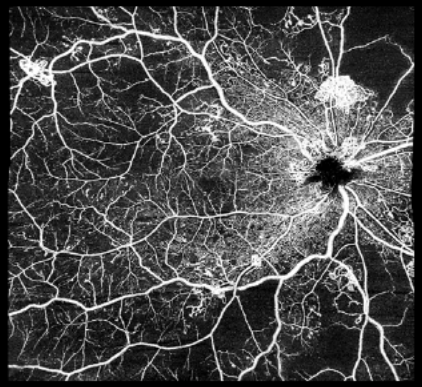
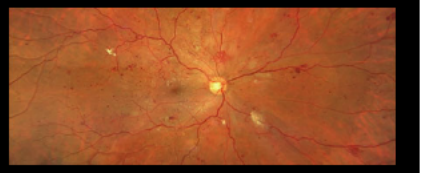
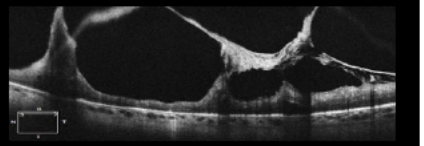
THE UTILITY OF DIAGNOSTIC IMAGING IN DIABETIC RETINOPATHY: A MULTIMODAL APPROACH







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Online high-resolution slides:
www.octangio.org

Contact:
- majcher@nsuok.edu
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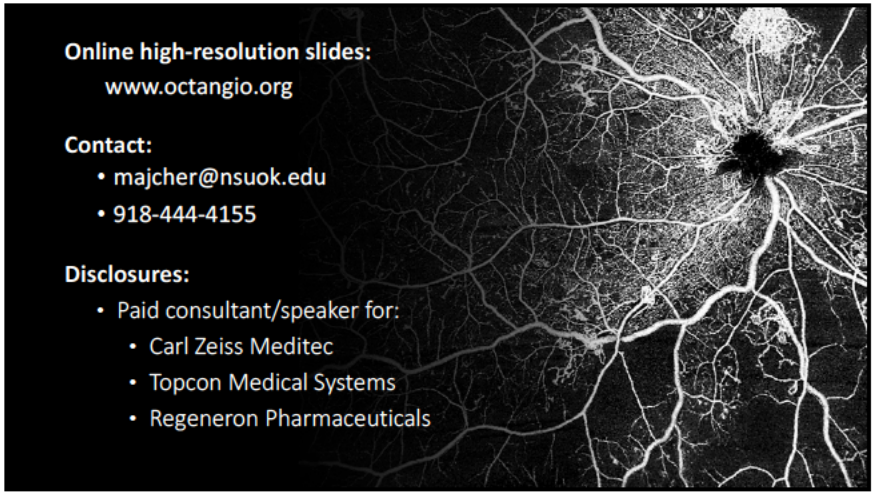
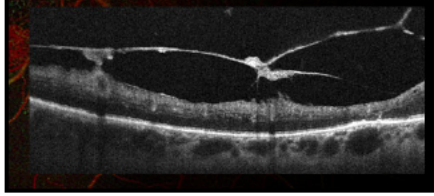
Disclosures:
- Paid consultant/speaker for:
  - Carl Zeiss Meditec
  - Topcon Medical Systems
  - Regeneron Pharmaceuticals

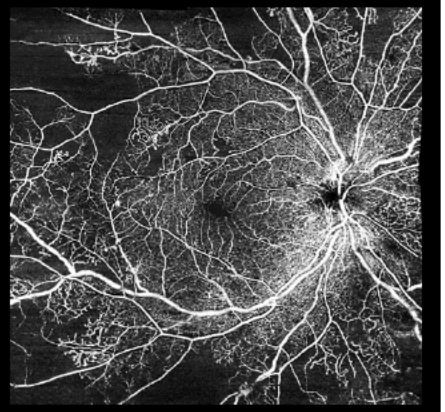


2

OVERVIEW

- DR Standard of care documents
- DM and multimodal imaging basics
- DR staging/classification
- DR management and role of imaging
  1. Diabetic macular edema
  2. Mild –moderate NPDR
  3. Severe NPDR-low risk PDR
  4. High risk PDR





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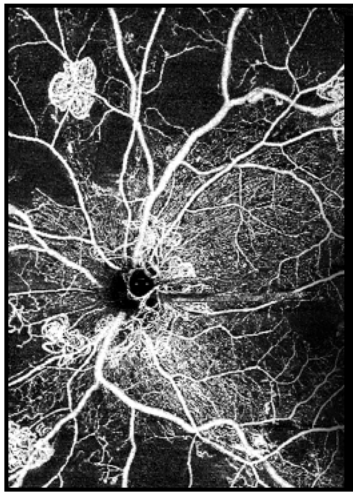


DIABETIC RETINOPATHY

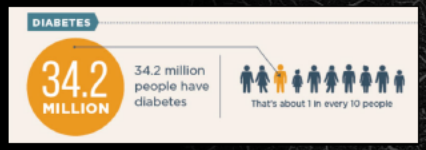
Standard of Care Documents
- American Optometric Association Clinical Practice Guideline (AOA CPG)- last revision Oct 2019
- American Academy of Ophthalmology Preferred Practice Pattern (AAO PPP)- last revision Sept 2019
- DRCR.net= Diabetic Retinopathy Clinical Research Network, a collaborative network dedicated to facilitating multicenter clinical research of DR, >109 participating sites, funded by the NEI of the NIH
  - https://public.jaeb.org/drcrnet

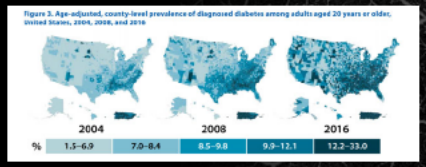
4

DIABETES

Diabetes is a worldwide epidemic

- 10.5% in the U.S. (34.2 million, CDC 2018)
- Expected to increase to nearly 1 billion by 2050



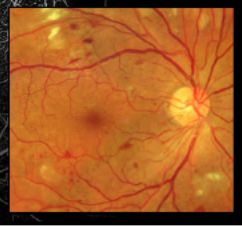


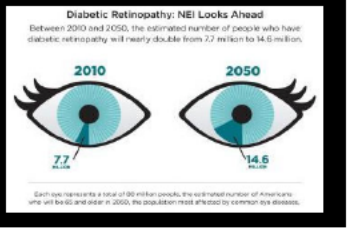
5

DIABETIC RETINOPATHY

Increasing demand for diabetic retinopathy care

- Leading cause of new cases of blindness among working aged Americans
- Affects 28.5% of diabetics over age 40 in the US (4.2 million, CDC 2005-2008)
  - # with DR is expected to nearly triple by 2050



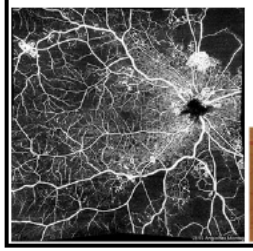


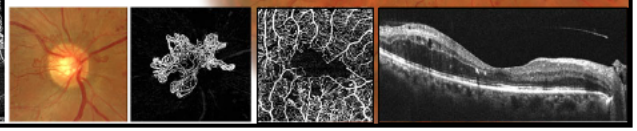
6

THE POWER OF IMAGING IN DR

Multimodal Imaging = more accurate and efficient staging of DR

- Wide field (WF)/ultra wide field (UWF) fundus imaging
- Structural OCT
- OCT angiography (macula, ONH, montage)
- B-scan





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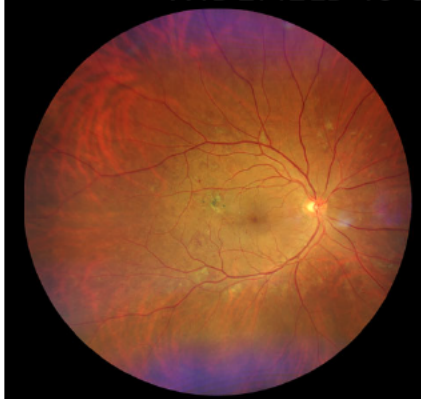
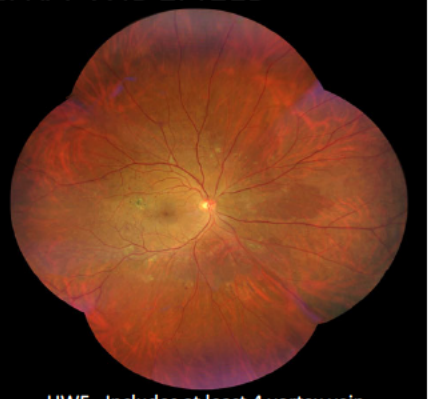
WIDEFIELD vs ULTRA-WIDEFIELD



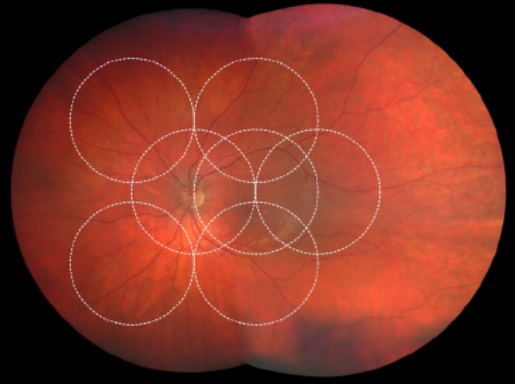


WF= Up to the vortex vein ampullae, 133°

UWF= Includes at least 4 vortex vein ampullae, ~200° and 80% retinal surface

8

ULTRA-WIDEFIELD

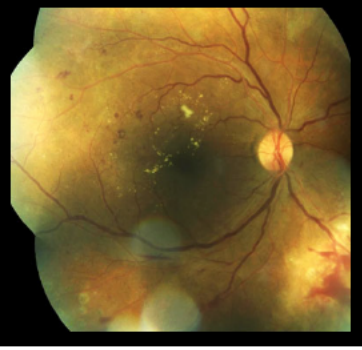


200 ° UWF vs 75 ° Standard 7 field ETDRS

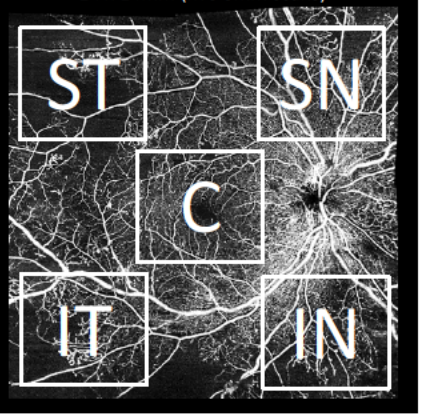
9

MONTAGE OCT ANGIOGRAPHY (OCTA)

Smaller individual component scan size =
- Greater resolution
- More images and capture time



14 x 14mm (five 8mm scans)



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DIABETIC RETINOPATHY STAGING

AAO PPP 2019 (p8)

TABLE 1 Diabetic Retinopathy Disease Severity Scale and International Clinical Diabetic Retinopathy Disease Severity Scale

Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR (see Glossary)	Microaneurysms only
Moderate NPDR (see Glossary)	More than just microaneurysms but less than severe NPDR
Severe NPDR	
International Definition	Any of the following and no signs of proliferative retinopathy: • More than 20 intraretinal hemorrhages in each of **four** quadrants • Definite venous beading in **two** or more quadrants • Prominent IRMA in **one** or more quadrants • Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR.
PDR	One or both of the following: • Neovascularization • Vitreous/preretinal hemorrhage

IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

***AOA CPG Mild NPDR** - marked by at least one retinal MA. Only hemorrhages & MAs are present and the severity is less than that depicted in ETDRS standard photograph 2A

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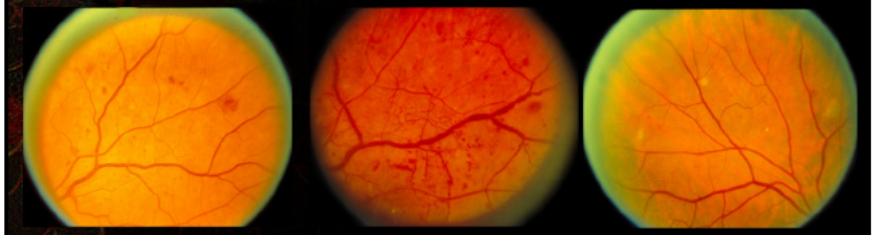
SEVERE / VERY SEVERE NPDR (4-2-1 RULE)

4	2	1
Severe retinal hemorrhages (≥ standard photograph 2A)	**Definite venous beading** (≥ standard photograph 6B)	**Prominent IRMA** (≥ standard photograph 8A)



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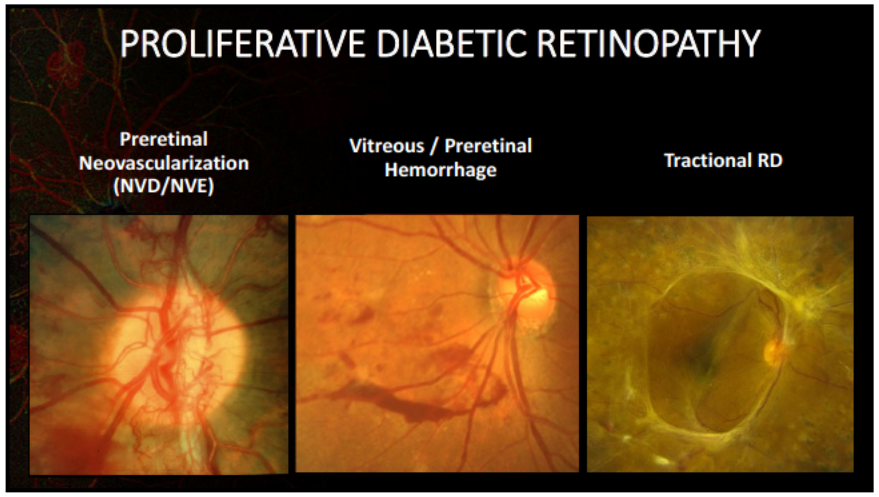
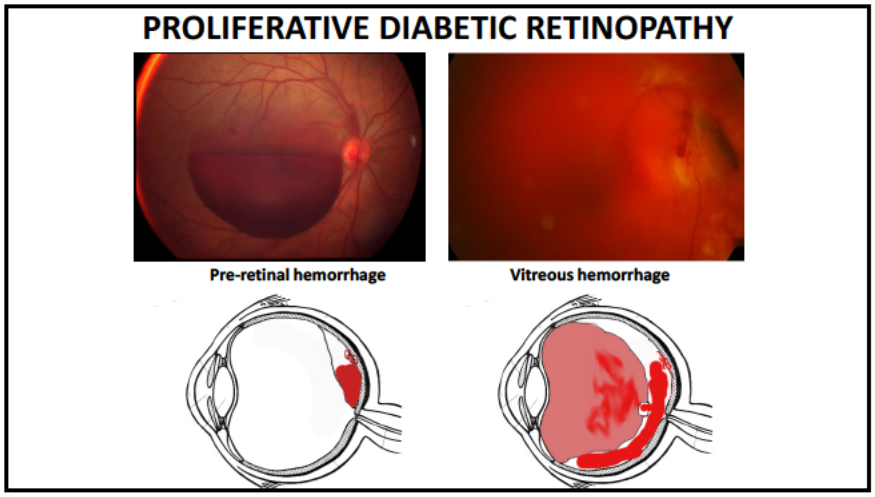
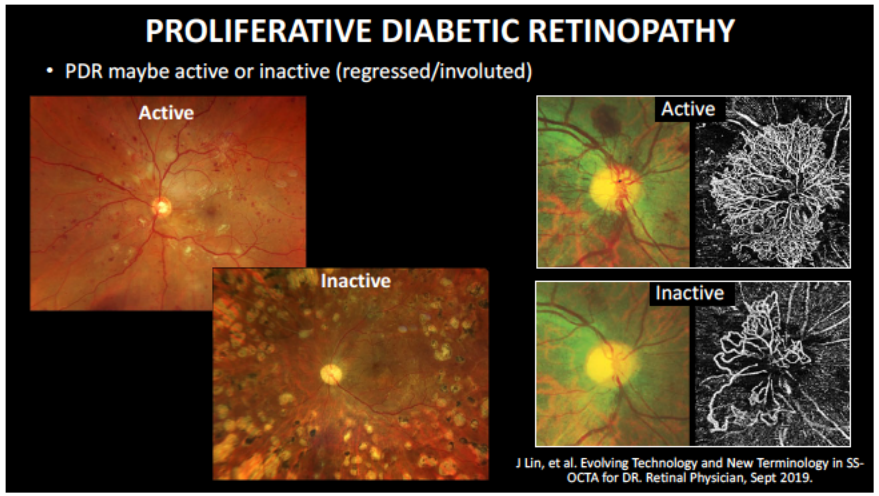

PROLIFERATIVE DIABETIC RETINOPATHY
Preretinal Neovascularization (NVD/NVE)
Vitreous / Preretinal Hemorrhage
Tractional RD

13


PROLIFERATIVE DIABETIC RETINOPATHY
Pre-retinal hemorrhage
Vitreous hemorrhage

14


PROLIFERATIVE DIABETIC RETINOPATHY
• PDR maybe active or inactive (regressed/involuted)
Active
Inactive
Active
Inactive
J Lin, et al. Evolving Technology and New Terminology in SS-OCTA for DR. Retinal Physician, Sept 2019.

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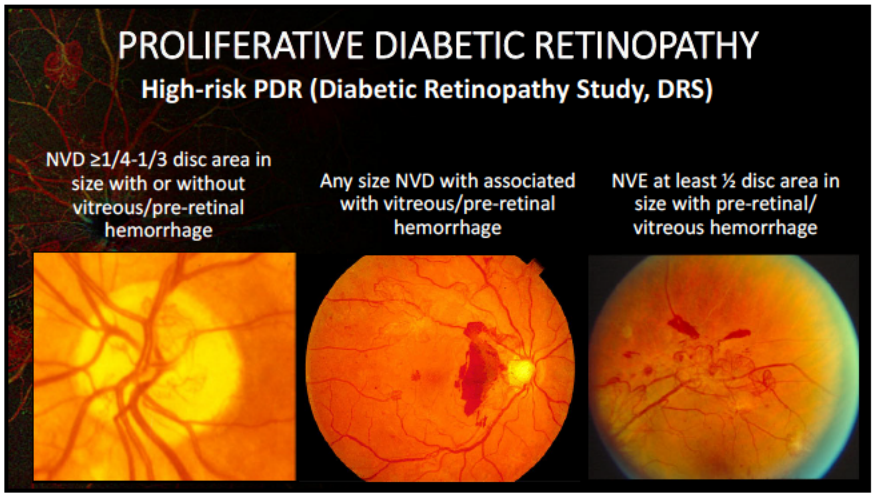
PROLIFERATIVE DIABETIC RETINOPATHY
High-risk PDR (Diabetic Retinopathy Study, DRS)
NVD ≥1/4-1/3 disc area in size with or without vitreous/pre-retinal hemorrhage
Any size NVD with associated with vitreous/pre-retinal hemorrhage
NVE at least ½ disc area in size with pre-retinal/ vitreous hemorrhage

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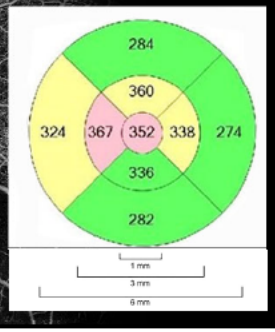
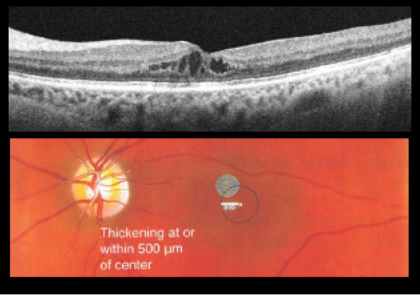
DME STAGING

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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UTILITY OF OCT/OCTA IN DME

- Aids in the classification of DME as center involved (CI-DME) vs non-center involved (NCI-DME)
- Identification of subclinical DME
- OCTA may aid in identifying sources of DME such as MAs or IRMA
- OCTA allows for detection of macular ischemia
  - Significant macular ischemia = guarded prognosis following treatment of DME
- Monitor response to treatment /determine when retreatment is necessary (change analysis)

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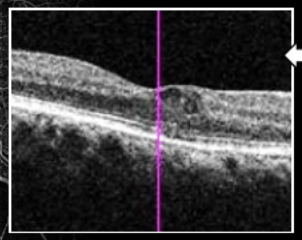
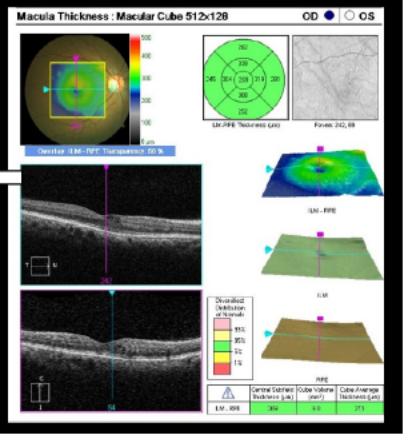
UTILITY OF OCT/OCTA IN DME

Identification of Subclinical DME





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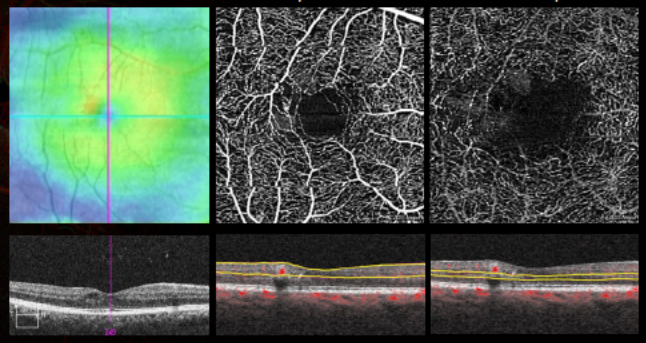
UTILITY OF OCT/OCTA IN DME

OCTA- Identify Sources of DME



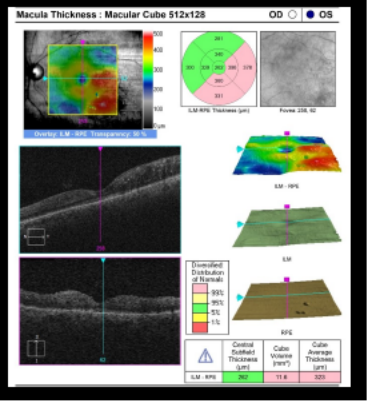
20

THE CASE OF THE FORLORN FOVEA

OCTA- Identify Macular Ischemia

61yo Hispanic Male

- DM type 2 x 27 years
- OS VA 20/100

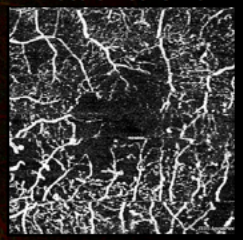


21

THE CASE OF THE FORLORN FOVEA

OCTA- Identify Macular Ischemia

Macular Ischemia



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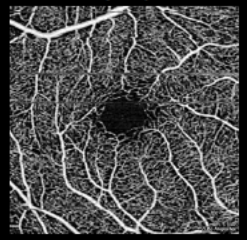
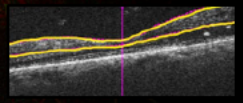


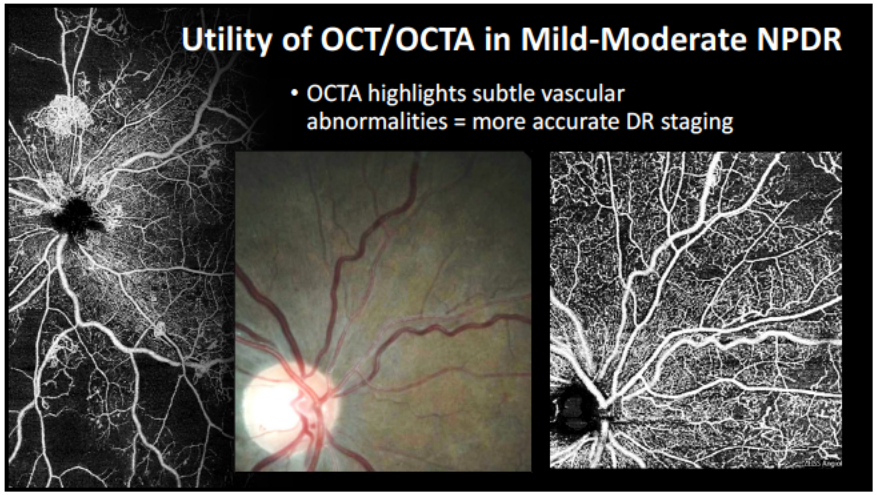


OCT Angiography
(3mm Macula)

22

Utility of OCT/OCTA in Mild-Moderate NPDR

- OCTA highlights subtle vascular abnormalities = more accurate DR staging



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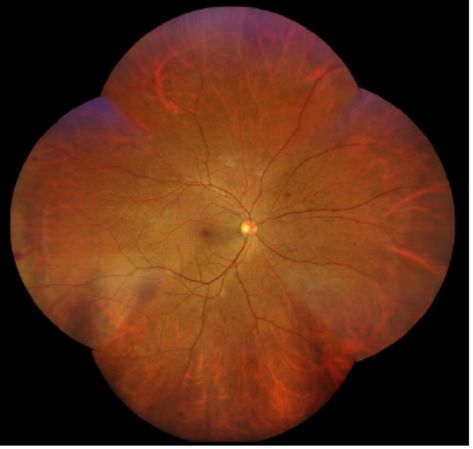
BEYOND THE POSTERIOR POLE.....

61yo American Indian male

- CC: Routine exam, no complaints
- Med Hx: Type 2 DM x 20 years (A1C 8.2%), HTN, CHF
- VA
  - OD/OS 20/20



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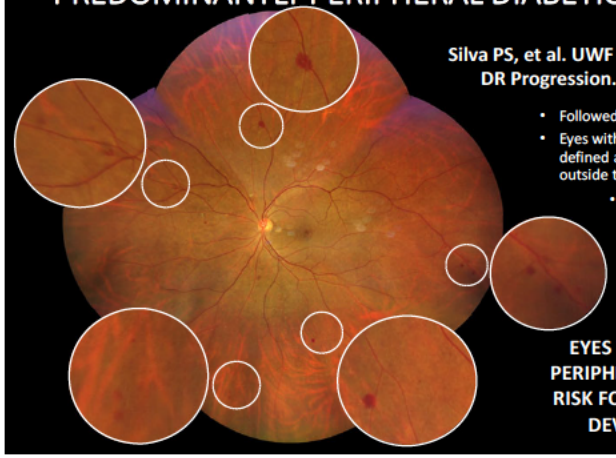
PREDOMINANTLY PERIPHERAL DIABETIC RETINOPATHY



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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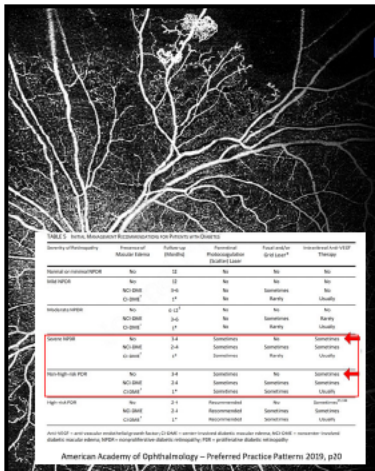
MANAGEMENT OF SEVERE NPDR-LOW RISK PDR



American Academy of Ophthalmology – Preferred Practice Pattern® 2019, p20

- Refer all regardless of DME status
- Start considering anti-VEGF therapy/PRP at the severe NPDR stage even without CI-DME (optional)
  - Anti-VEGF: reverse DR stage/prevent development of vision threatening complications
  - Both ranibizumab and aflibercept FDA approved even if no DME

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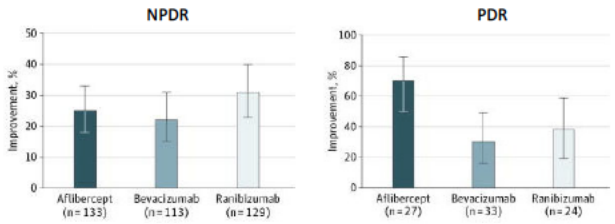
DRCR.net Protocol T- Change in DR Through 2 Years: Secondary Analysis of a RCT Comparing Aflibercept, Bevacizumab, and Ranibizumab

- All 3 anti-VEGF agents were associated with low rates of DR worsening
- Improvement in ~1/4-1/3rd of eyes depending on agent
- Eylea demonstrated superior DR improvement in eyes with PDR

% With Improvement of DR at 2 Years



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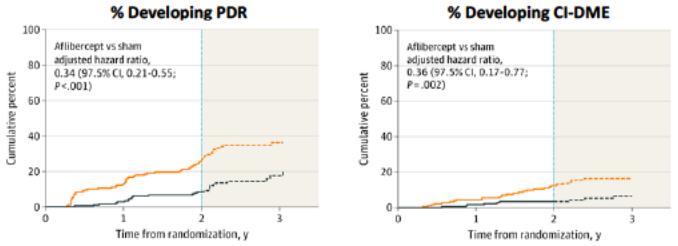
DRCR.net Protocol W- Effect of Intravitreous VEGF vs Sham for Prevention of Vision-Threatening Complications of DR, 2 Year Results

- 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)



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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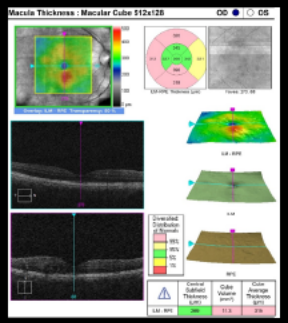
MANAGEMENT OF SEVERE NPDR-LOW RISK PDR

- Consider early PRP/anti-VEGF treatment if:
  - Concurrent DME (anti-VEGF)
  - More severe stage (low risk PDR)
  - T2DM esp long duration (PRP)
  - Anticipated cataract surgery
  - Complete PVD absent
  - Noncompliance
  - Rapid progression
  - Poor glycemic control
  - Fellow eye status



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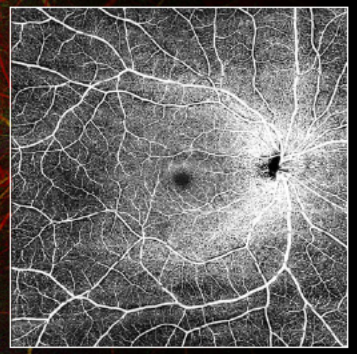
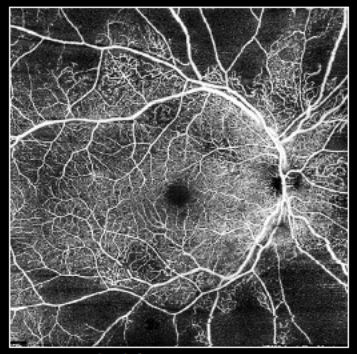
MANAGEMENT OF SEVERE NPDR-LOW RISK PDR

Normal



Low Risk PDR



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

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UTILITY OF IMAGING IN SEVERE NPDR-LOW RISK PDR

Wide-field Fundus Imaging

- Efficient identification/documentation of DR lesions
- Document predominately peripheral DR

OCT/OCTA

- Live scan OCT to look for neo and determine PVD status
  - Complete PVD = lower risk for neo growth and resultant vitreoretinal traction
- OCTA definitely differentiates severe NPDR from early PDR
  - Distinguish small NVE from IRMA
  - Early detection of NVD
- Detection and quantification of nonperfusion to determine likelihood of neo/risk for progression

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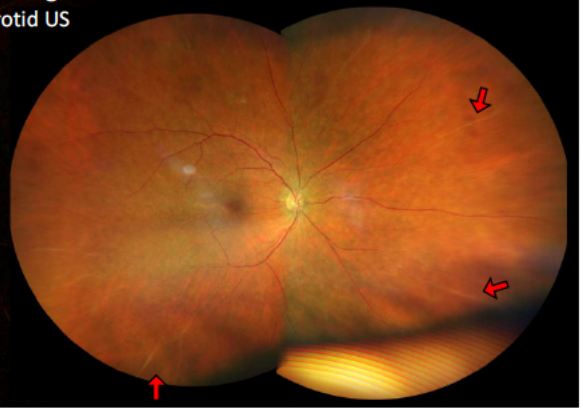
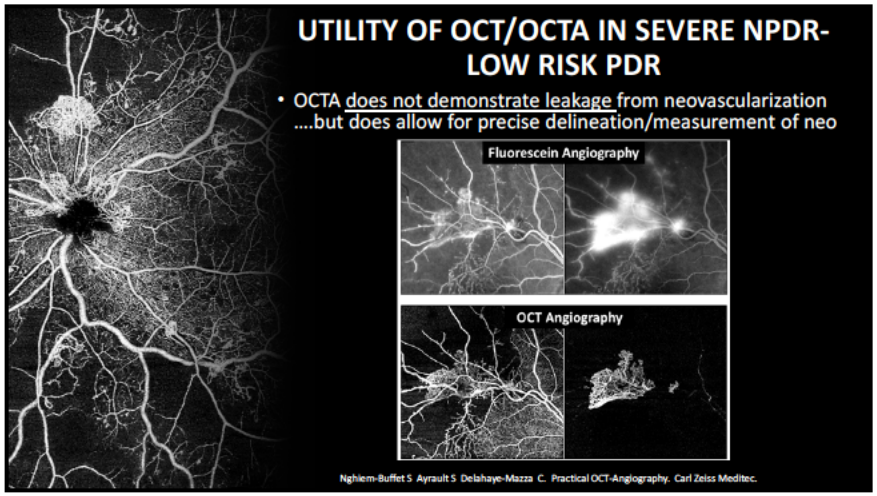
PREDOMINANTLY PERIPHERAL DIABETIC RETINOPATHY

Peripheral vascular sheathing

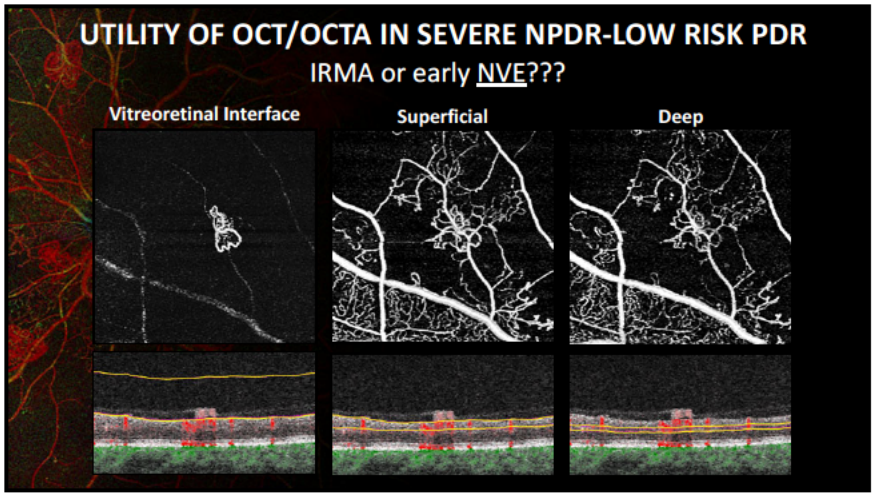
- No sig blockage per carotid US
- Now S/P PRP OU



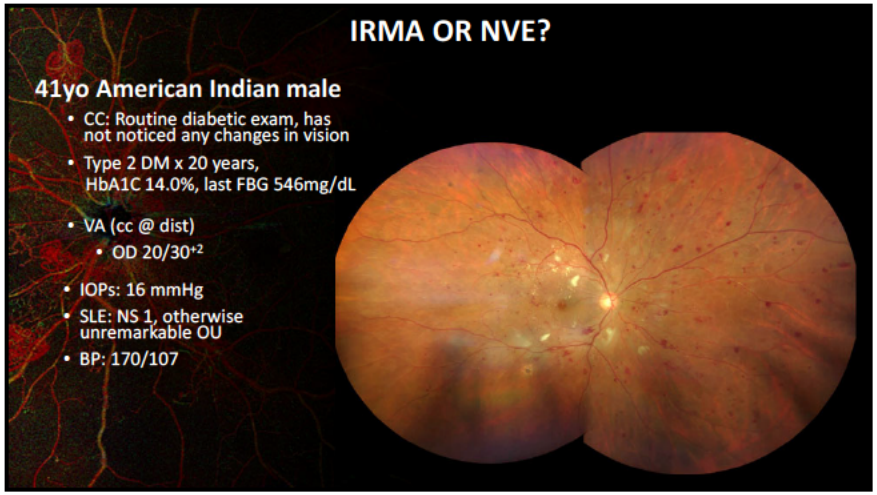
32


UTILITY OF OCT/OCTA IN SEVERE NPDR-LOW RISK PDR
• OCTA does not demonstrate leakage from neovascularization ….but does allow for precise delineation/measurement of neo
Fluorescein Angiography
OCT Angiography
Nghiem-Buffet S Ayrault S Delahaye-Mazza C. Practical OCT-Angiography. Carl Zeiss Meditec.

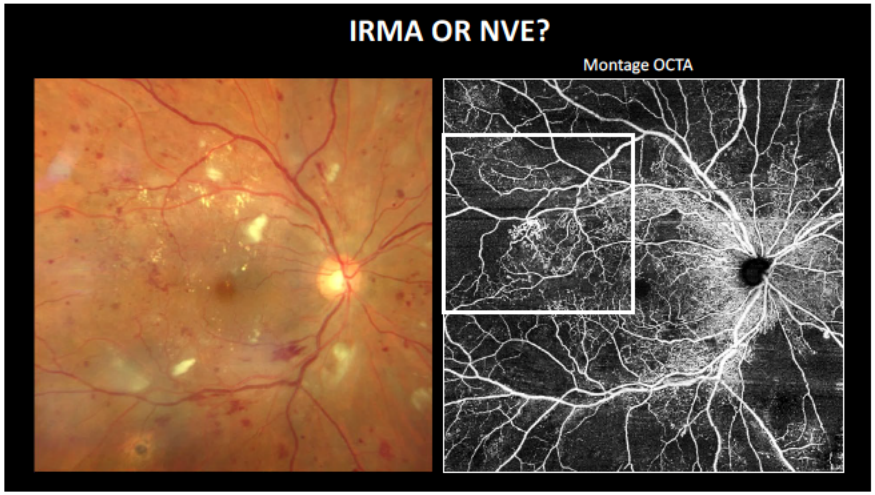
33


UTILITY OF OCT/OCTA IN SEVERE NPDR-LOW RISK PDR
IRMA or early NVE???
Vitreoretinal Interface
Superficial
Deep

34

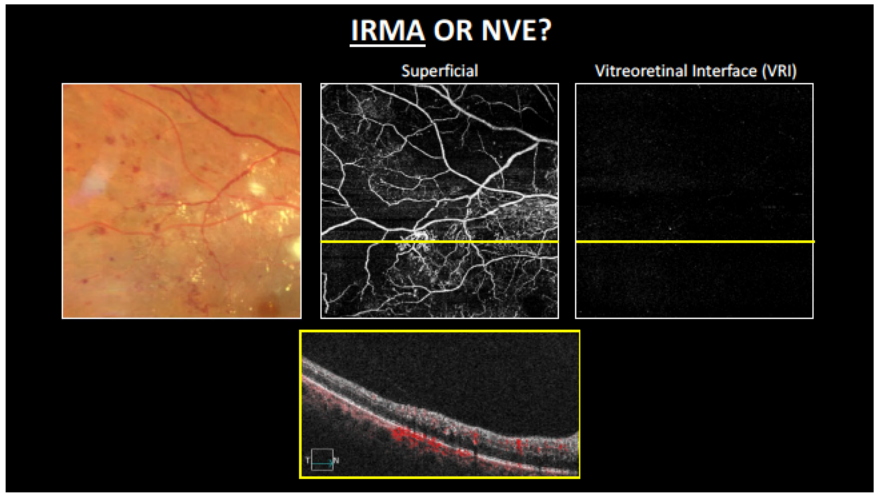

IRMA OR NVE?
41yo American Indian male
• CC: Routine diabetic exam, has not noticed any changes in vision
• Type 2 DM x 20 years, HbA1C 14.0%, last FBG 546mg/dL
• VA (cc @ dist)
• OD 20/30+2
• IOPs: 16 mmHg
• SLE: NS 1, otherwise unremarkable OU
• BP: 170/107

35


IRMA OR NVE?
Montage OCTA

36

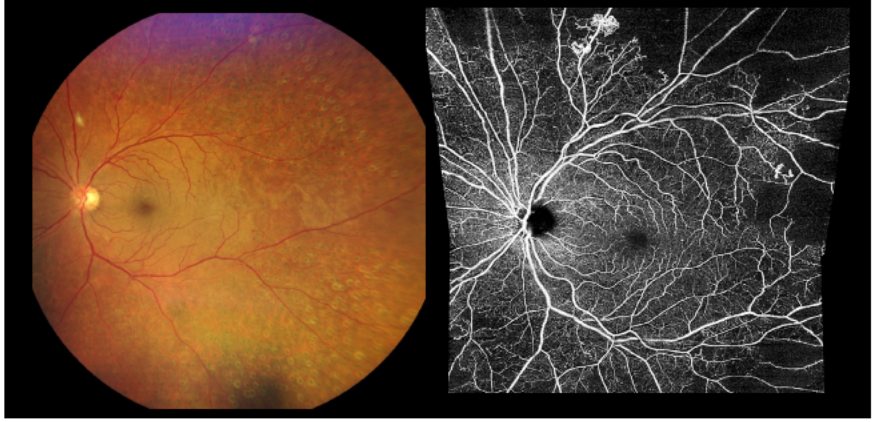
IRMA OR NVE?



37

UTILITY OF OCT/OCTA IN SEVERE NPDR-LOW RISK PDR

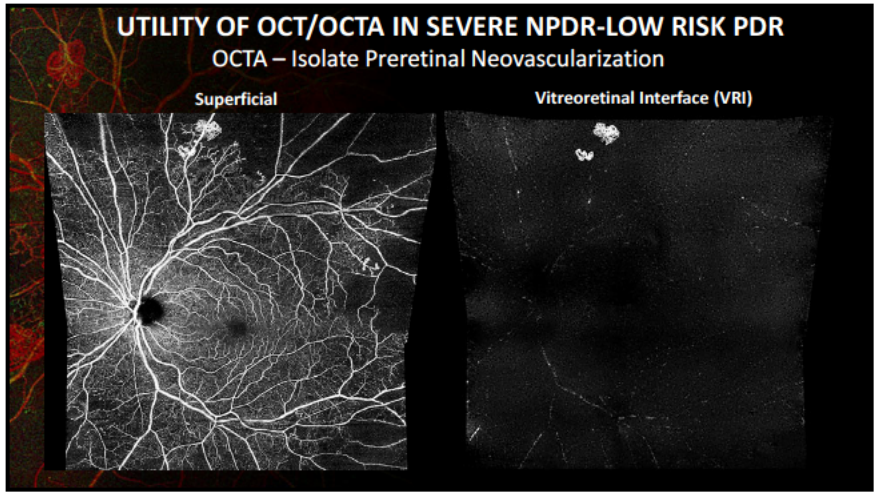
OCTA – Visualization of peripheral NP (nearly invisible without)



38

UTILITY OF OCT/OCTA IN SEVERE NPDR-LOW RISK PDR

OCTA – Isolate Preretinal Neovascularization

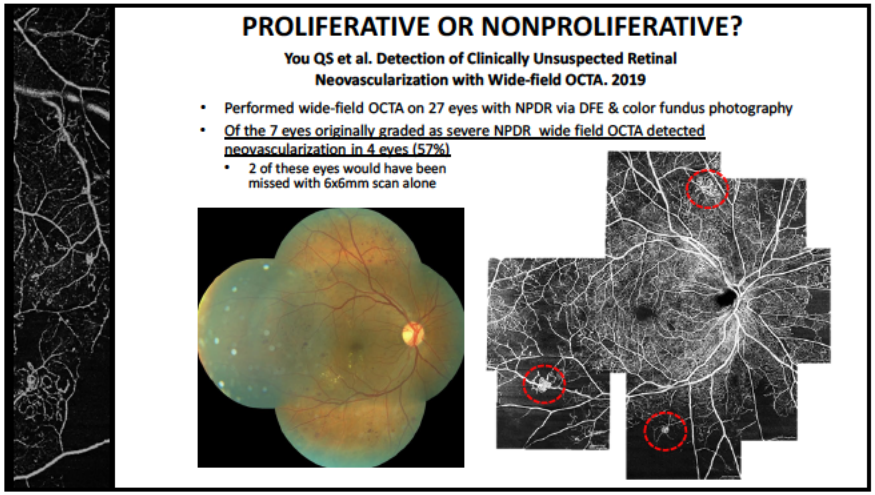


39

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



40

Management of High-Risk PDR

- Refer all regardless of DME status
- PRP and /or anti-VEGF therapy recommended **(NOT optional)**
  - AAO PPP 2017 originally stated that anti-VEGF therapy was an alternative to PRP but retracted somewhat in 2019 version……
- Both Lucentis and Eylea are FDA approved to treat PDR even if no DME present
- If concurrent HR-PDR and CI-DME present, usually start with anti-VEGF then perform delayed PRP, or less likely continue with anti-VEGF alone

41

UTILITY OF IMAGING IN HIGH-RISK PDR

- Detect subtle vitreous hemorrhage
- OCTA- monitor for regression/ progression of neovascular tissue
- Detect and monitor vitreoretinal traction
- Determine proximity to macula and macular status in tractional retinal detachment (TRD)
- Detect retinal tears
- Confirm macular attachment and detect macular edema in mild-moderate vitreous hemorrhage
- B scan- Eval retinal status in severe vitreous heme

42

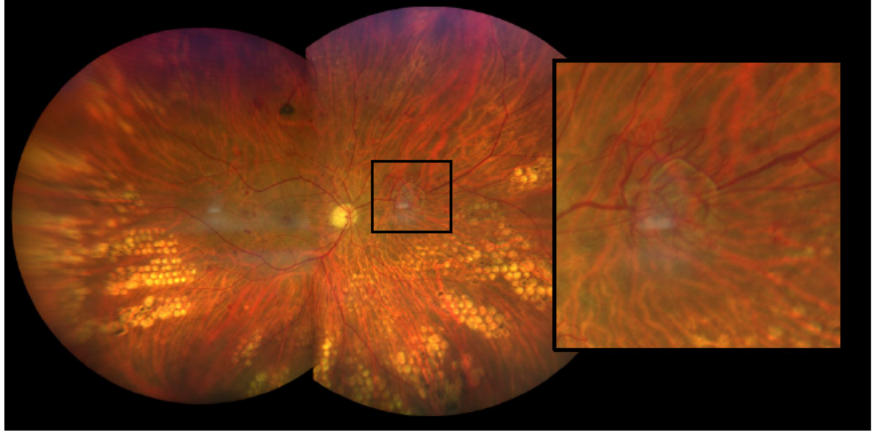
A LOT CAN HAPPEN IN 1 WEEK…..

59yo American Indian male

- CC: Increased floaters OD x 2-3 months, rare flashes
- Oc Hx: OS enucleated 2015 due to sequalae of chronic inflammation, PRP OD 2017
- Med Hx: Type 2 DM x 12 years, last A1C 7.3%
- VA OD: 20/70 PHNI

43

A LOT CAN HAPPEN IN 1 WEEK…..



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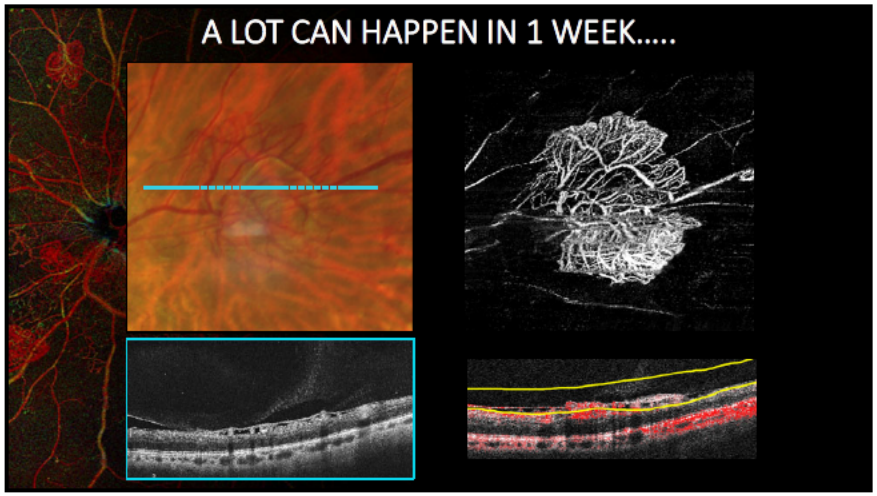
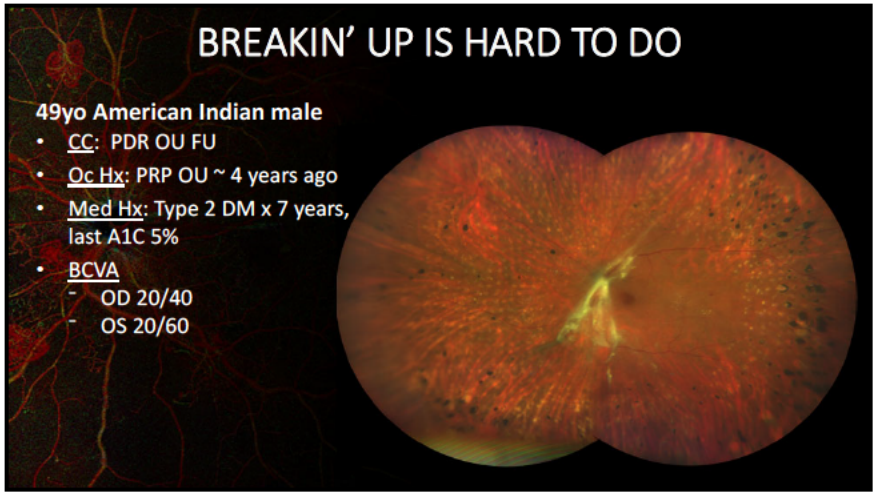

A LOT CAN HAPPEN IN 1 WEEK.....

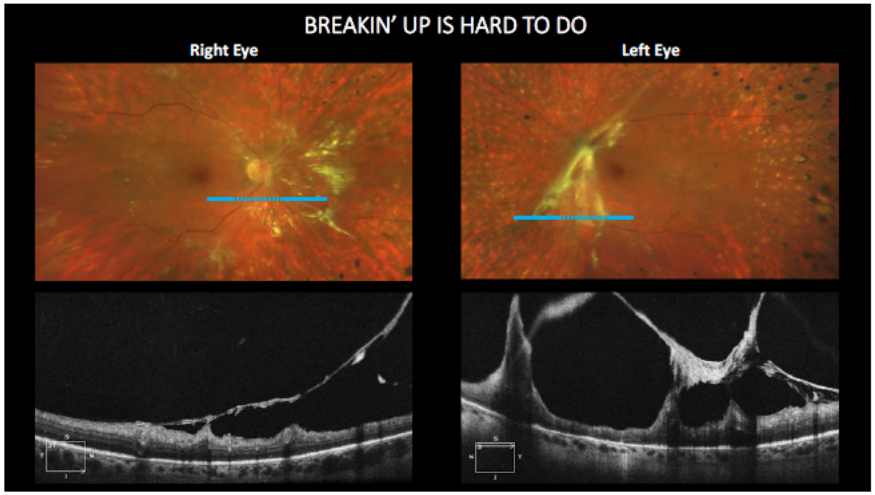
45


A LOT CAN HAPPEN IN 1 WEEK.....
8 days later...complaining of even more floaters OD, like "looking through gauze"
VA OD: CF PHNI

46


BREAKIN' UP IS HARD TO DO
49yo American Indian male
CC: PDR OU FU
Oc Hx: PRP OU ~ 4 years ago
Med Hx: Type 2 DM x 7 years, last A1C 5%
BCVA
OD 20/40
OS 20/60

47

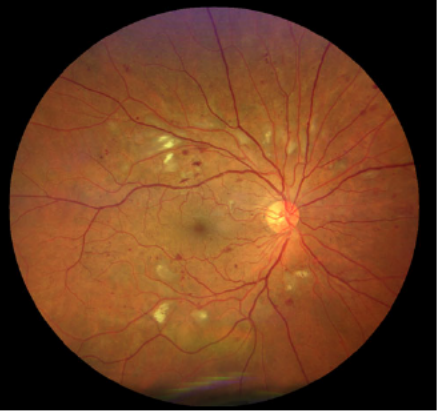

BREAKIN' UP IS HARD TO DO
Right Eye
Left Eye

48

DON'T BE DISTRACTED BY THE 20/20 VISION!

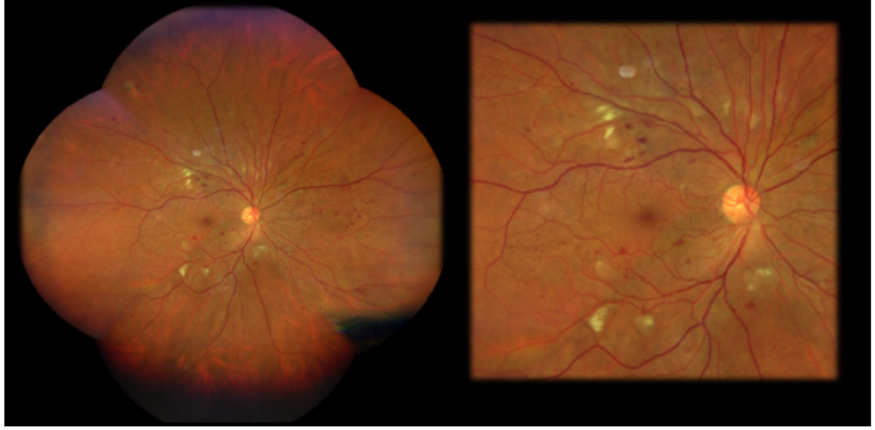
50yo American Indian male

- CC: Decreased vision
- Oc Hx: Severe NPDR OU at LEE 2 yrs ago
- Med Hx:
  - Type 2 DM x 11 years, last A1C 11.8%, admits poor compliance and has been out of meds x 1 wk
  - HTN, ↑chol, sleep apnea
- BCVA
  - OD 20/20



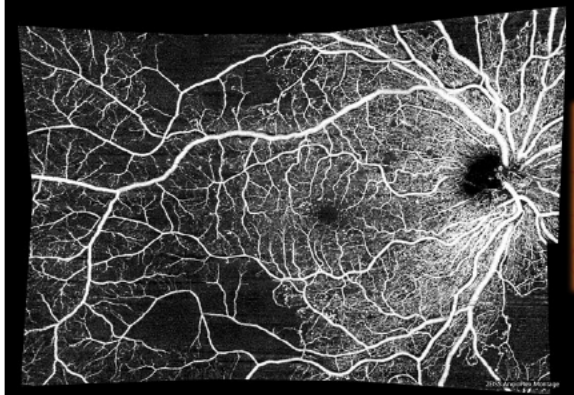
49

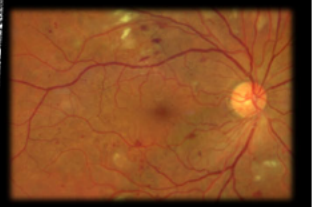
DON'T BE DISTRACTED BY THE 20/20 VISION!



50

DON'T BE DISTRACTED BY THE 20/20 VISION!





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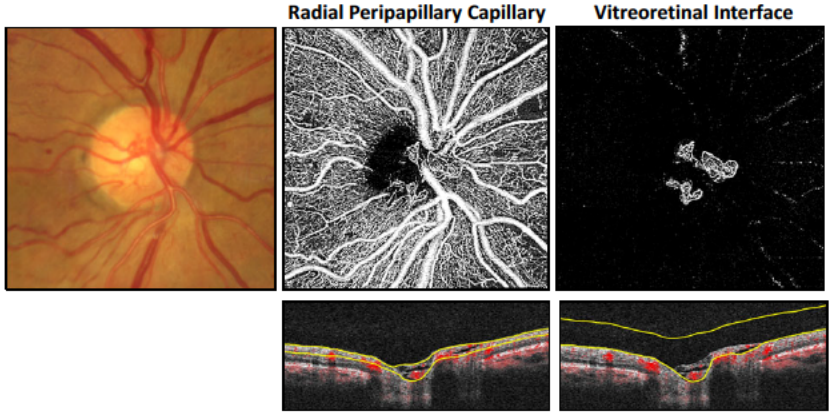
OCTA 4.5mm Optic Nerve



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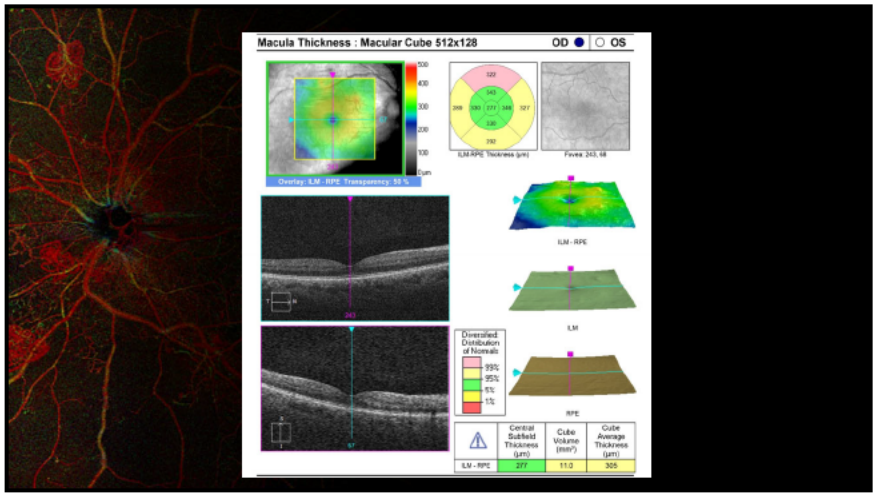

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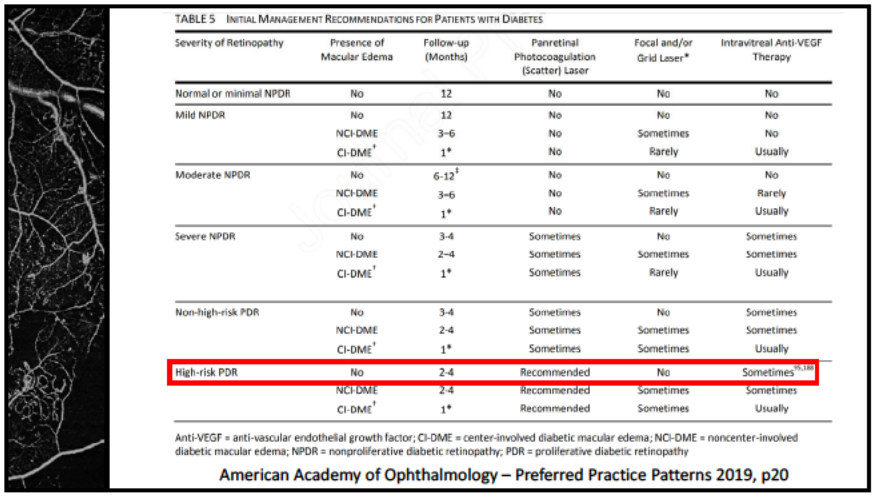

TABLE 5 Initial Management Recommendations for Patients with Diabetes

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[55,188]
	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

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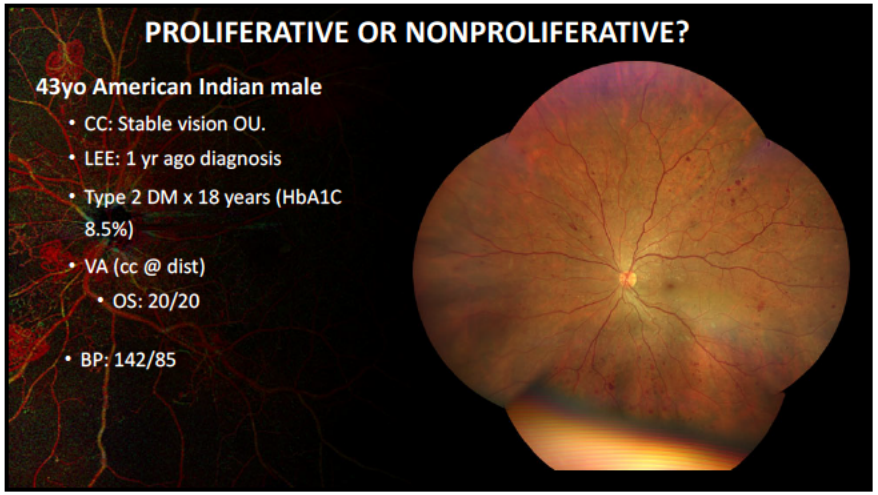

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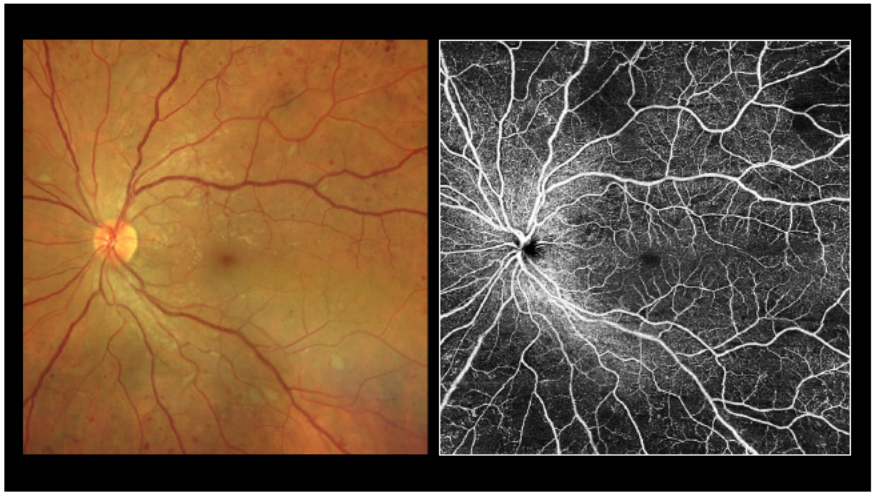

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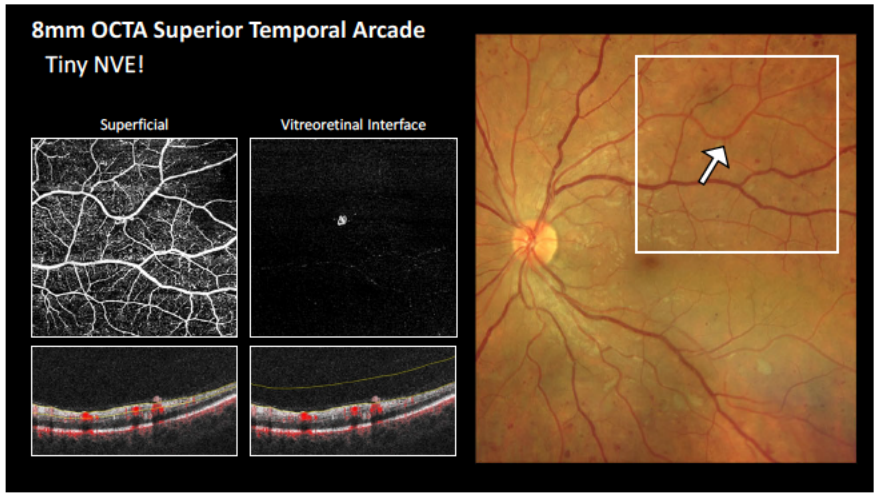
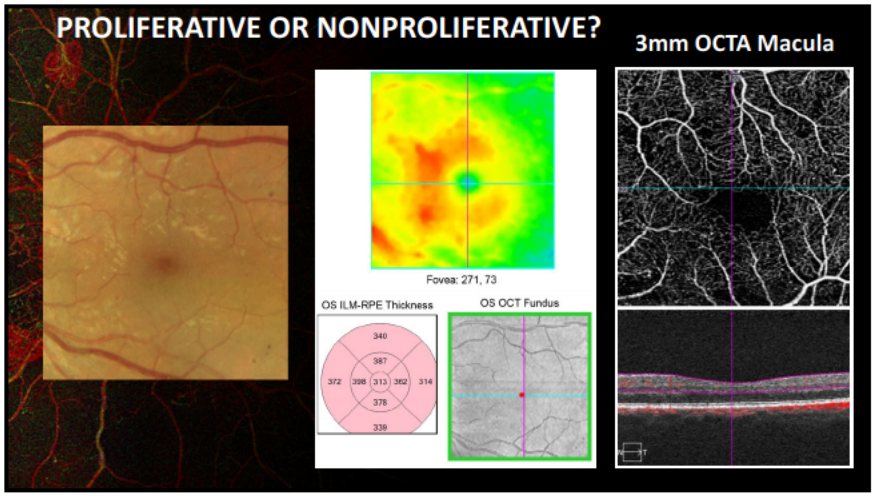
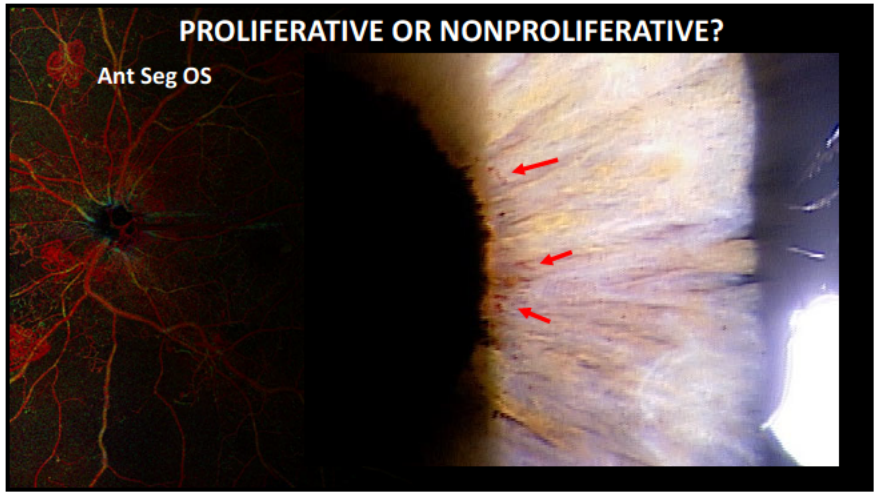

8mm OCTA Superior Temporal Arcade
Tiny NVE!
Superficial
Vitreoretinal Interface

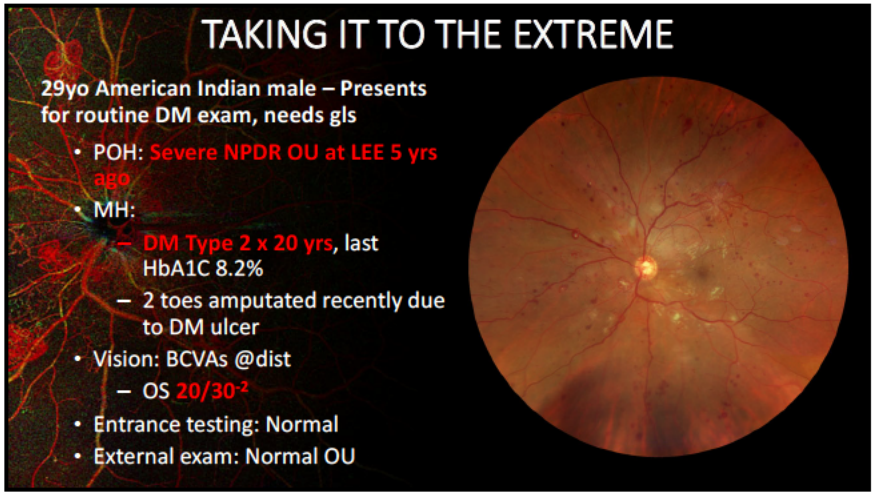
57


PROLIFERATIVE OR NONPROLIFERATIVE?
3mm OCTA Macula
Fovea: 271, 73
OS ILM-RPE Thickness
OS OCT Fundus

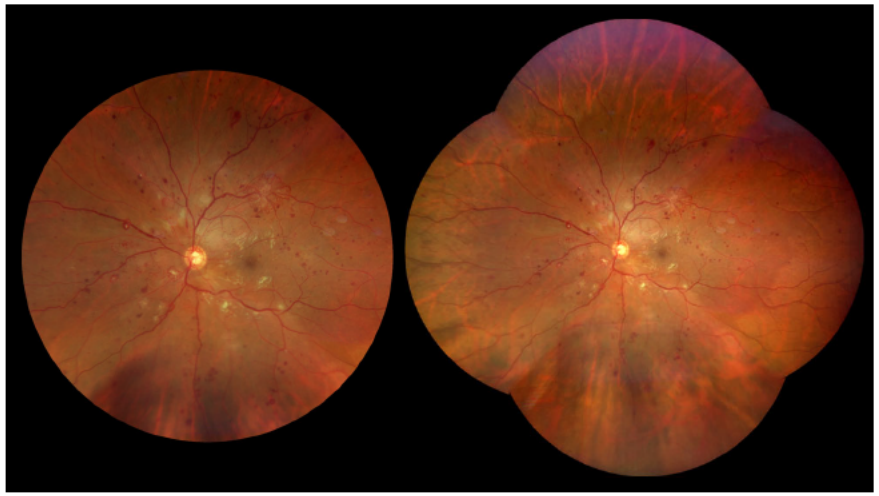
58


PROLIFERATIVE OR NONPROLIFERATIVE?
Ant Seg OS

59


TAKING IT TO THE EXTREME
29yo American Indian male – Presents for routine DM exam, needs gls
• POH: Severe NPDR OU at LEE 5 yrs ago
• MH:
– DM Type 2 x 20 yrs, last HbA1C 8.2%
– 2 toes amputated recently due to DM ulcer
• Vision: BCVAs @dist
– OS 20/30-2
• Entrance testing: Normal
• External exam: Normal OU

60



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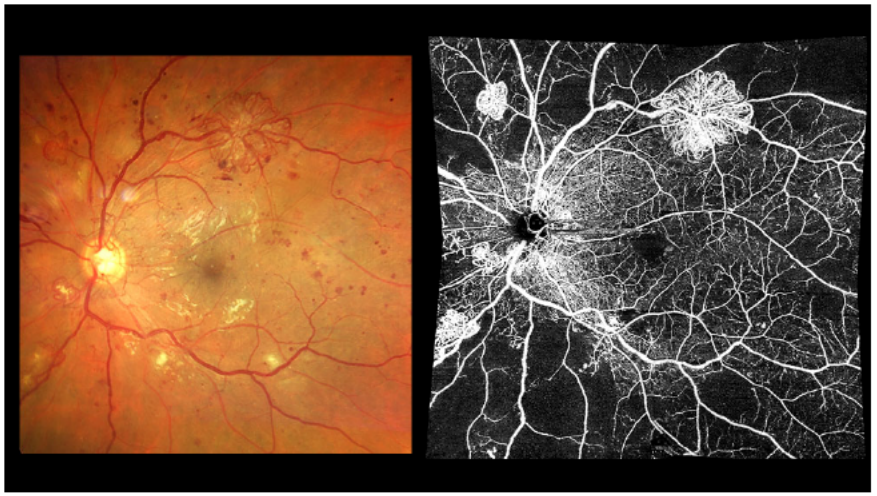

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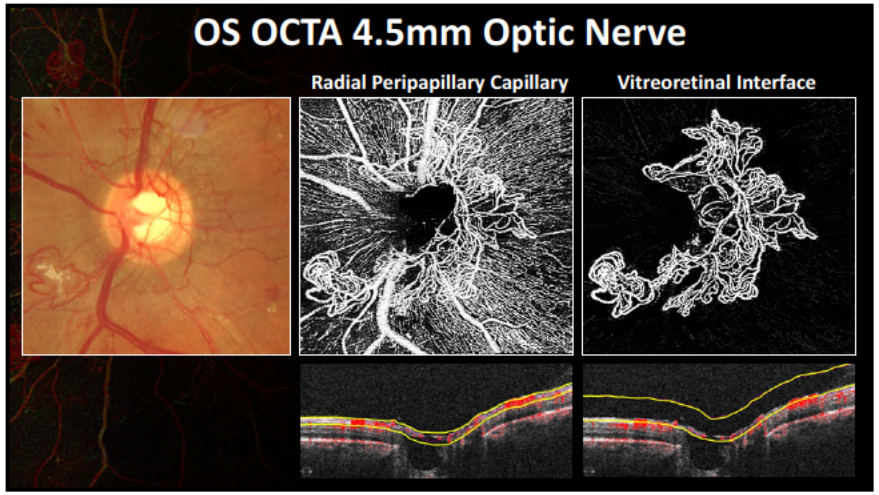
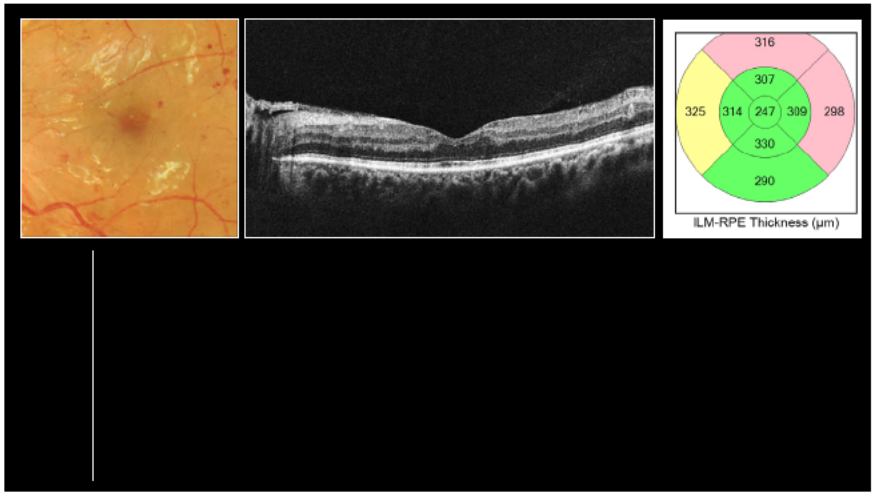
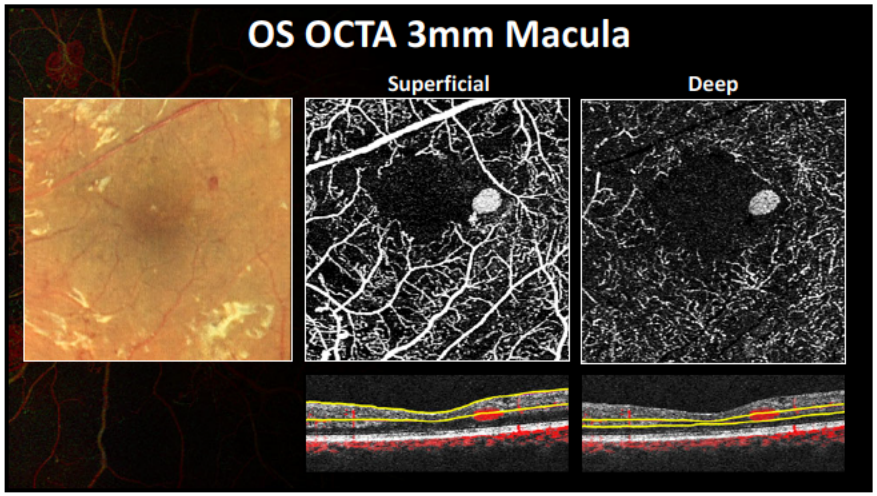

OS OCTA 4.5mm Optic Nerve
Radial Peripapillary Capillary
Vitreoretinal Interface

63


316
307
325
314
247
309
298
330
290
ILM-RPE Thickness (µm)

64



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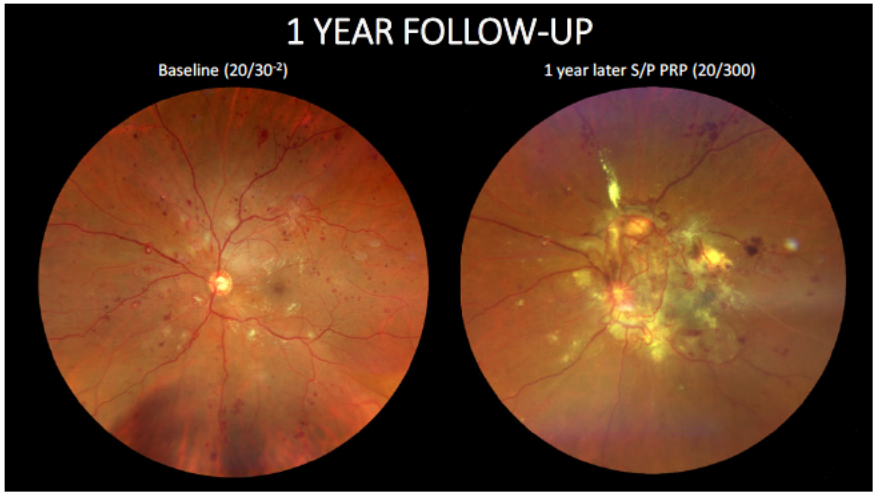

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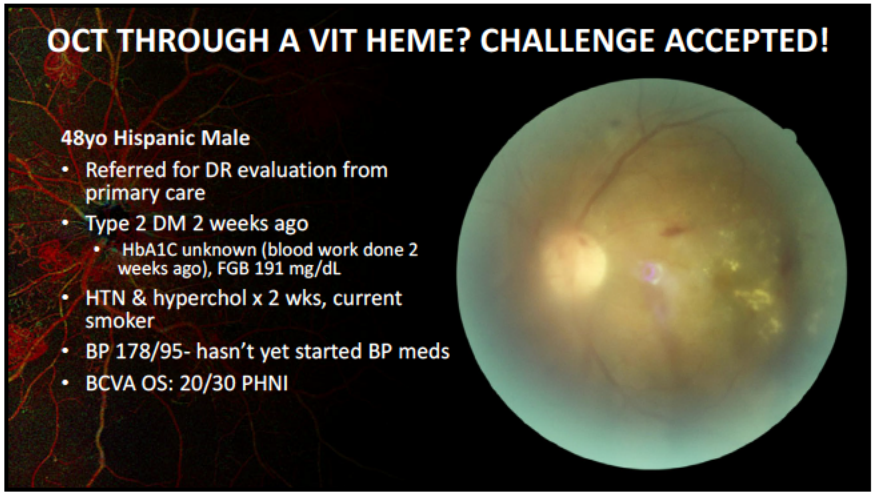

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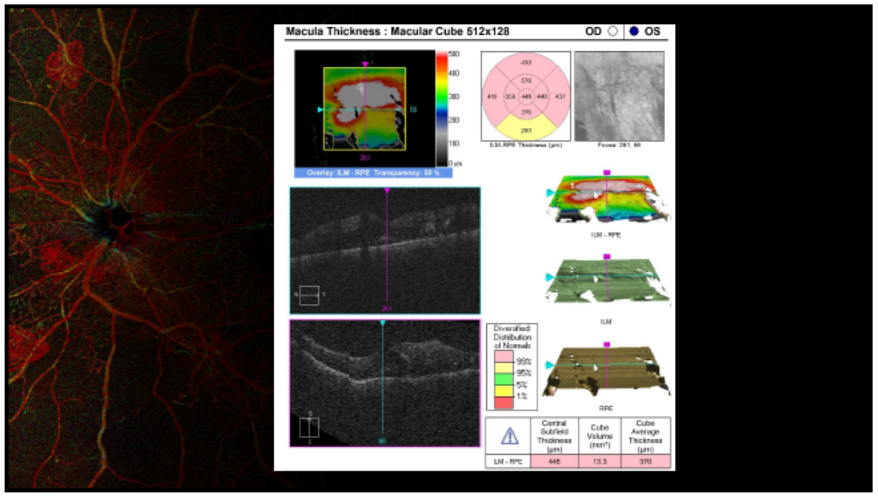

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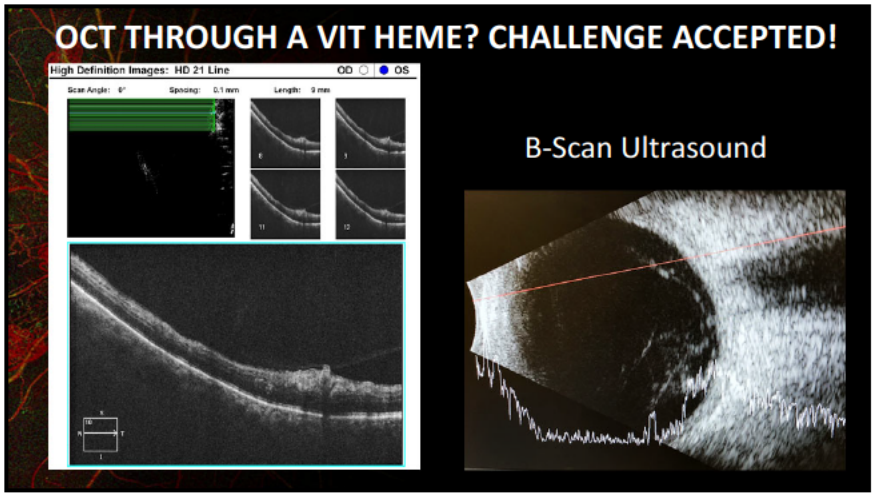

70

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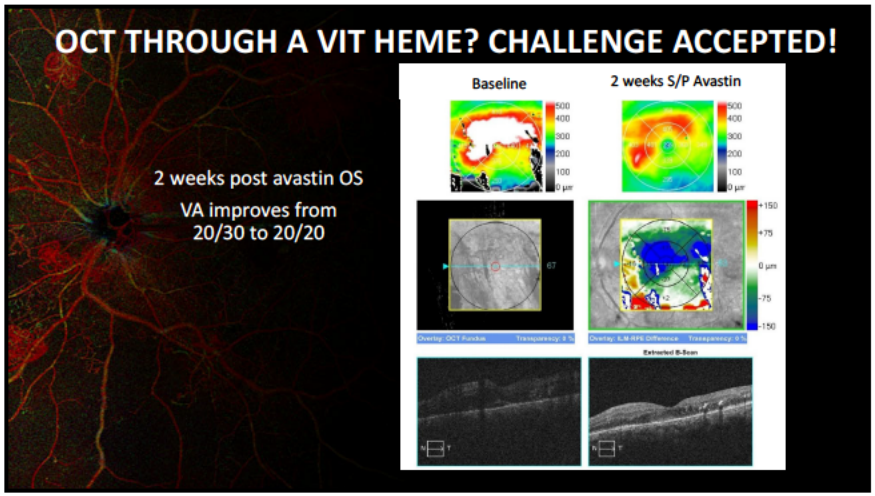
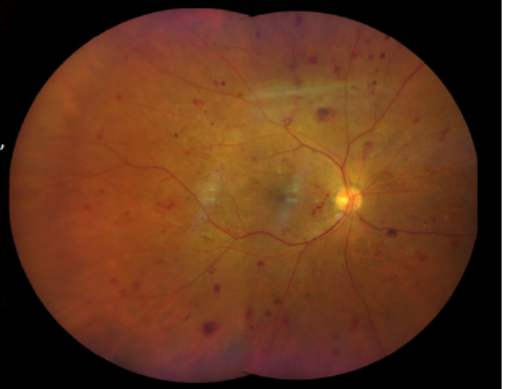


72

OCT/B-SCAN CORRELATES CASE 1

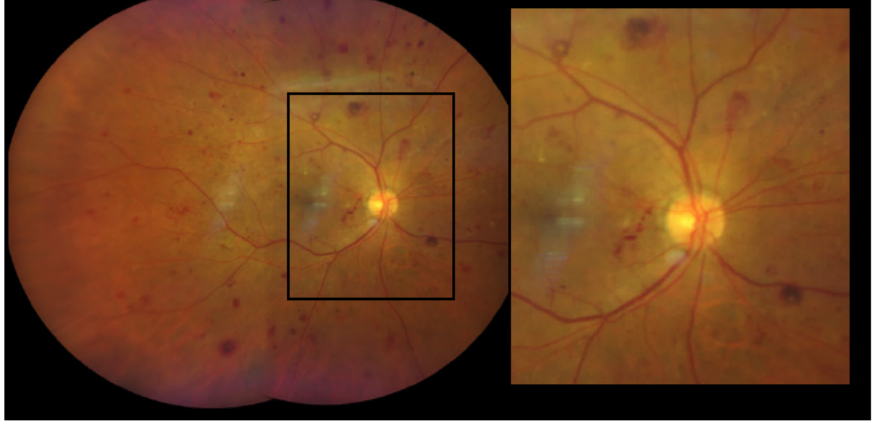
63yo American Indian male

- CC: Central blur OS, prior severe NPDR OU per LEE 1.5yrs ago. Went to retina consult but no tx done.
- Type 2 DM x 20 years (HbA1C 7.7%), CHF
- VA (cc @ dist)
  - OD: 20/25-2
  - OS: 20/250 PHNI (20/40 1.5 yrs ago)
- BP: 170/106



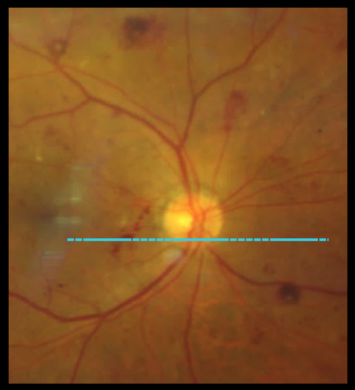
73

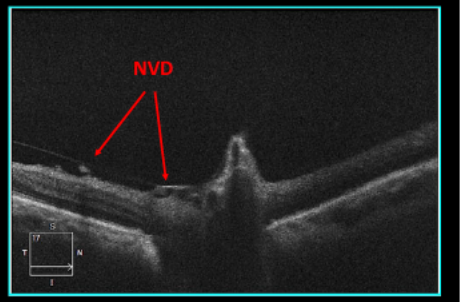
OCT/B-SCAN CORRELATES CASE 1



74

OCT/B-SCAN CORRELATES CASE 1





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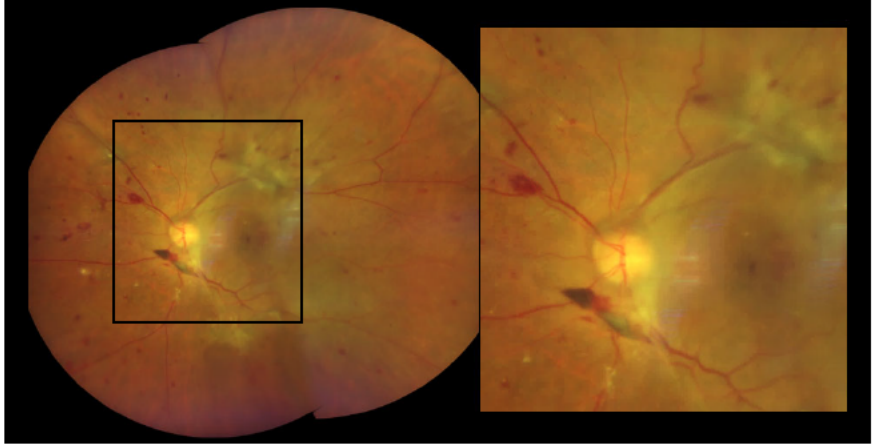
OCT/B-SCAN CORRELATES CASE 1



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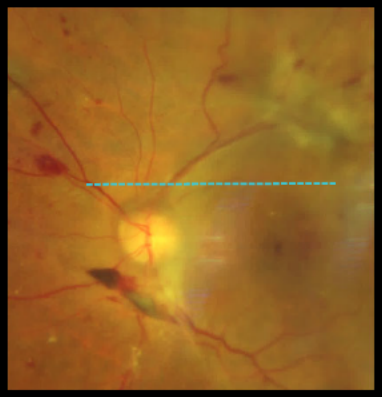
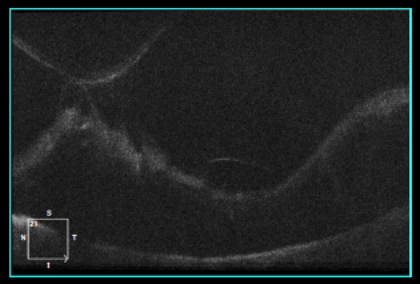
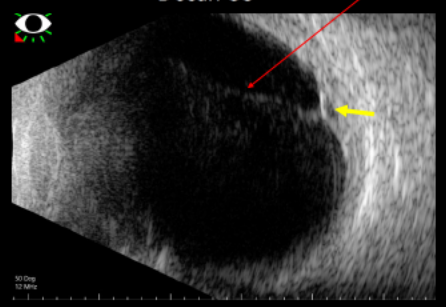
OCT/B-SCAN CORRELATES CASE 1

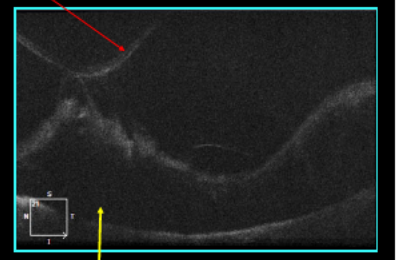




77

OCT/B-SCAN CORRELATES CASE 1





Peripapillary SRF (tractional RD)

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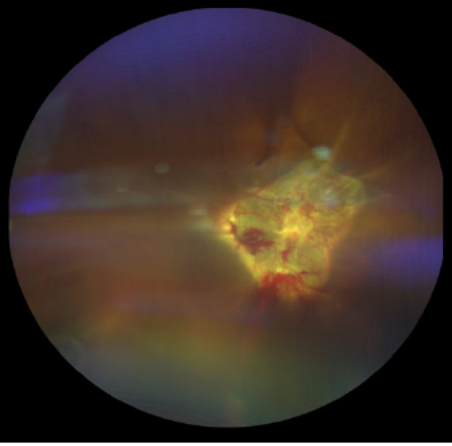
OCT/B-SCAN CORRELATES CASE 2

59yo American Indian female

- CC: Worsening vision OD, prior documented vit heme
- Type 2 DM x ? years (HbA1C 5.8%)
- VA (cc @ dist)
  - OD: HM
- BP: 194/94



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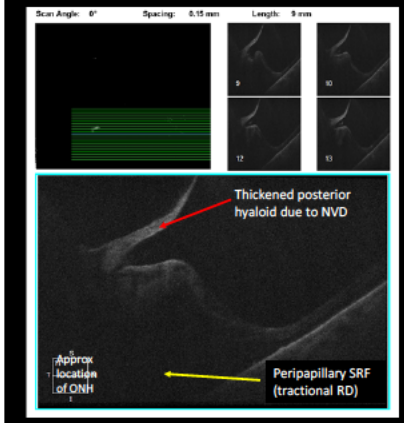
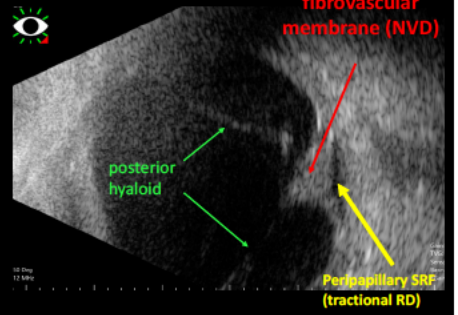
OCT/B-SCAN CORRELATES CASE 2





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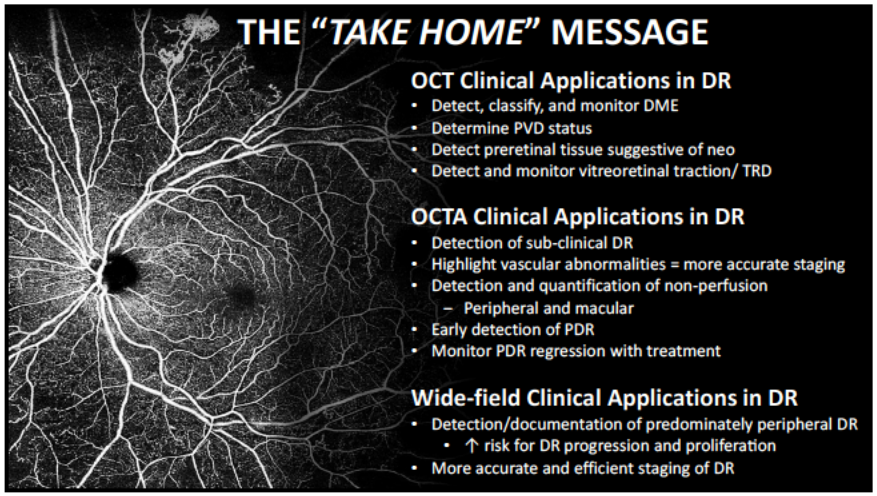
THE "*TAKE HOME*" MESSAGE
OCT Clinical Applications in DR
• Detect, classify, and monitor DME
• Determine PVD status
• Detect preretinal tissue suggestive of neo
• Detect and monitor vitreoretinal traction/ TRD
OCTA Clinical Applications in DR
• Detection of sub-clinical DR
• Highlight vascular abnormalities = more accurate staging
• Detection and quantification of non-perfusion
– Peripheral and macular
• Early detection of PDR
• Monitor PDR regression with treatment
Wide-field Clinical Applications in DR
• Detection/documentation of predominately peripheral DR
• ↑ risk for DR progression and proliferation
• More accurate and efficient staging of DR

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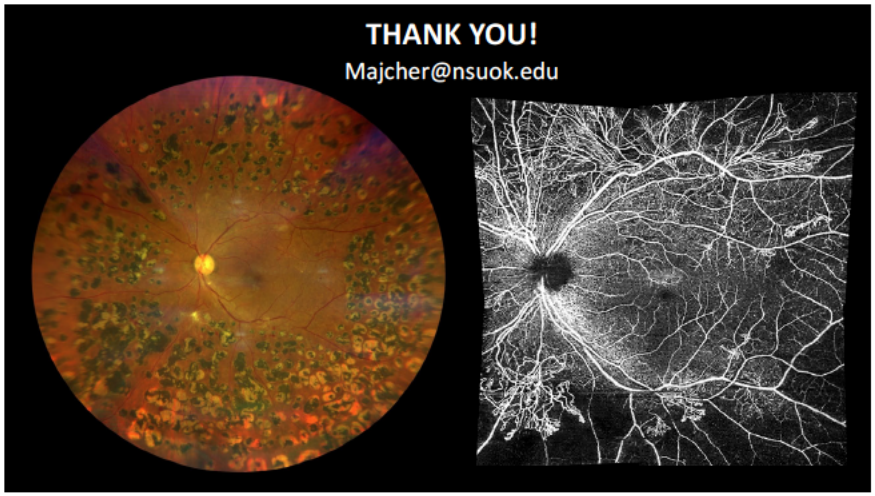
THANK YOU!
Majcher@nsuok.edu

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