS with Ranibizumab for Neovascular ARMD. Ophthalmology. 2022 Mar;129(3):295-307

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GENETIC TESTING FOR IRD

Why perform testing?

- Can confirm or change diagnosis
- More accurate prognosis
- Confirms inheritance pattern, risk for other family members
- Potential qualification for clinical trial or gene therapy

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NO COST GENETIC TESTING, COUNSELING AND ACCESS TO CLINICAL TRIALS

OPEN ACCESS, NO COST GENETIC TESTING!!!

- 2 programs available
  - ID YOUR IRD via Invitae (Sponsored by Spark Therapeutics) - 325 gene panel
  - My Retina Tracker via Blueprint genetics (Sponsored by Foundation Fighting Blindness) - 322 gene panel
- Need clinical diagnosis or symptoms of IRD
- Identifies copy number variants (insertions, deletions) and non coding variants (intronic mutations)
- OD orders genetic test online, collects saliva sample and mails to lab
- Results in ~1 month

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NO COST GENETIC TESTING, COUNSELING AND ACCESS TO CLINICAL TRIALS

Step 2: Genetic counseling

- Telephone based
- 60-75 minute sessions
- Following the session pts and ODs are given formal summary report and a detailed pedigree

Step 3: My Retina Tracker® Registry

- Way to connect pts with IRDs to researchers recruiting for clinical trials
- Patient can upload genetic test results
- Patient controlled, secure and HIPAA compliant
- Only de-identified data is shared with researchers
- ~ 16,000 registrants

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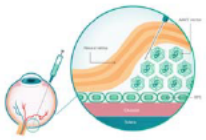
GENE THERAPY FOR IRD

Luxturna® (voretigene neparvovec-rzyl)

- First FDA-approved gene therapy for an eye IRD, Dec 2017
- Administered via one-time subretinal injection w/ PPV
- Must have mutations in both copies of the RPE65 gene to be eligible
  - Clinical presentation is leber's congenital amaurosis or RP
- Can locate retinal specialist who will perform treatment here: https://luxturna.com/specialist-locator/



Phase 3 gene therapy clinical trials underway currently for choroideremia and X-linked RP

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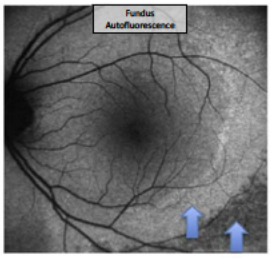
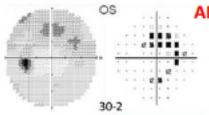
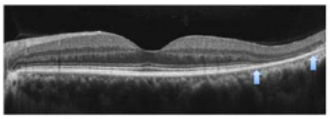
Hydroxychloroquine Retinal Toxicity

Toxicity often occurs outside the macula and near the arcades in Asians







PERFORM 30-2 VF AND OCT NEAR THE ARCADES IN ASIANS!!!

AAO. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy 2016.

56

HYDROXYCHLOROQUINE RETINAL TOXICITY OR AMD?

66yo American Indian female

- Taking Plaquenil 200mg BID x 20+ years
- Weight: 157lbs (max daily dose = 356mg)
- + ANA, possible SLE
- Stage 3 CKD
- Ex- heavy smoker of 45yrs
- History of nonexudative AMD OU
- BCVAs OD 20/25^{+2}, OS 20/25

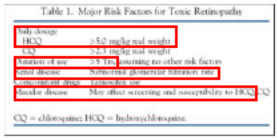


Table 1. Major Risk Factors for Toxic Retinopathy

Daily dosage	
HCQ	>5.0 mg/kg real weight
CQ	>2.3 mg/kg real weight
Duration of use	>5 Yrs (assuming no other risk factors
Renal disease	Substantial glomerular filtration rate
Concomitant drugs	Tamoxifen use
Macular disease	May affect screening and susceptibility to HCQ, CQ

CQ = chloroquine; HCQ = hydroxychloroquine.

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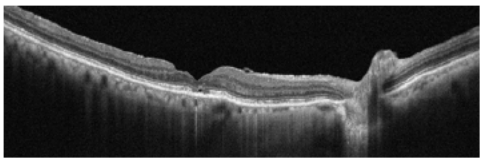
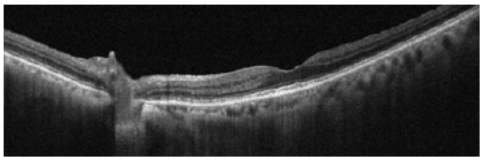
HYDROXYCHLOROQUINE RETINAL TOXICITY OR AMD?

OD



OS



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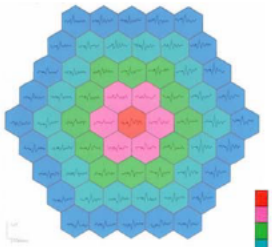
HYDROXYCHLOROQUINE RETINAL TOXICITY OR AMD?



RING AMPLITUDES

	OD Amp (nV/deg2)	OS Amp (nV/deg2)
R1	32.05	38.00
R2	20.49	11.85
R3	18.29	14.02
R4	12.49	12.35
R5	9.55	7.27

RING RATIOS

Ring Ratios	Our pt OD	Our pt OS	Norm mean	99% Limits
R1/R2 =	1.56	3.21	1.943	2.64
R1/R3 =	1.75	2.71	3.161	4.51
R1/R4 =	2.57	3.08	4.613	6.87
R1/R5 =	3.36	5.22	5.46	8.43

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PENTOSAN POLYSULFATE TOXIC MACULOPATHY

- Maculopathy associated with chronic pentosan polysulfate (Elmiron®) therapy
- A common treatment for interstitial cystitis
  - A chronic regional pain syndrome of the bladder and pelvis
  - Predominately affects females manifesting with urinary urgency and dyspareunia

Table 1: Consolidated Clinical Observations

Median Age:	60 years (range: 37 to 79 years)
Median Duration of PPS Intake:	14.5 years (range: 3 to 22 years)
Common Presenting Symptoms:	Blurred vision while reading (48.6 percent) Prolonged dark adaptation (48.6 percent) Metamorphopsia (11.4 percent)
Median Duration of Visual Symptoms:	4 years (range: 1 to 9 years)
Median Visual Acuity:	OU: 20/25 OD Range: 20/20 to 20/300 OS Range: 20/15 to 20/400

Data documented in a series of 35 confirmed cases of PPS-associated maculopathy.[12]

https://www.reviewofophthalmology.com/article/clinical-pearls-for-a-new-condition

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PENTOSAN POLYSULFATE TOXIC MACULOPATHY

Color fundus photography:
- Bilateral, symmetric pathology
- Paracentral hyperpigmented spots and yellowish subretinal deposits
- Hyperpigmented spots appear to be an early manifestation of the condition and are often absent late

FAF: Striking AF abnorm, with a fairly well circumscribed central patch of hyper and hypo autoFl spots

OCT:
- Focal nodules of hyoer-reflectance at the level of the RPE, localize to hyper pigmented spots
- Ill-defined irregularity in outer retinal bands

https://www.reviewofophthalmology.com/article/clinical-pearls-for-a-new-condition

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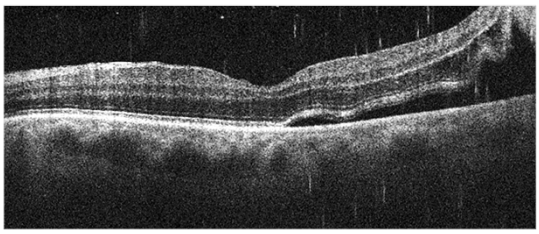
VITREOUS

"Falling Ash" Sign = Posterior Shaffer's Sign



Ophthalmology. 2015;122: 1946–1947.

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THE "TAKE HOME" MESSAGE

Diabetic Retinopathy
- Multimodal imaging = more accurate and efficient staging of DR & earlier detection of PDR
- Shifting practice patterns toward earlier treatment of DR
- Consider nutritional supplementation & PO fenofibrate

Retinal Vein Occlusion
- Montage OCTA & ERG = classify as ischemic vs non ischemic & predict risk for neo
- OCTA detection of macular ischemia

Choroidal Tumors
- Multimodal imaging to differentiate small melanoma from choroidal nevus

Pachychoroid Spectrum
- EDI-OCT to demonstrate ↑ choroidal thickness & OCTA to detect CNV
- Oral mineralocorticoid antagonism for tx of chronic CSCR

AMD
- OCT and home monitoring device early detection of exudation/nAMD
- OCTA detection of OCTA = risk factor for exudative conversion
- Anticipate FDA approval of ranibizumab PDS shortly

IRD
- OCT and home monitoring device early detection of exudation/nAMD

Toxic Maculopathy
- Perform more peripheral HCQ assessment in Asians
- Be aware of pentosan polysulfate maculopathy

Peripheral Lesions
- Posterior Shaffer's sign indicative of retinal break or vitritis

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