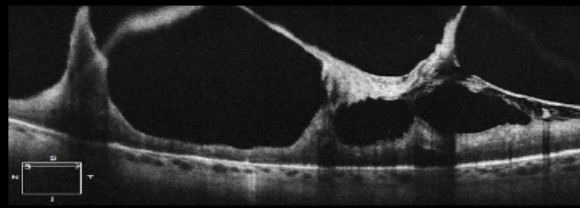
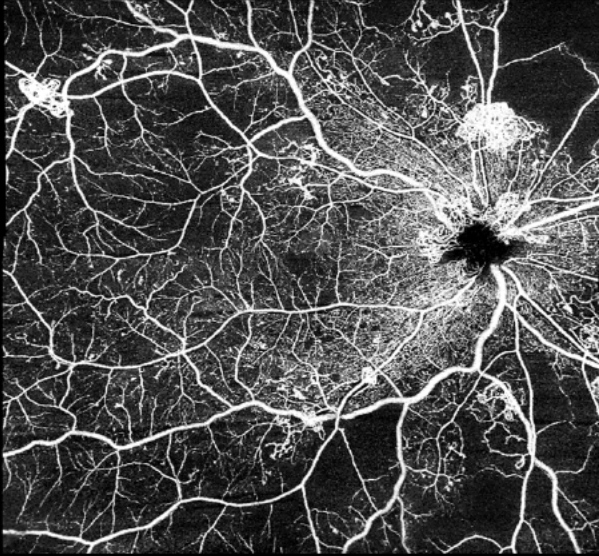


DIAGNOSIS DIABETES: THE OPTOMETRIC MODERN MANAGEMENT GUIDE



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1

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Disclosures:

- Paid consultant/speaker for:
 - Carl Zeiss Meditec
 - Regeneron Pharmaceuticals
 - Iveric Bio (Astellas)
 - Optomed
 - Apellis Pharmaceuticals
- Paid advisory board member for LENZ Therapeutics, Notal Vision, Topcon, Tarsus, Genentech

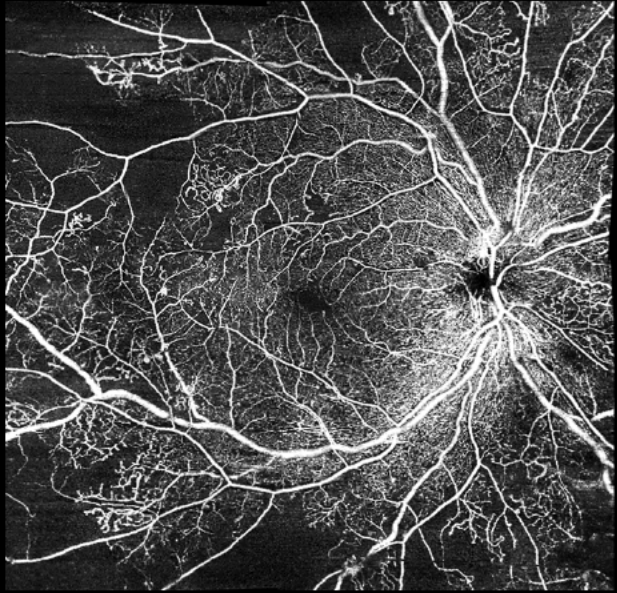
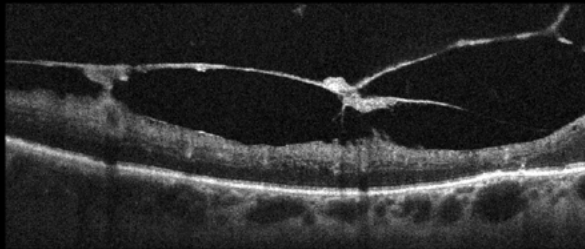
All relevant relationships have been mitigated



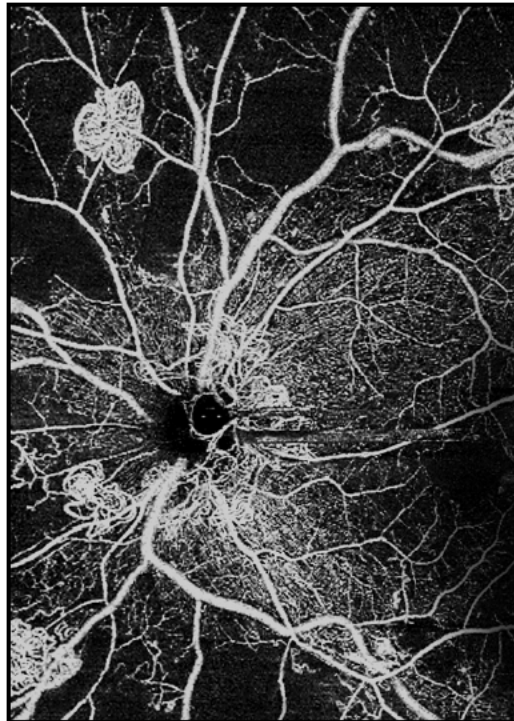
2

OVERVIEW

- DR Standard of care documents
- Introduction to DM and DR, multimodal imaging technologies
- 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
- Management updates



3



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 2024
- 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

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 ^{95,188}
	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 2024, p25

5

	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

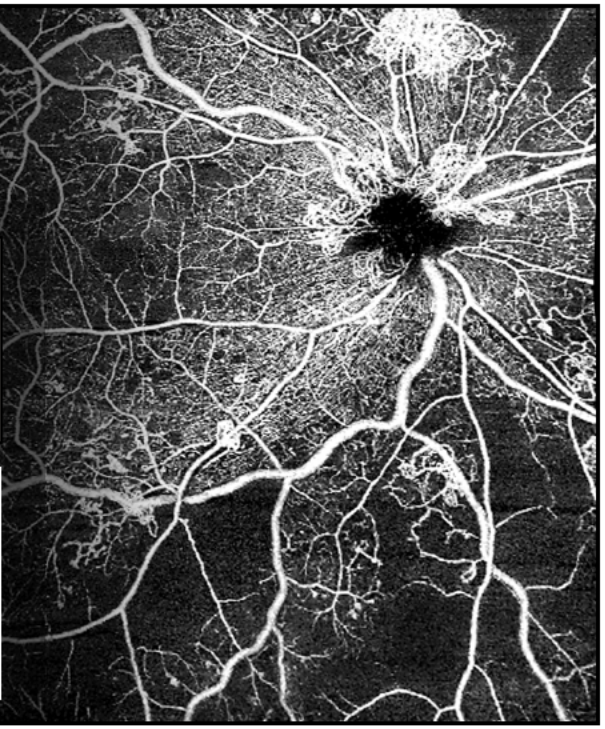
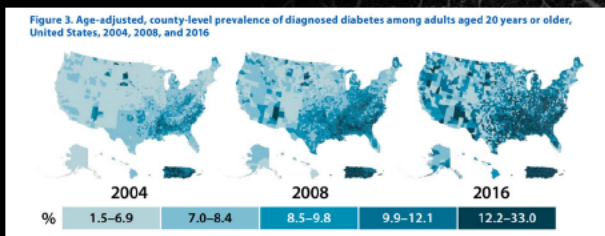
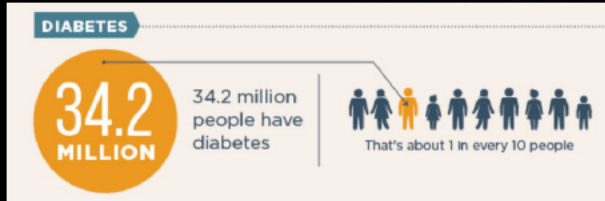
American Optometric Association– Clinical Practice Guideline 2019, p61-63

6

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



7

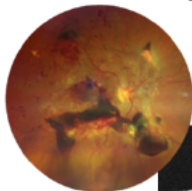
Global Prevalence of Diabetic Retinopathy (DR) in 2020

The global prevalence of DR among adults with DM is ~22.3%

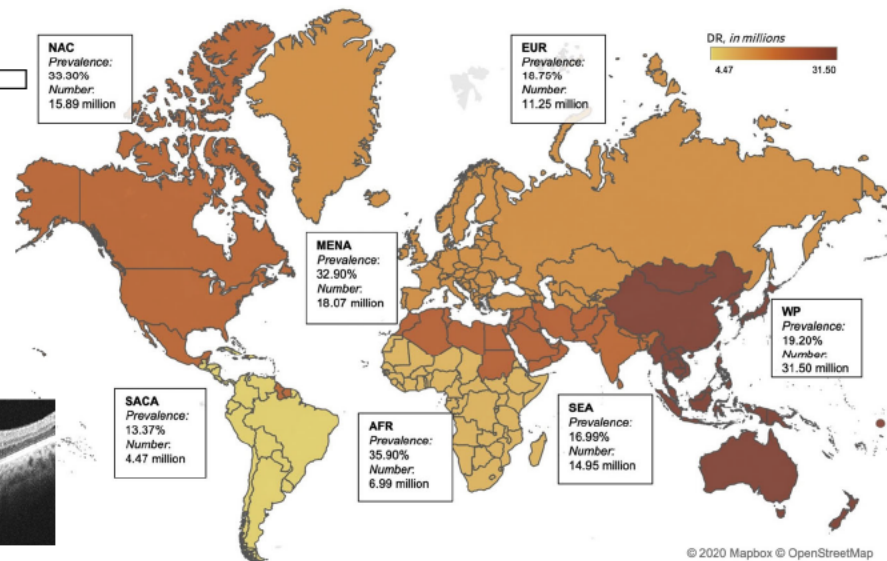
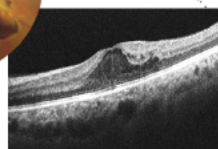
In North America and the Caribbean
~ 1 in 3 adults with DM has DR



8% Vision-Threatening DR



5% CSME

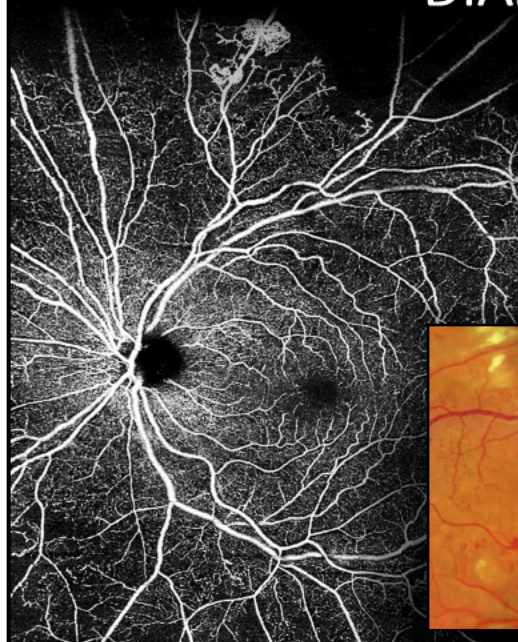


© 2020 Mapbox © OpenStreetMap

Teo ZL, et al. Global Prevalence of DR and Projection of Burden through 2045: Systematic Review and Meta-analysis. Ophthalmology 2021

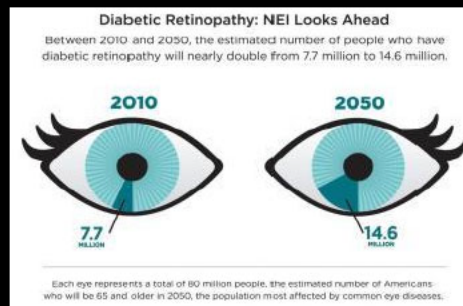
8

DIABETIC RETINOPATHY



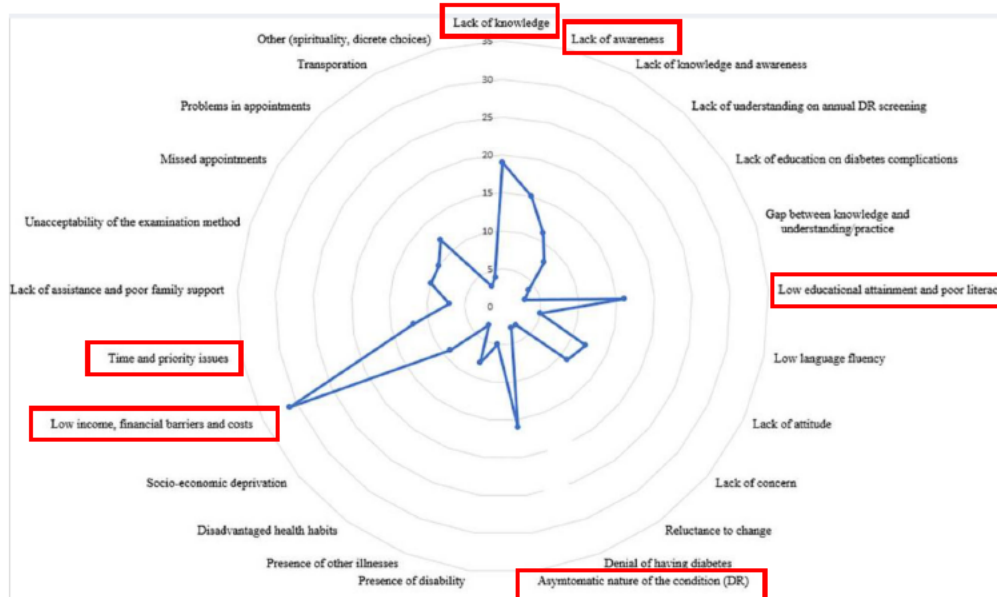
Increasing demand for diabetic retinopathy care

- 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



9

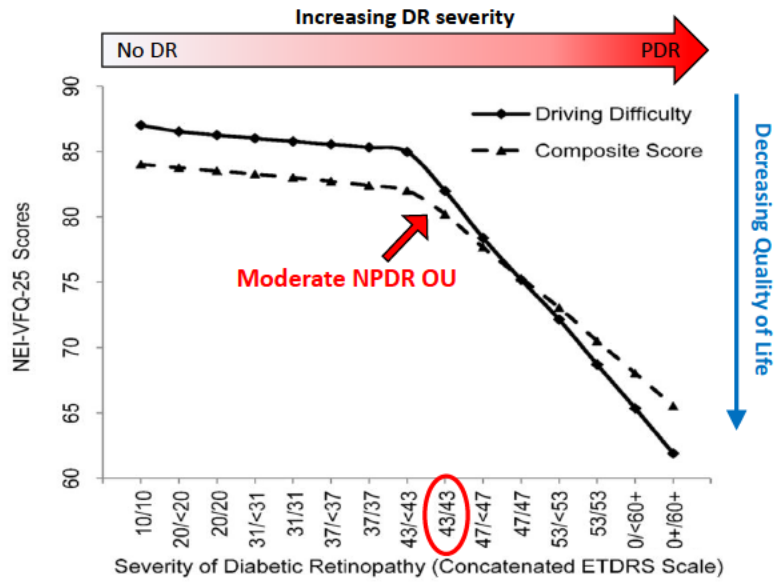
Systematic review on barriers for access to DR screening services: Frequent themes harvest plot



Piyasena MMPN, et al. Systematic review on barriers and enablers for access to DR screening services in different income settings. PLoS One. 2019;14(4):e0198979.

10

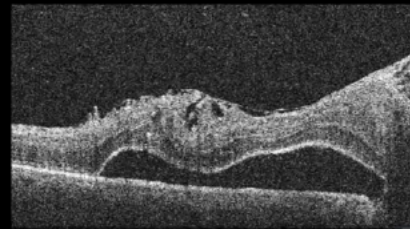
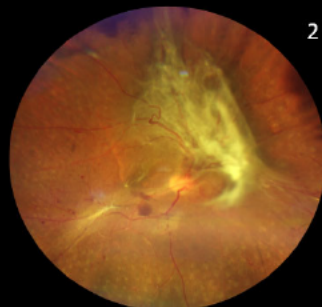
PATIENTS ARE OFTEN ASYMPTOMATIC UNTIL MODERATE NPDR



Los Angeles Latino Eye Study Group. Severity of DR and health-related QOL. Ophthalmology. 2011

11

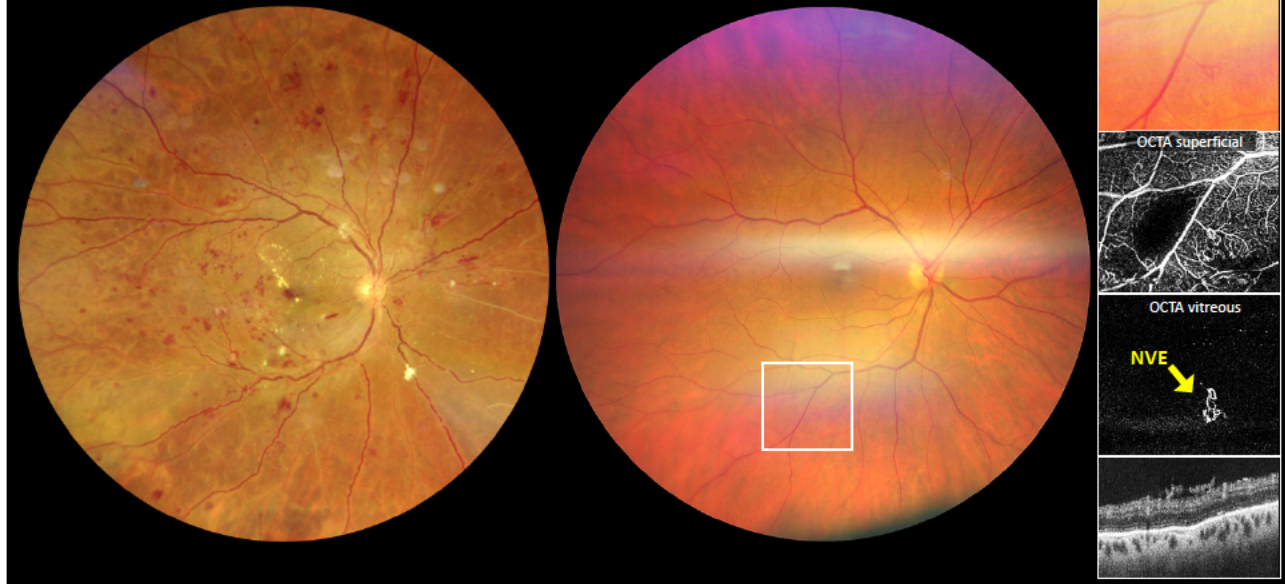
FAST DR PROGRESSION 32yo: Type 2 DM diagnosed at age 13



12

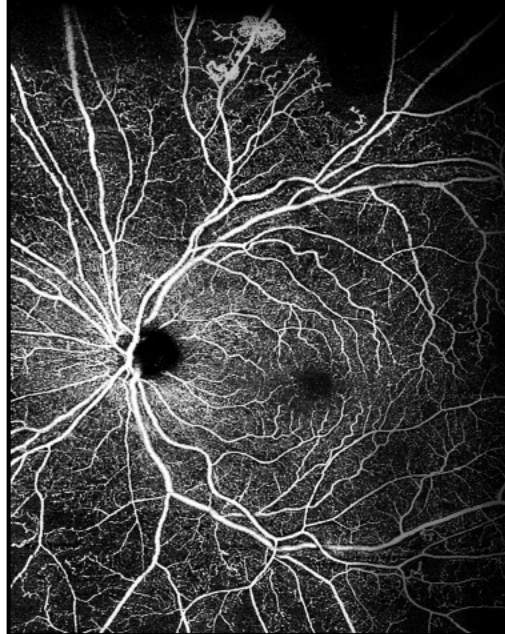
TWO DRASTICALLY DIFFERENT PRESENTATIONS OF PDR!!

"FEATURELESS RETINA" = Minimal background DR signs...yet PDR is present



13

DIABETIC RETINOPATHY RISK FACTORS



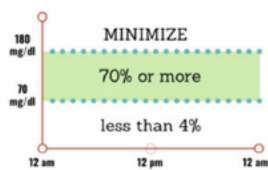
- Longer duration of DM!!!!
 - Actual duration in T2DM usually longer than that reported
- Poor glycemic control
- Uncontrolled systemic HTN
- Dyslipidemia
- Insulin use and duration of insulin use
- Pregnancy
- Sleep apnea
- Puberty
- Nephropathy
- Smoking
- Ocular surgery
- Vasculitis
- Vitamin D deficiency

"Once retinopathy is present, duration of DM appears to be a less important factor than glycemic control in forecasting retinopathy progression" (AAO PPP 2019)

14

EFFECT OF GLYCEMIC CONTROL ON DR

“Time in range” with continuous glucose monitoring



- Patients with the most advanced DR show significantly less time in range and higher glycemic variability
- DR severity is inversely correlated with time in range
- Prevalence of DR decreases with greater time in range

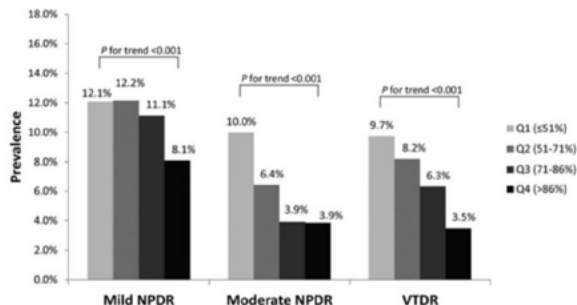
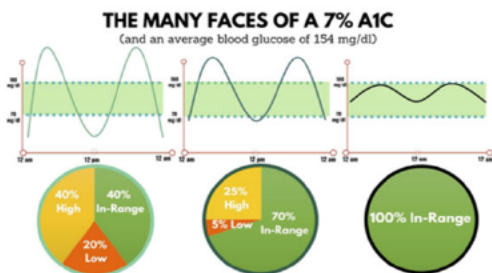


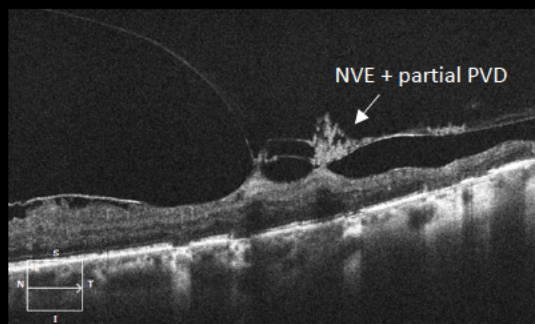
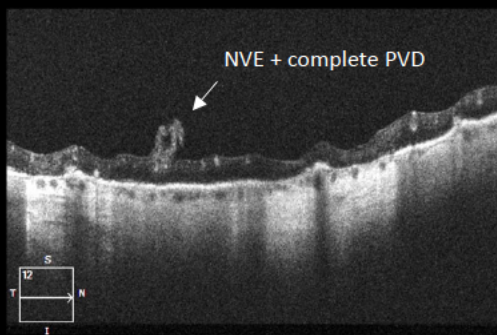
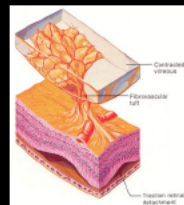
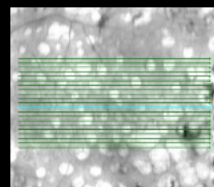
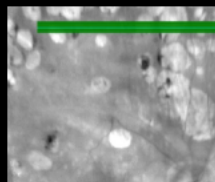
Figure 1—Prevalence of DR by severity, as a function of TIR quartile.

Lu J, et al. Association of time in range, as assessed by CGM, with DR in type 2 DM. Diabetes Care. Sept, 2018.

15

DIABETIC RETINOPATHY PROTECTIVE FACTORS

PVD Status?



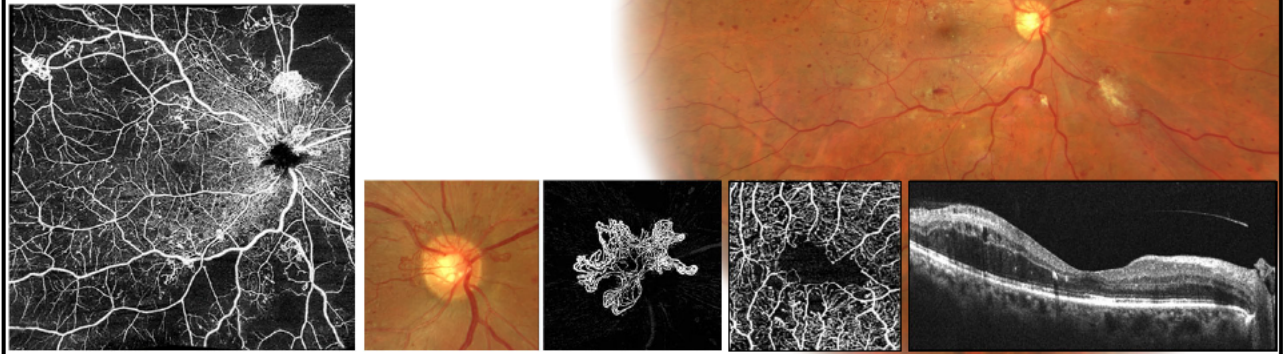
COMPLETE PVD IS PROTECTIVE!

16

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



17

WIDEFIELD & ULTRA-WIDEFIELD CFP



WF= Up to the vortex vein ampullae, >50%

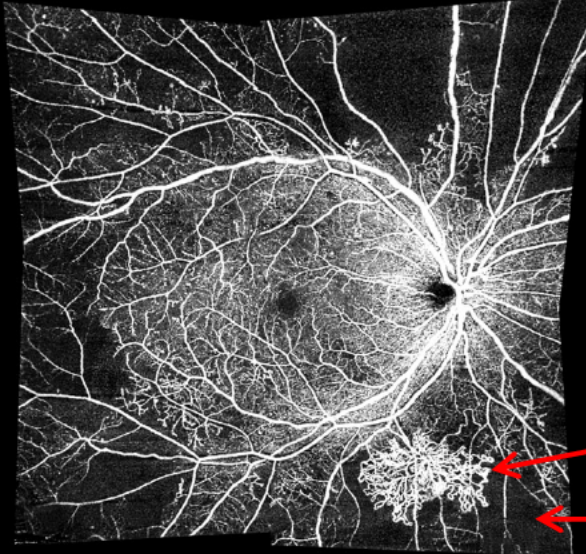


UWF= Includes at least 4 vortex vein ampullae, ~200° and 80% retinal surface

18

OCT ANGIOGRAPHY (OCTA)

- Non-invasive “flow” imaging (**NO DYE INJECTION REQUIRED**)



New CPT CODE:
92137

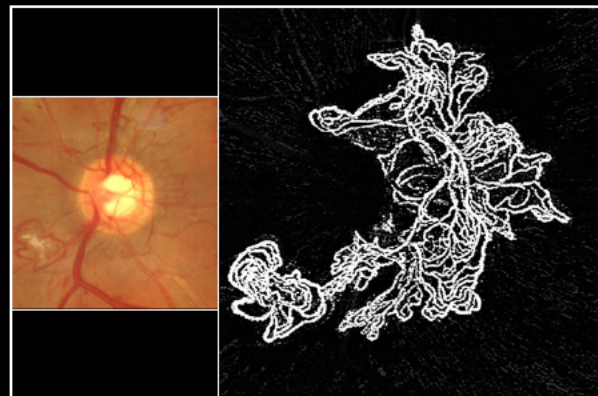
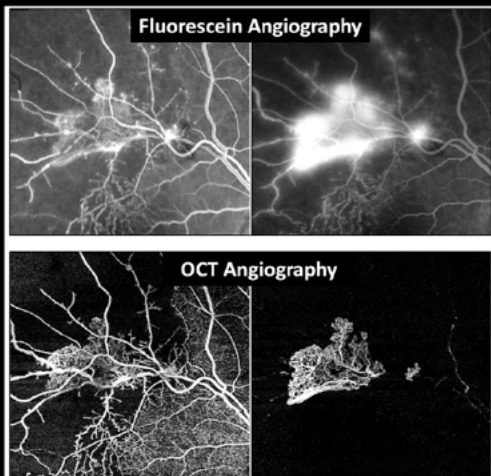
Bright → blood flow

Dark → no flow or too slow to detect

19

OCT ANGIOGRAPHY: THE BASICS

- Absence of late stage hyperfluorescence patterns (aka leakage)
= Precise delineation/measurement of neo

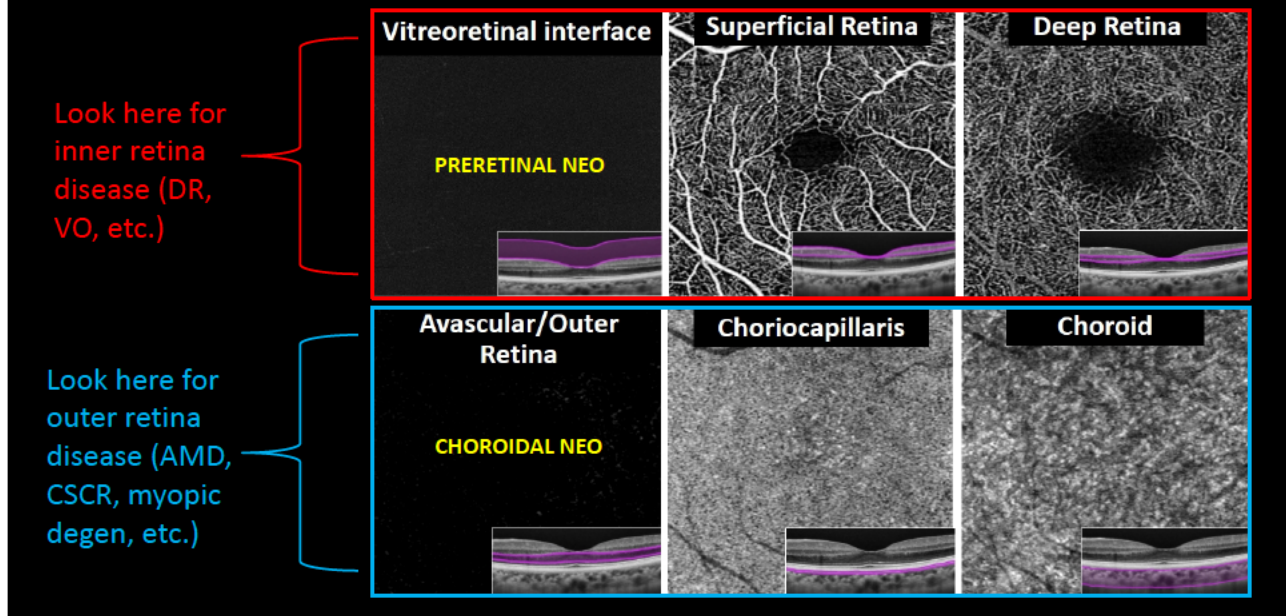


HIGH RESOLUTION IMAGING OF NEOVASCULAR MEMBRANES = MEASURE SIZE & CLASSIFY MORPHOLOGY PATTERNS

20

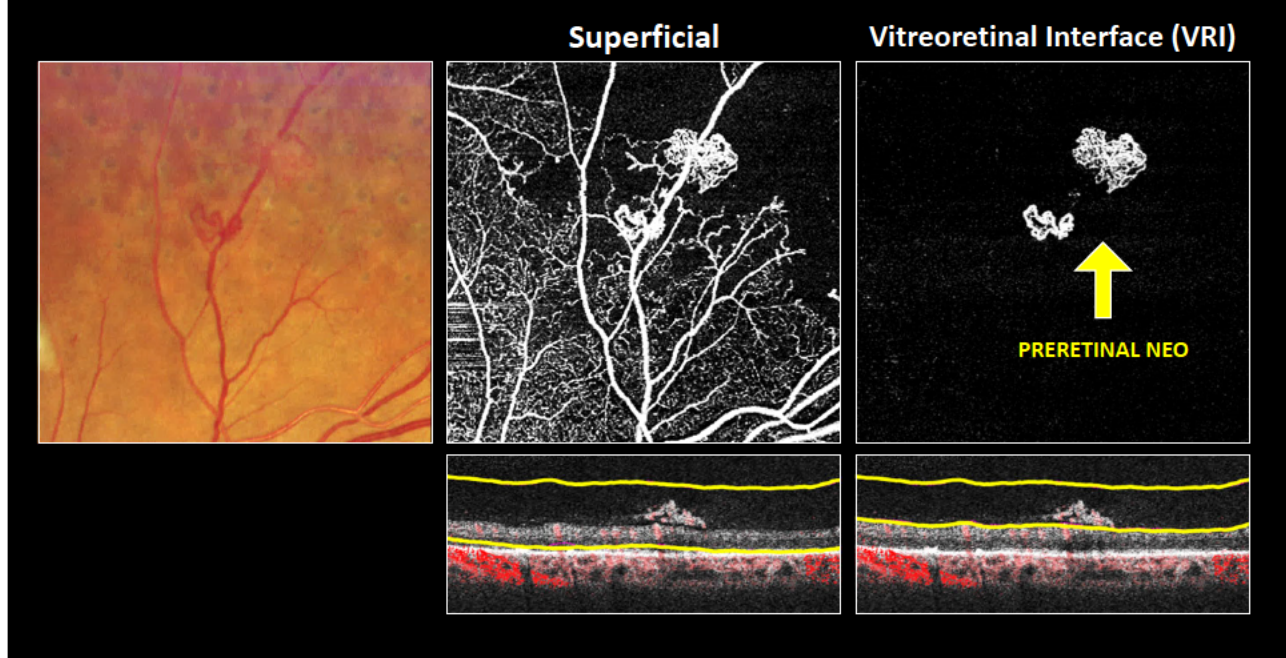
OCT ANGIOGRAPHY: THE BASICS

Enface Displays (3mm macula)

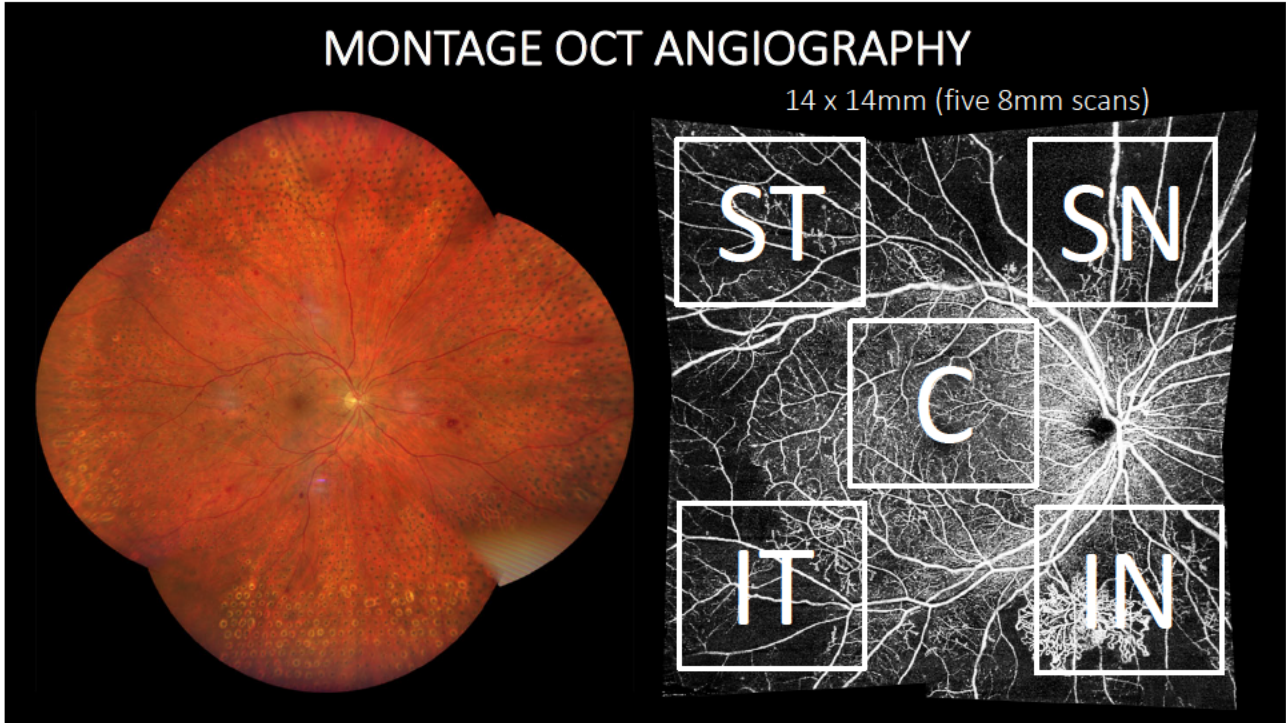


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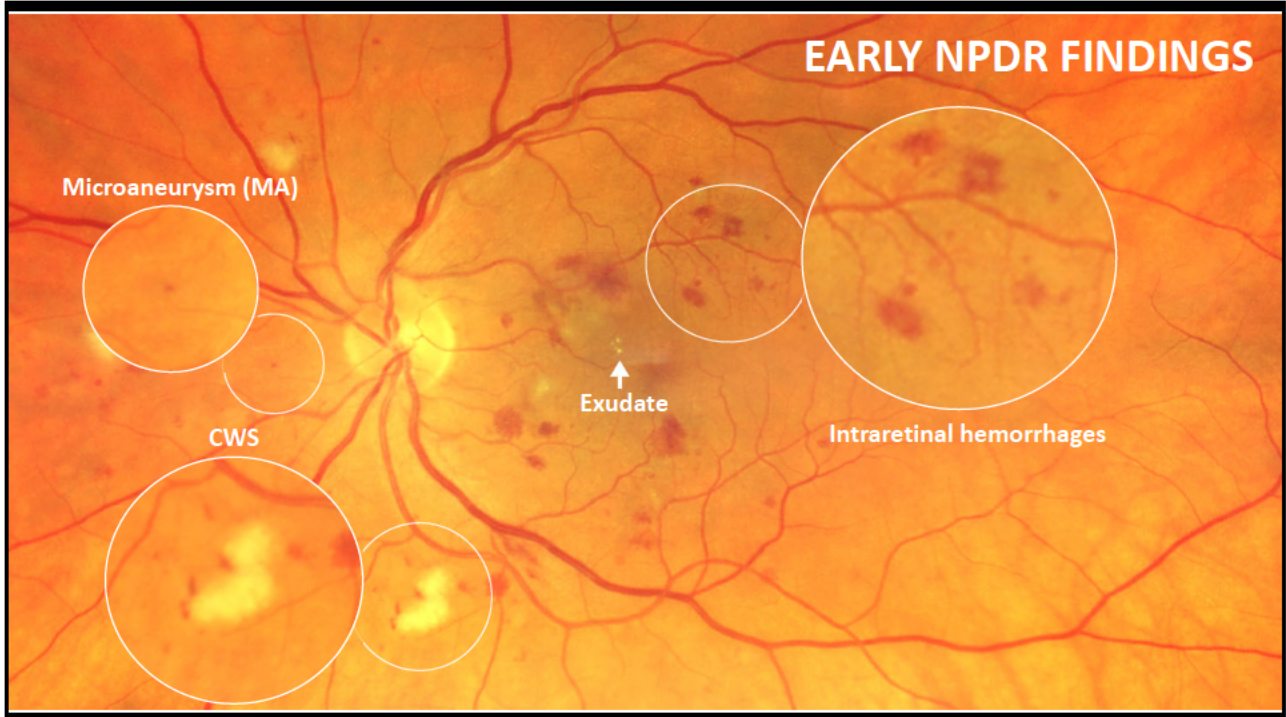
OCT ANGIOGRAPHY: THE BASICS



22



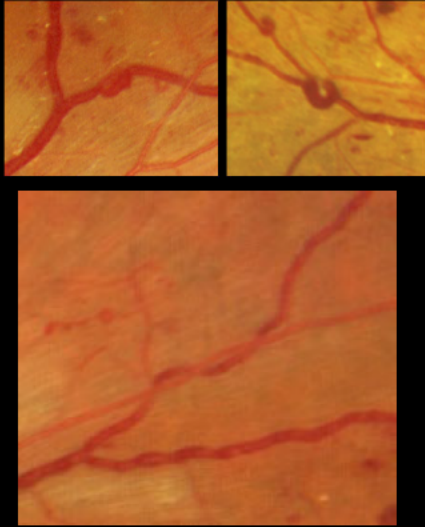
23



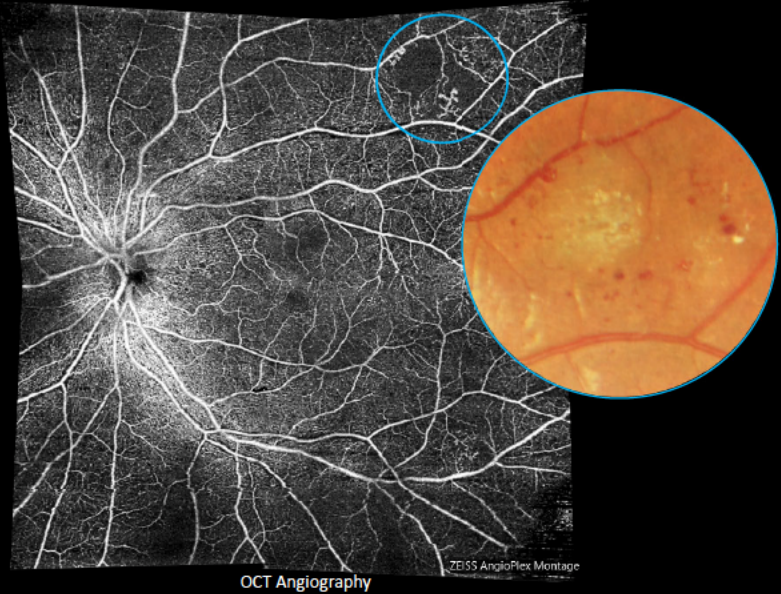
24

ADVANCED DR FINDINGS

Venous Beading



IRMA



25

DIABETIC RETINOPATHY STAGING

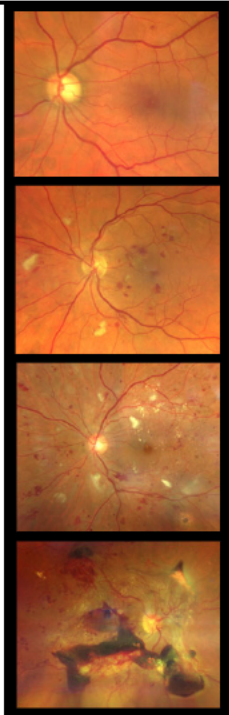
AAO PPP 2024 (p18)

TABLE 1 DIABETIC RETINOPATHY DISEASE SEVERITY SCALE AND INTERNATIONAL CLINICAL DIABETIC RETINOPATHY DISEASE SEVERITY SCALE

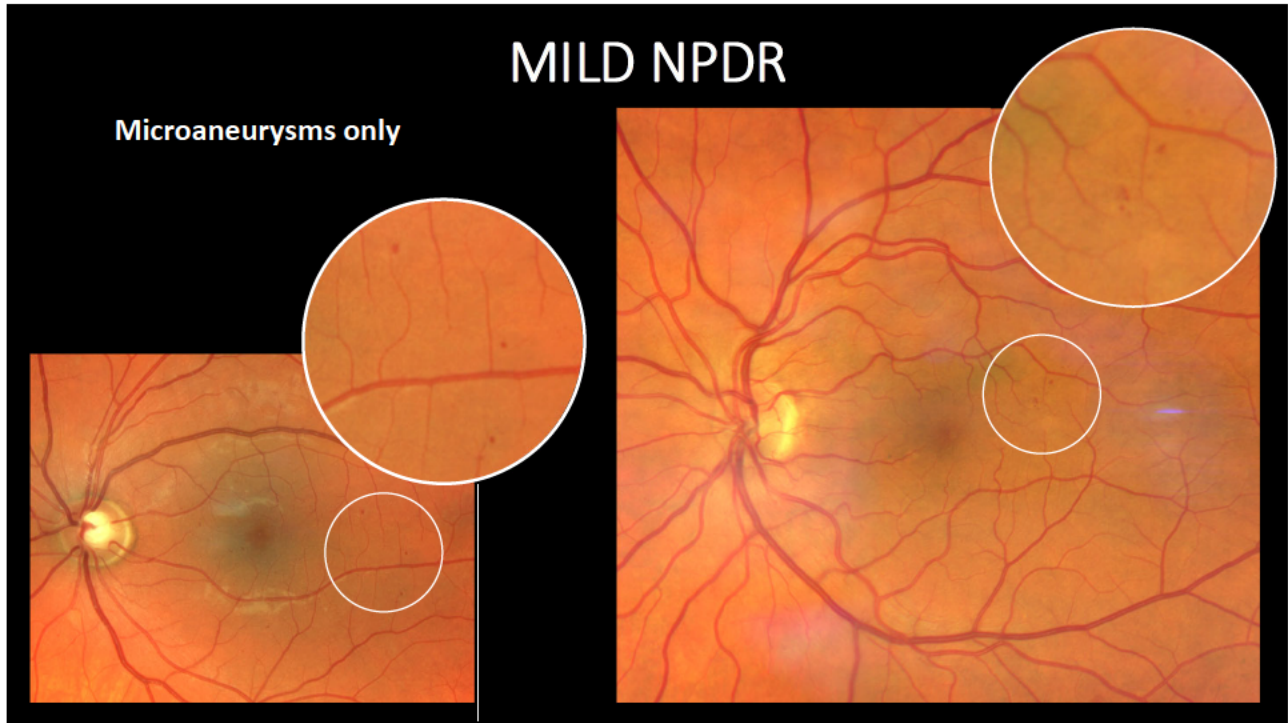
Disease Severity Level	Findings Observable upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR (see Glossary)	Microaneurysms only
Moderate NPDR (see Glossary)	More than just microaneurysms but less than severe NPDR
Severe NPDR	<p>International Definition</p> <p>Any of the following and no signs of proliferative retinopathy:</p> <ul style="list-style-type: none"> • 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 <p>• Any patient with two or more of the characteristics of severe NPDR is considered to have very severe NPDR.</p>
PDR	<p>One or both of the following:</p> <ul style="list-style-type: none"> • Neovascularization • Vitreous/preretinal hemorrhage

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

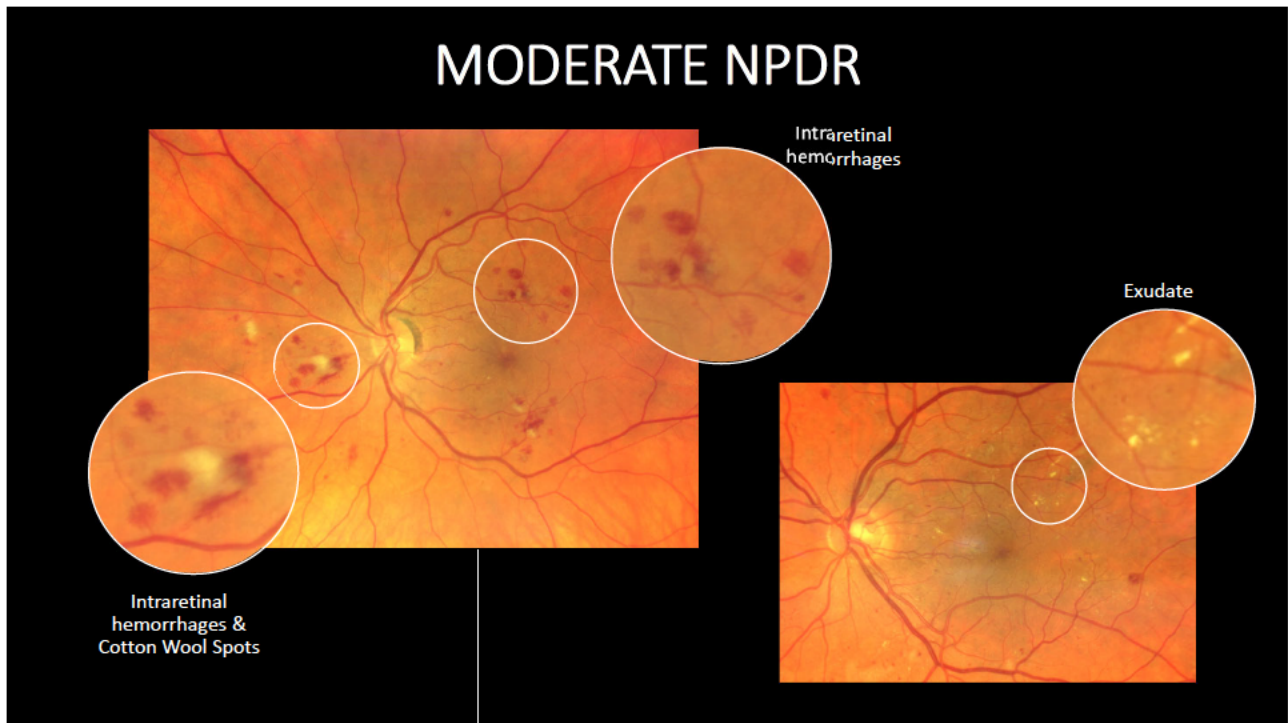
*AOA CPG Mild NPDR - marked by at least one retinal MA. Only hemorrhages & MAs are present and the severity is less than that depicted in ETDRS standard photograph 2A



26



27

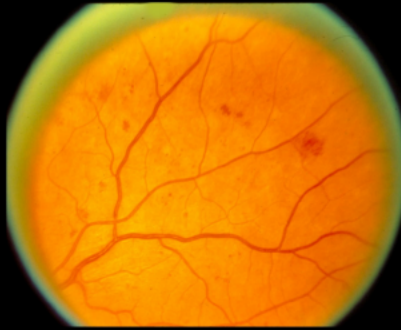


28

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

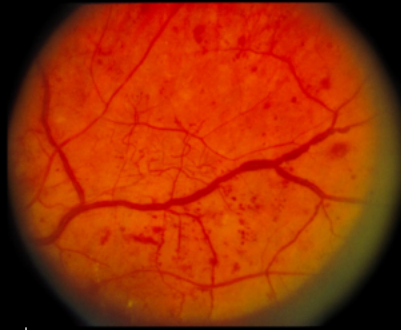
4

Severe retinal hemorrhages
(≥ standard photograph 2A)



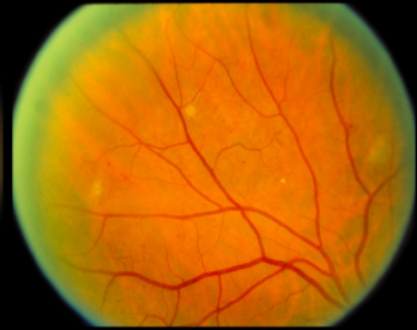
2

Definite venous beading
(≥ standard photograph 6B)



1

Prominent IRMA
(≥ standard photograph 8A)



29

www.pollev.com/retina

When poll is active, respond at pollev.com/retina
Text **RETINA** to **37607** once to join

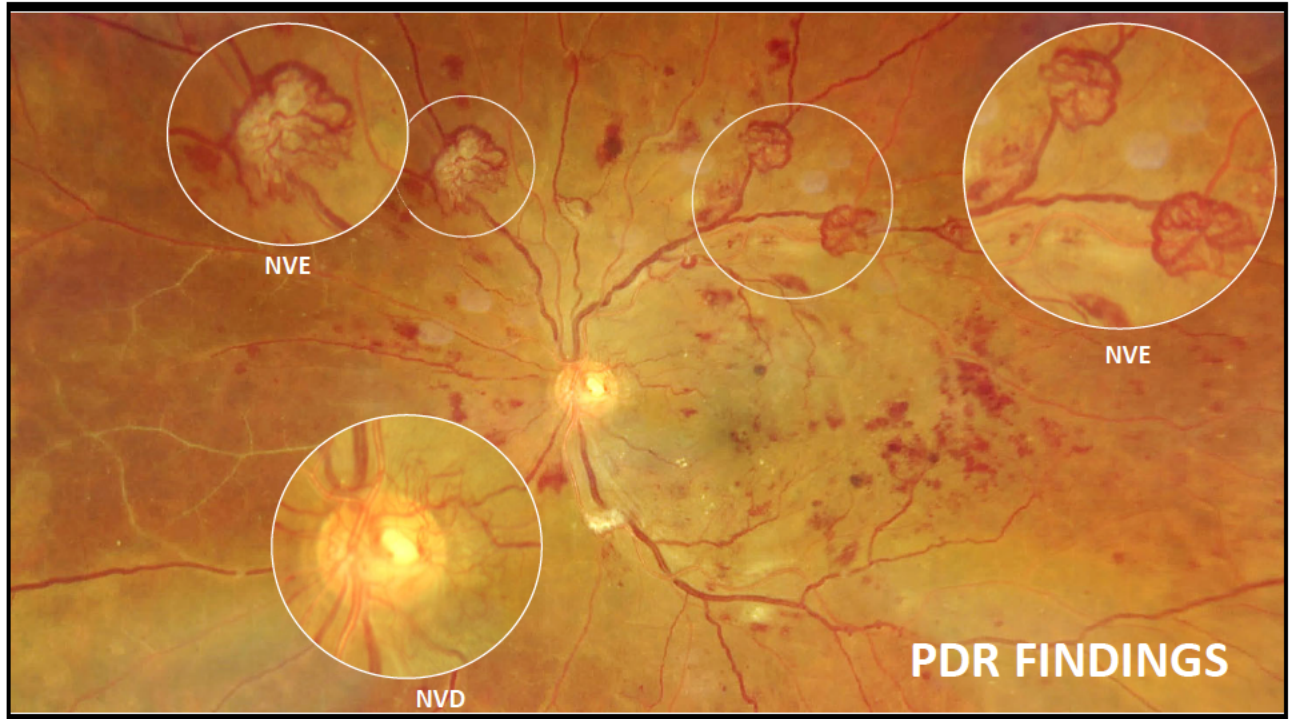
Of eyes with severe NPDR, what percent will develop PDR within 1 yr?

A bar chart with a vertical axis labeled with percentages: 5%, 25%, 50%, and 75%. The chart area is currently empty, indicating that no data has been entered for this poll.

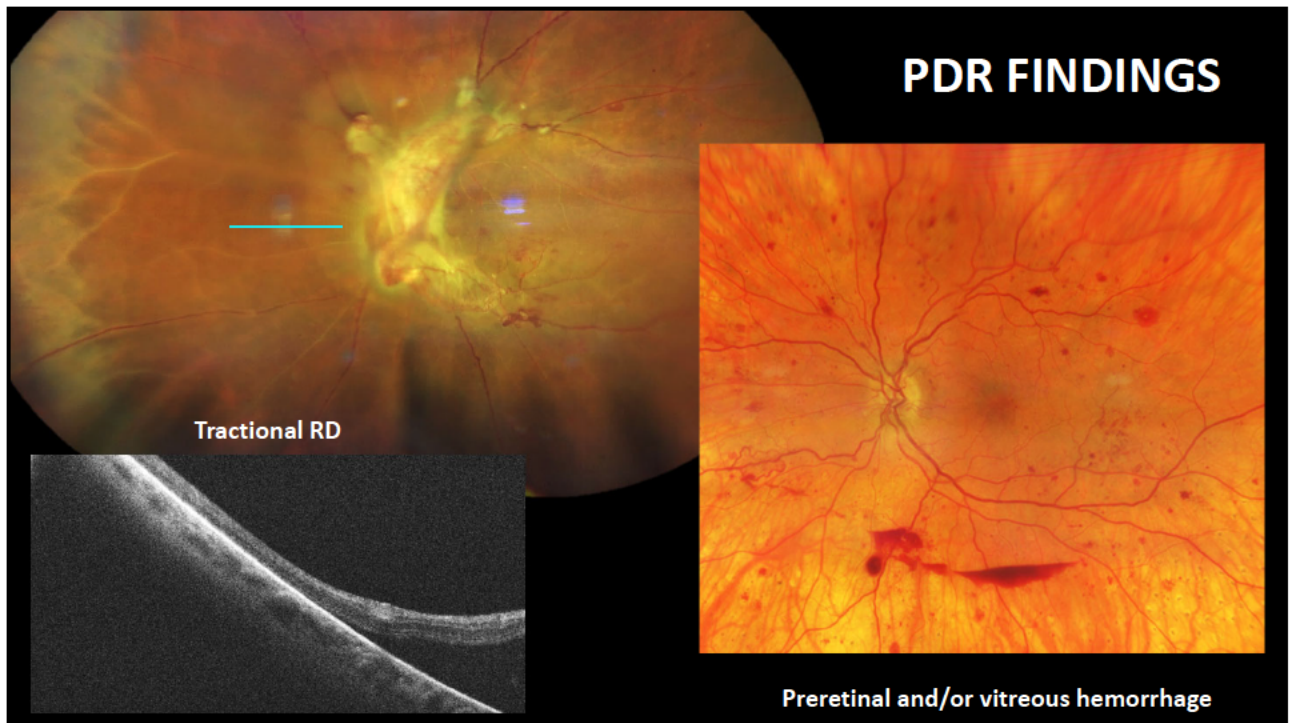
Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

A square QR code located in the top right corner of the slide, which likely links to the poll page.

30



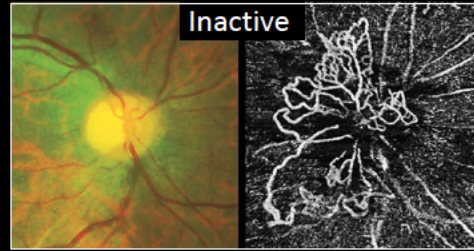
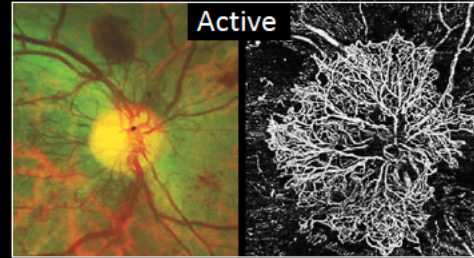
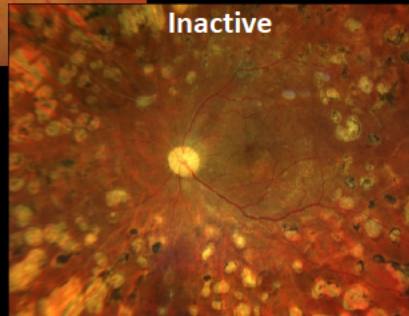
31



32

PROLIFERATIVE DIABETIC RETINOPATHY

- PDR maybe active or inactive (regressed/involved)



J Lin, et al. Evolving Technology and New Terminology in SS-OCTA for DR. Retinal Physician, Sept 2019.

33

PROLIFERATIVE DIABETIC RETINOPATHY

High-risk PDR (Diabetic Retinopathy Study, DRS)

50% RISK OF SEVERE VL WITHIN 5 YRS IF LEFT UNTREATED!!!

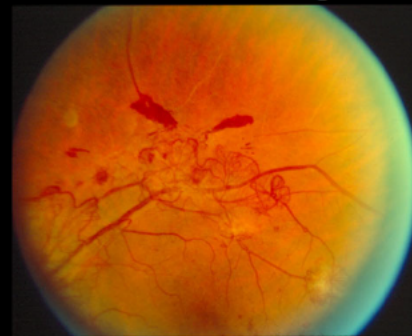
NVD $\geq 1/4$ - $1/3$ disc area in size with or without vitreous/pre-retinal hemorrhage



Any size NVD with associated with vitreous/pre-retinal hemorrhage

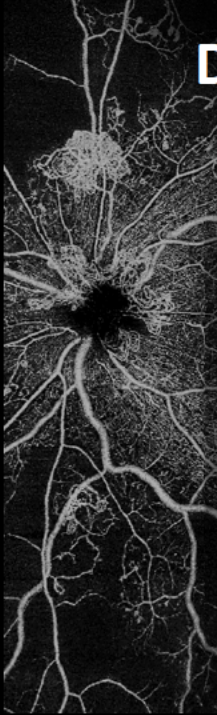


NVE at least $1/2$ disc area in size with pre-retinal/vitreous hemorrhage



34


DME STAGING

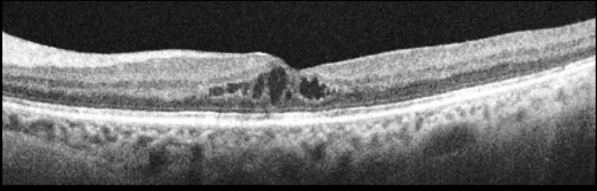
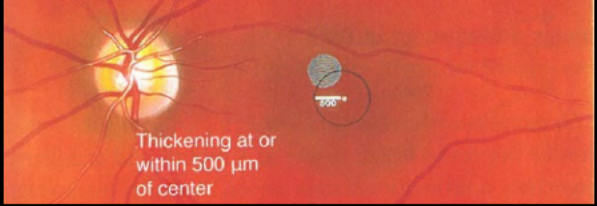


Macular edema: Retinal thickening within 2 DD of the center of the fovea

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

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



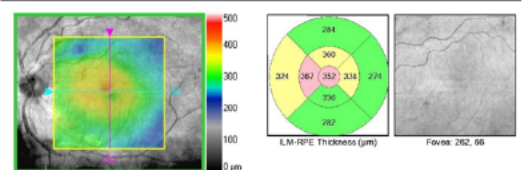
Thickening at or within 500 µm of center

35

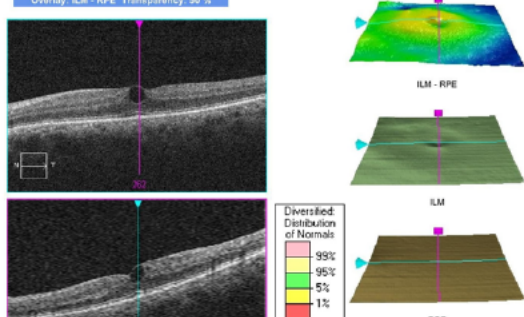
Center-involved DME (CI-DME)

Mild

Macula Thickness : Macular Cube 512x128 OD ○ ● OS



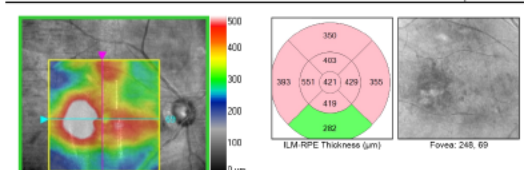
Overlay: ILM - RPE Transparency: 50 %



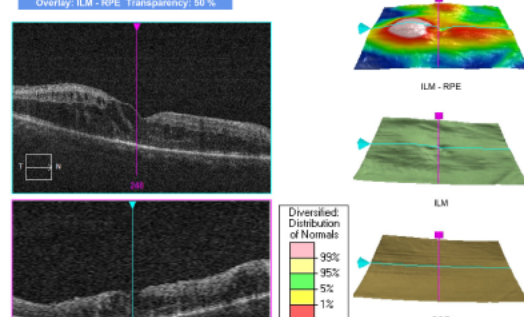
	Central Subfield Thickness (µm)	Cube Volume (mm ³)	Cube Average Thickness (µm)
ILM - RPE	352	10.7	258

Severe

Macula Thickness : Macular Cube 512x128 OD ● ○ OS



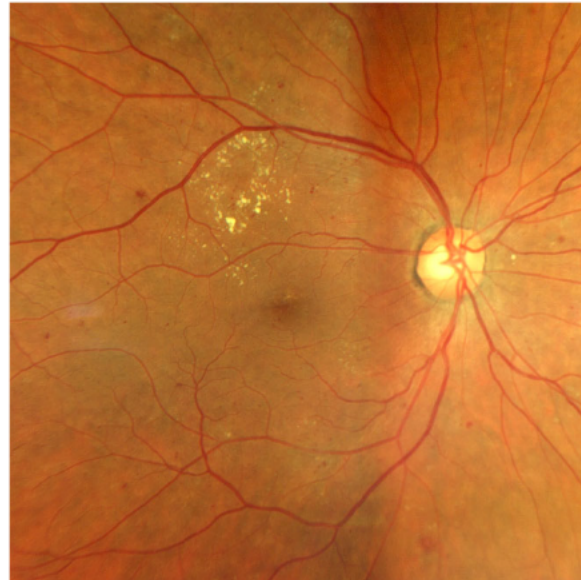
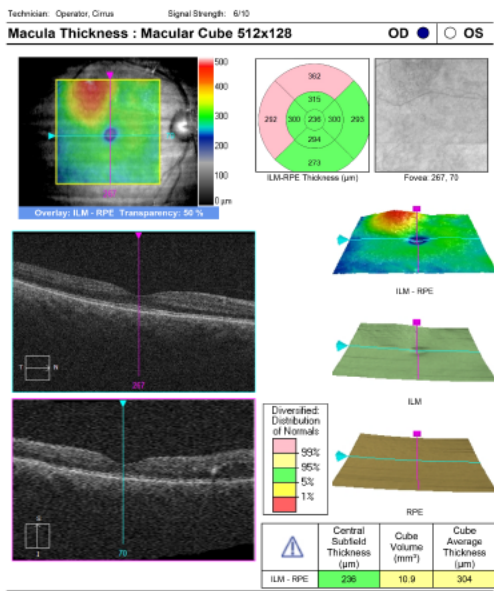
Overlay: ILM - RPE Transparency: 50 %



	Central Subfield Thickness (µm)	Cube Volume (mm ³)	Cube Average Thickness (µm)
ILM - RPE	421	12.6	351

36

Non-center involved DME (NCI-DME)

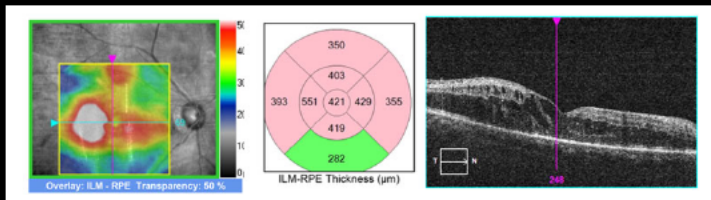


37

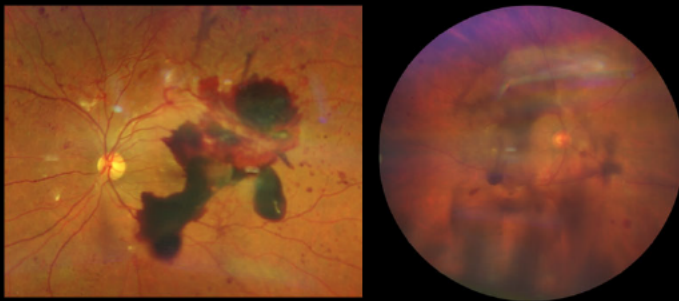
COMMON CAUSES OF VISION LOSS IN DR

Center-Involved DME (CI-DME)

Most common cause of VL & can occur at any stage of DR

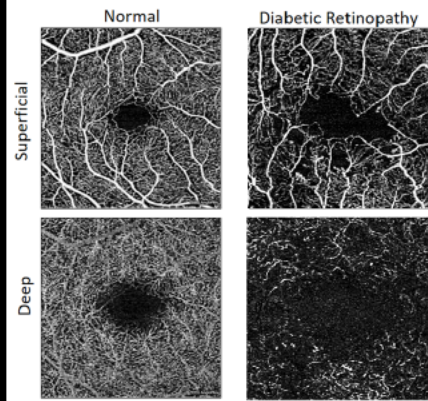


Preretinal/Vitreous Hemorrhage (Sudden onset)



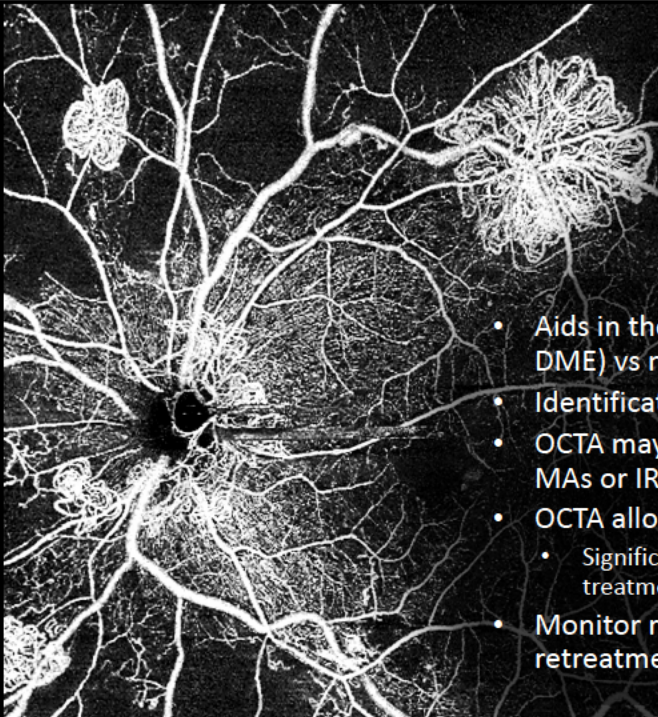
Macular Ischemia

OCTA 3mm Macula



38

UTILITY OF OCT/OCTA IN DME

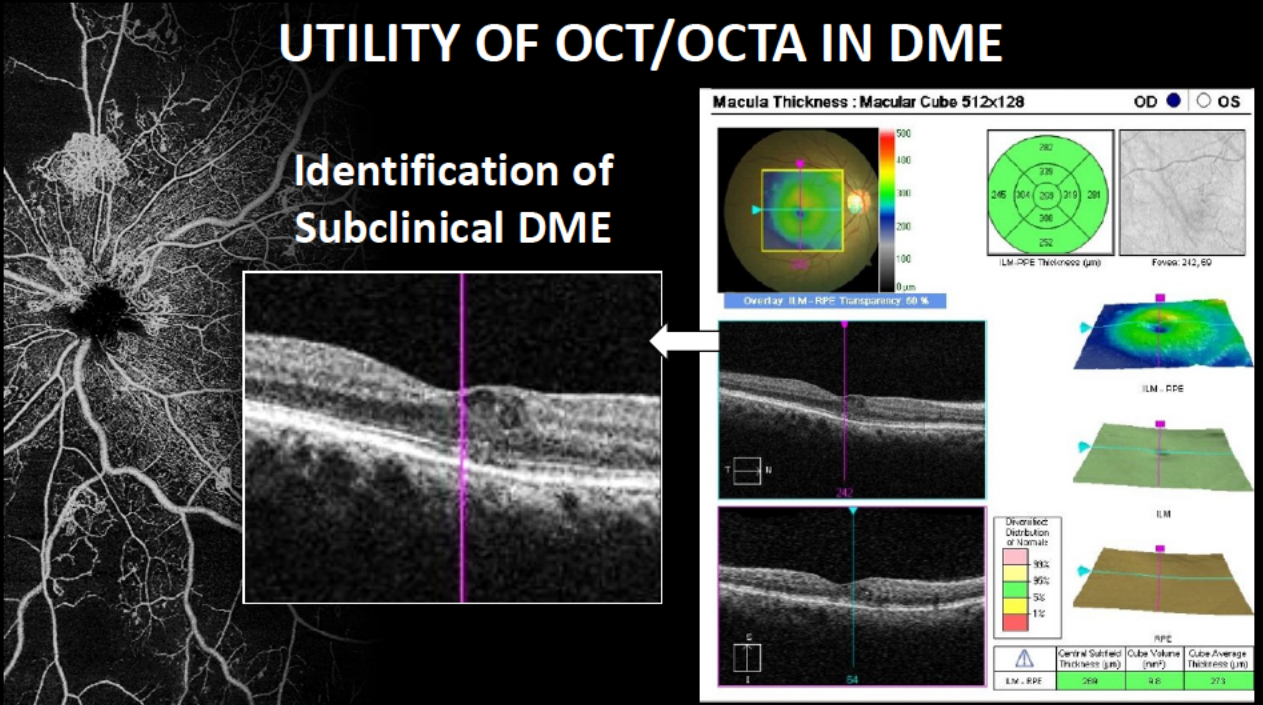


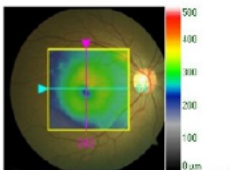
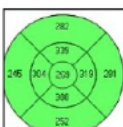
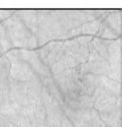
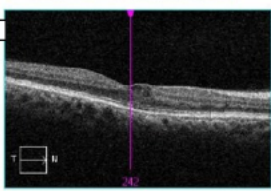
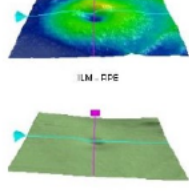
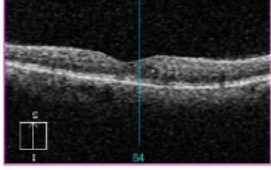
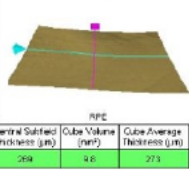
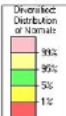
- Aids in the classification of DME as center involved (CI-DME) vs non-center involved (NCI-DME)
- Identification of subclinical DME
- OCTA may aid in identifying sources of DME such as MAs or IRMA
- OCTA allows for detection of macular ischemia
 - Significant macular ischemia = guarded prognosis following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

39

UTILITY OF OCT/OCTA IN DME

Identification of Subclinical DME



Macula Thickness : Macular Cube 512x128											
		OD	OS								
											
											
											
		<table border="1"> <thead> <tr> <th></th> <th>Central Subfield Thickness (µm)</th> <th>Cube Volume (µm³)</th> <th>Cube Average Thickness (µm)</th> </tr> </thead> <tbody> <tr> <td>ILM - DPE</td> <td>294</td> <td>40</td> <td>273</td> </tr> </tbody> </table>			Central Subfield Thickness (µm)	Cube Volume (µm³)	Cube Average Thickness (µm)	ILM - DPE	294	40	273
	Central Subfield Thickness (µm)	Cube Volume (µm³)	Cube Average Thickness (µm)								
ILM - DPE	294	40	273								

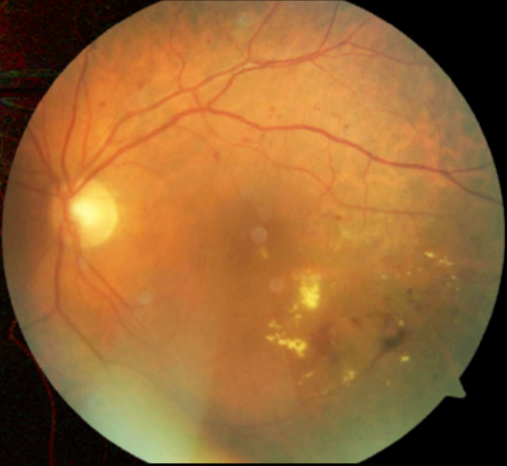
40

THE CASE OF THE FORLORN FOVEA

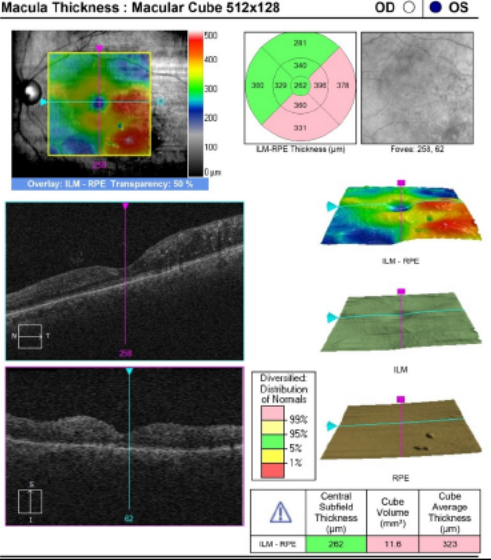
OCTA- Identify Macular Ischemia

61yo Hispanic Male

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



Macula Thickness : Macular Cube 512x128 OD ○ ● OS



Overlay: ILM - RPE Transparency: 50.5%

ILM - RPE

ILM

RPE

	Central Subfield Thickness (µm)	Cube Volume (mm³)	Cube Average Thickness (µm)
ILM - RPE	262	11.6	323

Diversified Distribution of Normals

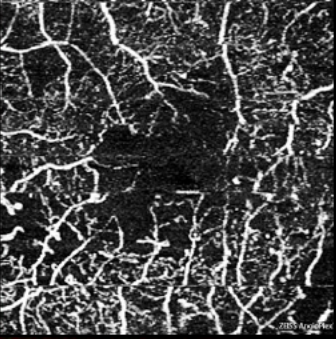
- 95%
- 5%
- 1%

41

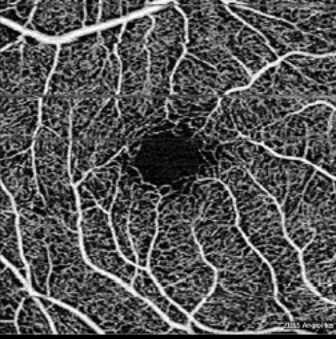
THE CASE OF THE FORLORN FOVEA

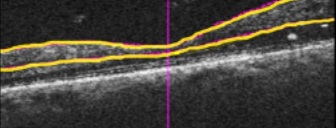
OCTA- Identify Macular Ischemia

Macular Ischemia



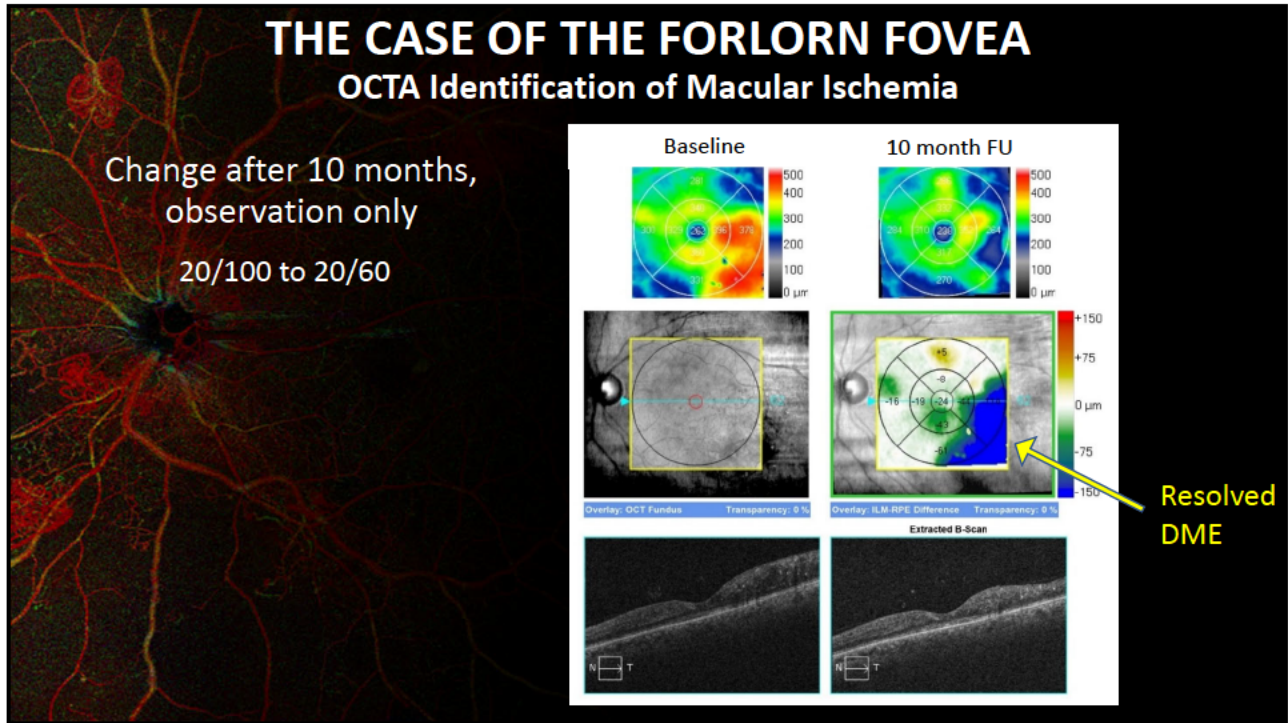
Normal





OCT Angiography (3mm Macula)

42



43

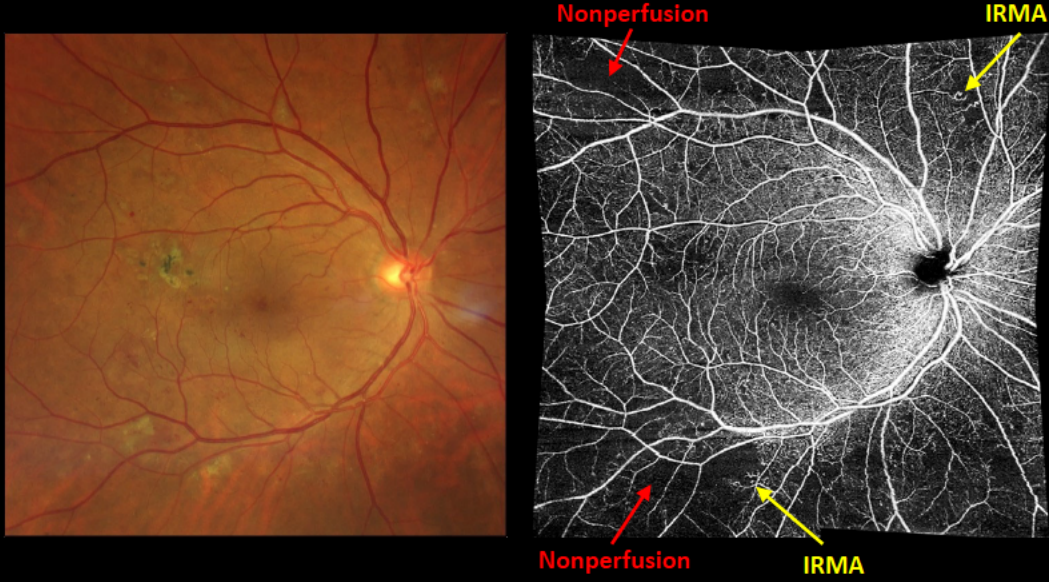
MANAGEMENT OF DME

- **Who should be treated (anti-VEGF 1st line therapy)?**
 - **CI-DME with VA 20/32 or worse- referral within 2-4 weeks (AOA-CPG 2019)**
- **Who can usually be observed?**
 - NCI-DME
 - 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
- 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

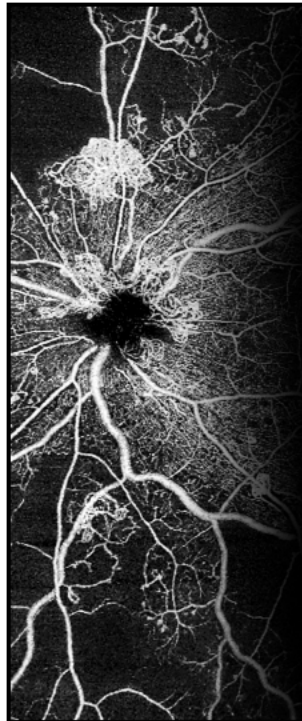
44

Utility of OCT/OCTA in **Mild-Moderate NPDR**

- OCTA highlights subtle vascular abnormalities = more accurate DR staging



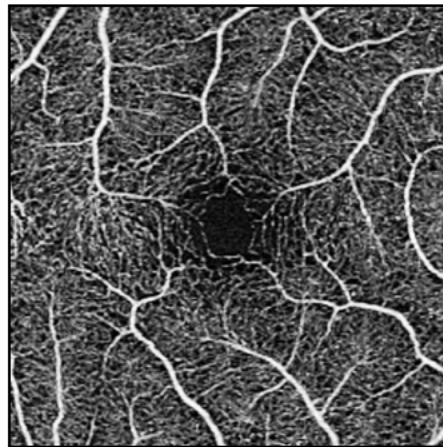
45



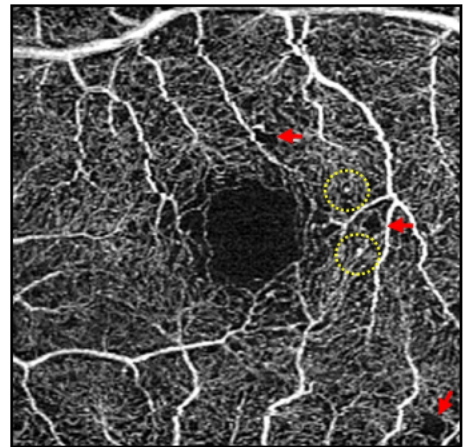
OCTA DETECTION OF SUBCLINICAL DR

NO CLINICALLY DETECTABLE DR!!!

Normal

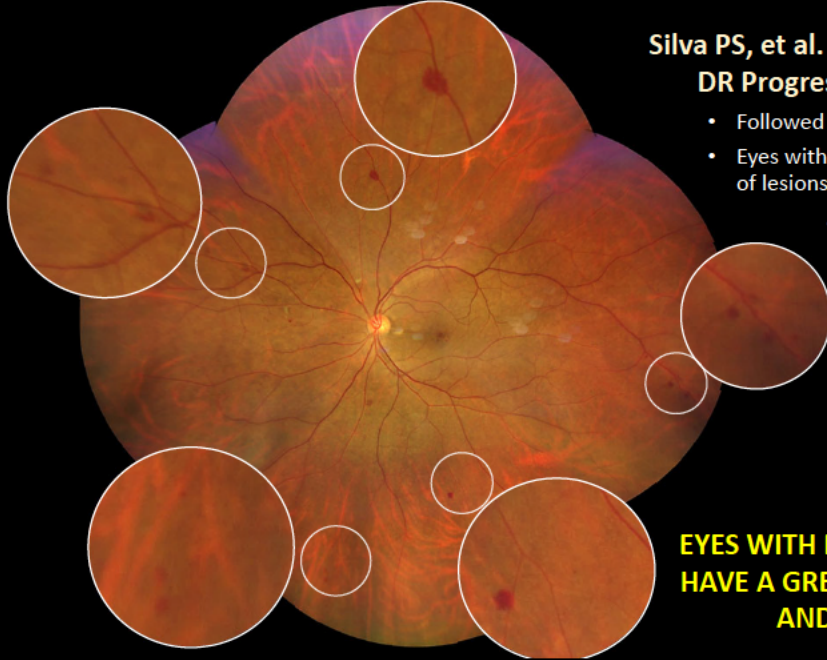


Diabetic without DR



46

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 = majority of lesions outside the 75° ETDRS standard 7 fields
- Compared to eyes without, eyes with predominately peripheral DR had ↑ risk of DR progression and a 4.7-fold ↑ risk for progression to PDR (6% vs. 25%).

DRCR.net Protocol AA

- ↑ risk of DR progression with UWF FA predominately peripheral lesions but not with CFP
- Greater risk with worsening FA NP index

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

47

MANAGEMENT OF SEVERE NPDR-LOW RISK PDR

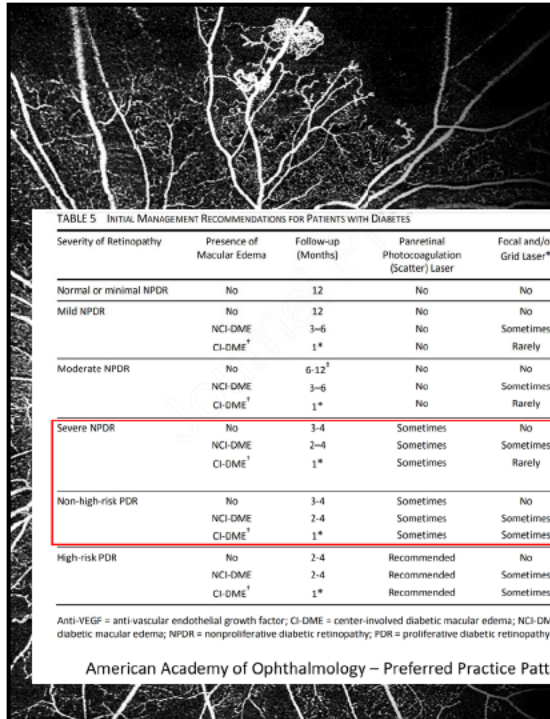


TABLE 5 INITIAL MANAGEMENT RECOMMENDATIONS FOR PATIENTS WITH DIABETES

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 CI-DME [†]	3-6 1*	No No	Sometimes Rarely	No Usually
Moderate NPDR	No	6-12 [‡]	No	No	No
	NCI-DME CI-DME [†]	3-6 1*	No No	Sometimes Rarely	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 ^{§,100}
	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

- Refer all regardless of DME status

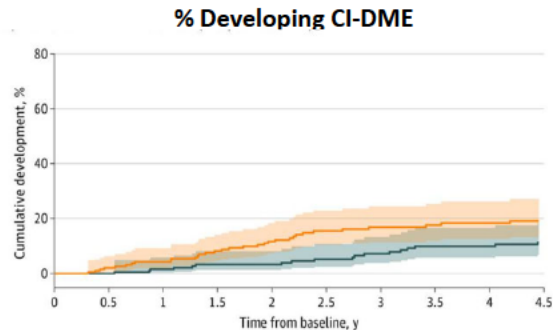
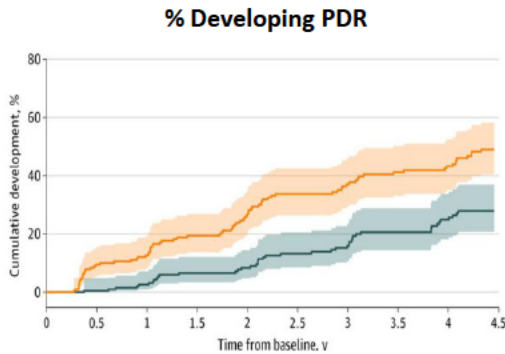
- Start considering anti-VEGF therapy/PRP at the severe NPDR stage **even without CI-DME** (optional)

- Anti-VEGF: reverse DR stage/prevent development of vision threatening complications
- Both ranibizumab and aflibercept FDA approved even if no DME

48

DRCR.net Protocol W- Effect of Intravitreal anti-VEGF vs Sham for Prevention of Vision-Threatening Complications of DR, 4 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 (11% vs 19%) or PDR (28% vs 49%) in treated eyes vs sham at 2 years
- Change in VA at 4 years: -2.7 letters vs -2.4 letters (not significant)



Maturi RK, et al. 4-Year Visual Outcomes in the Protocol W Randomized Trial of Intravitreal Aflibercept for Prevention of Vision-Threatening Complications of DR. JAMA Ophthalmology 2023.

49

UTILITY OF IMAGING IN SEVERE NPDR-LOW RISK PDR

Wide-field Fundus Imaging

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

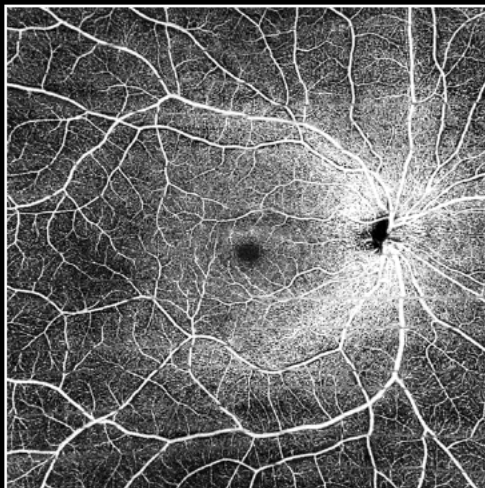
OCT/OCTA

- 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

50

MANAGEMENT OF SEVERE NPDR-LOW RISK PDR

Normal



Very Severe NPDR

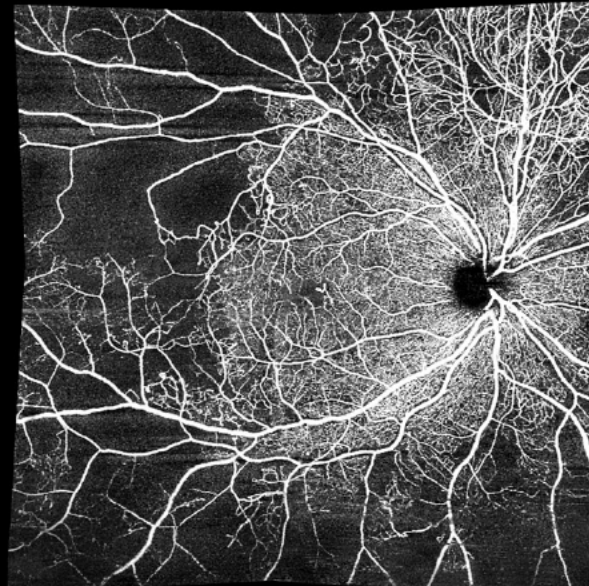


- Increased risk for progression to PDR
- Consider early PRP/anti-VEGF treatment

51

Utility of OCTA Montage Imaging in DR

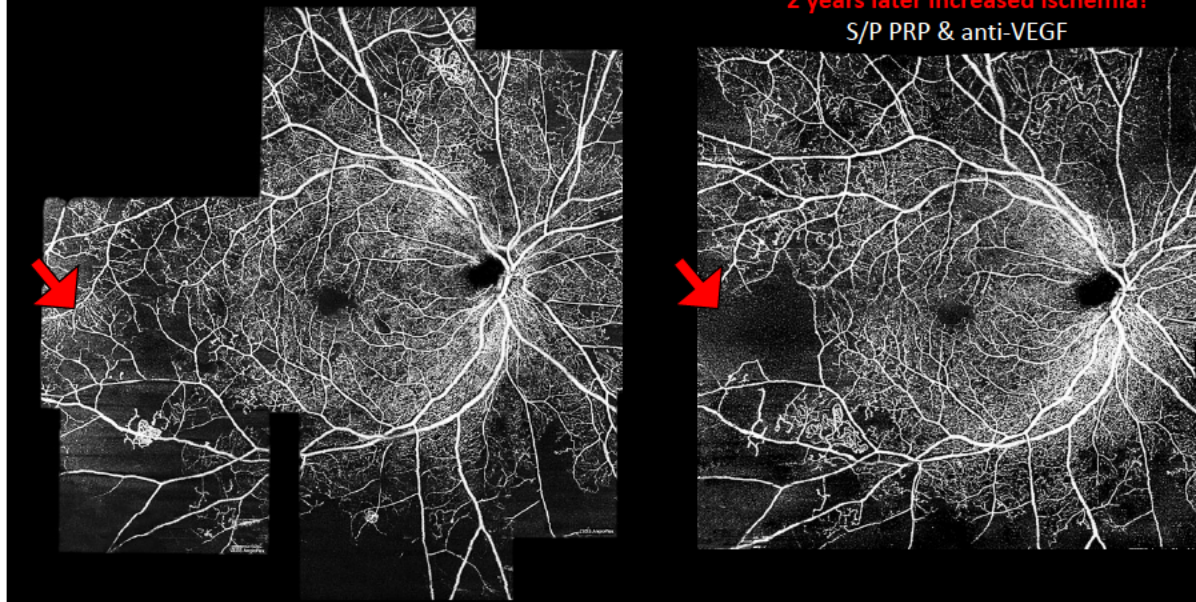
OCTA – Visualization of peripheral NP (nearly invisible without)



52

Ischemic disease progressing despite treatment!

~ 2 years later increased ischemia!
S/P PRP & anti-VEGF



53

www.pollev.com/retina



When poll is active, respond at pollev.com/retina

Text **RETINA** to **37607** once to join

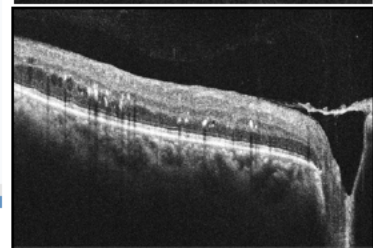
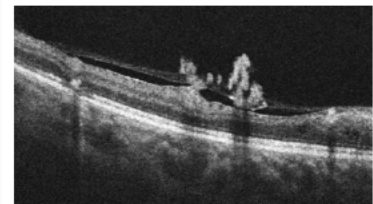
Pre-retinal neovascularization is best defined as:

Dilated, telangiectatic capillaries within the retina.

New vessels growing within the retina.

New vessels growing between the NFL and the ILM of the retina.

New vessels growing between the ILM of the retina and the posterior hyaloid of the vitreous.

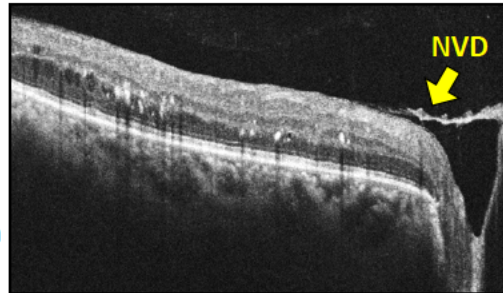
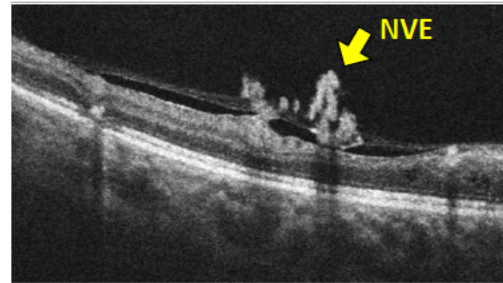
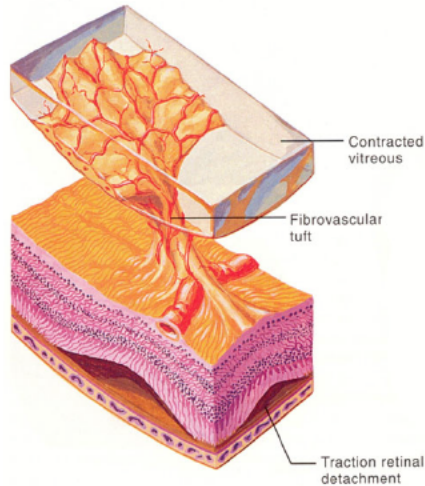


Start the presentation to see live content. For screen share software, share the entire screen. Get help at pollev.com/app

54

PROLIFERATIVE DIABETIC RETINOPATHY

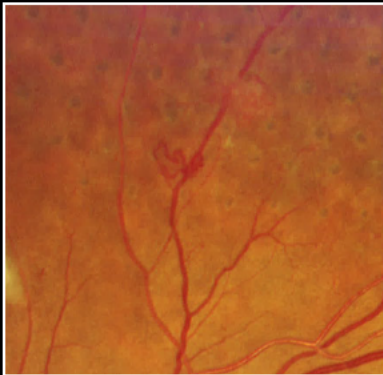
Preretinal Neovascularization



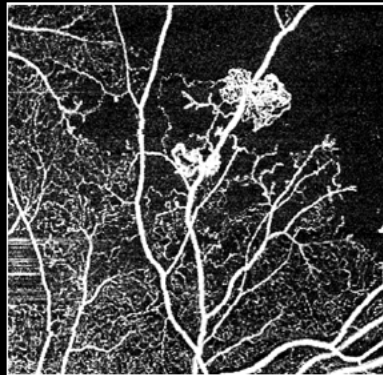
Most often characterized by **new blood vessel growth located between the ILM and the posterior hyaloid**

55

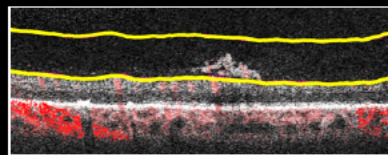
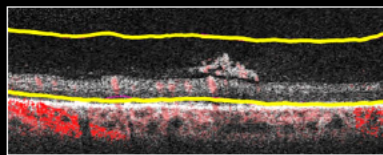
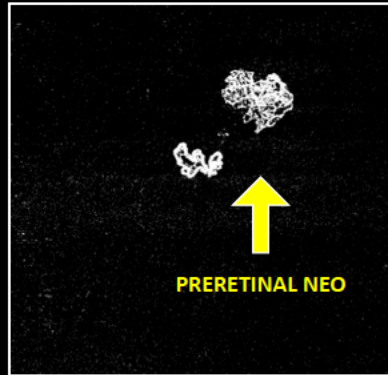
UTILITY OF OCT/OCTA IN SEVERE NPDR-LOW RISK PDR IRMA or early NVE???



Retina



Vitreoretinal Interface (VRI)

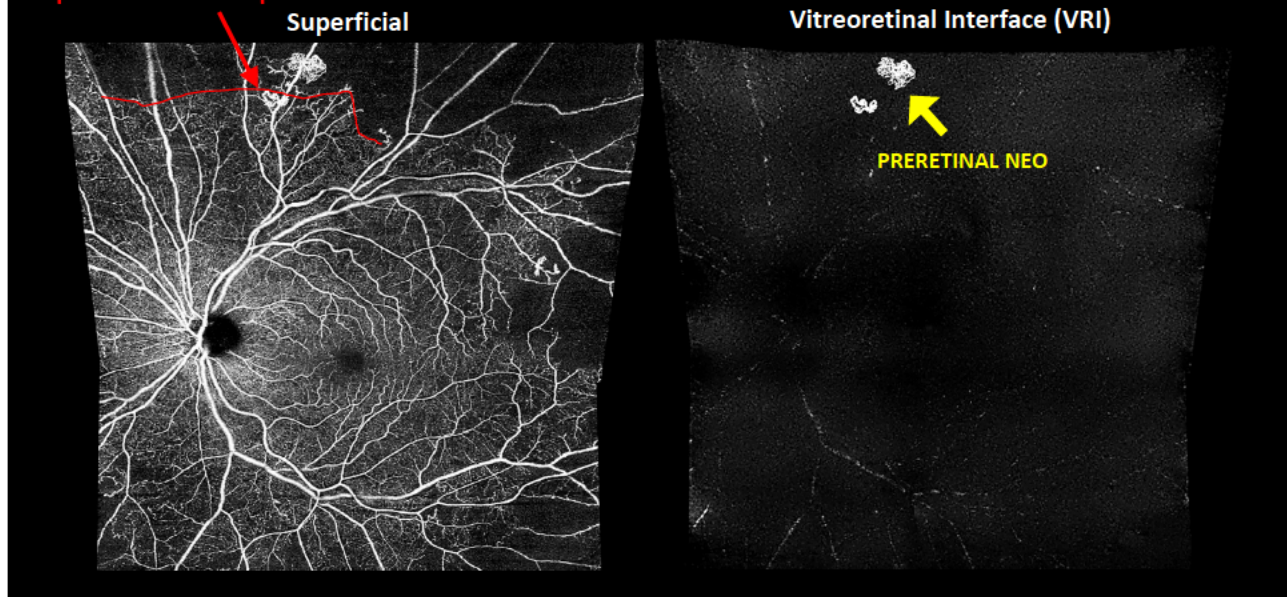


56

Utility of OCTA Montage Imaging in DR

Neo often forms at the border of perfusion and nonperfusion

Isolate Preretinal Neo!



57

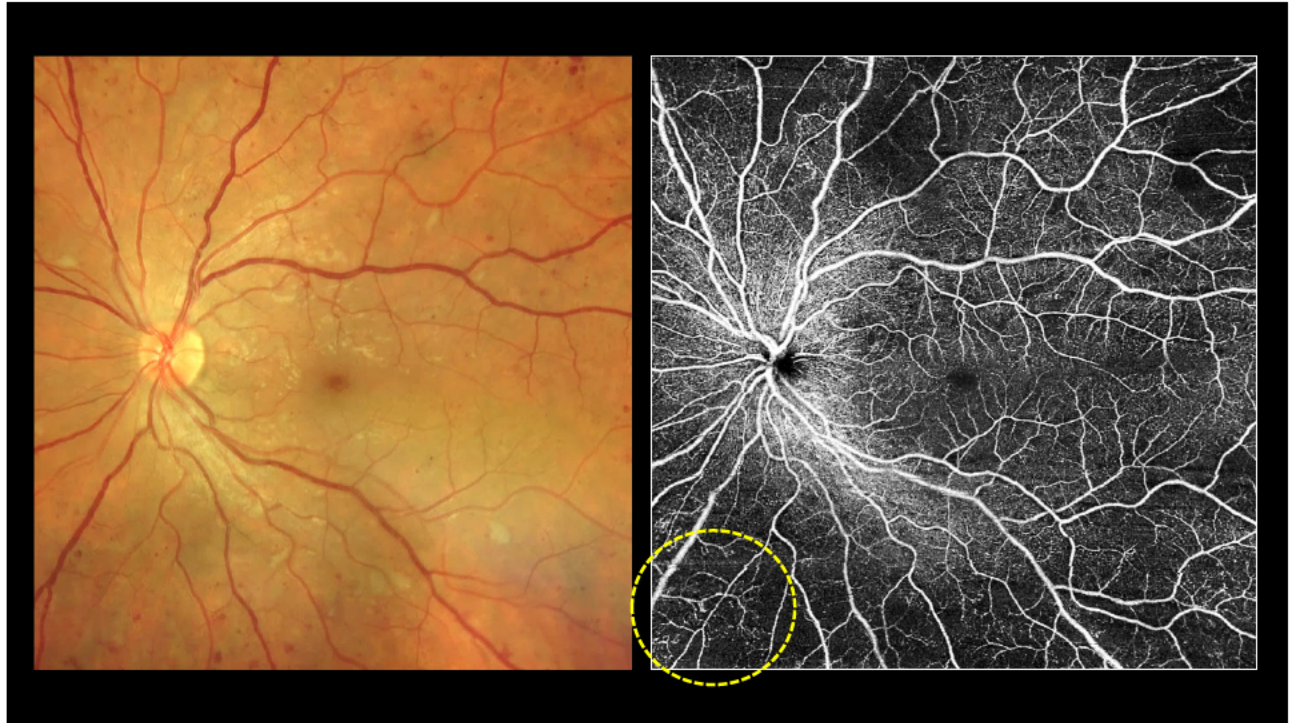
PROLIFERATIVE OR NONPROLIFERATIVE (NVE OR IRMA)?

43yo Native American male

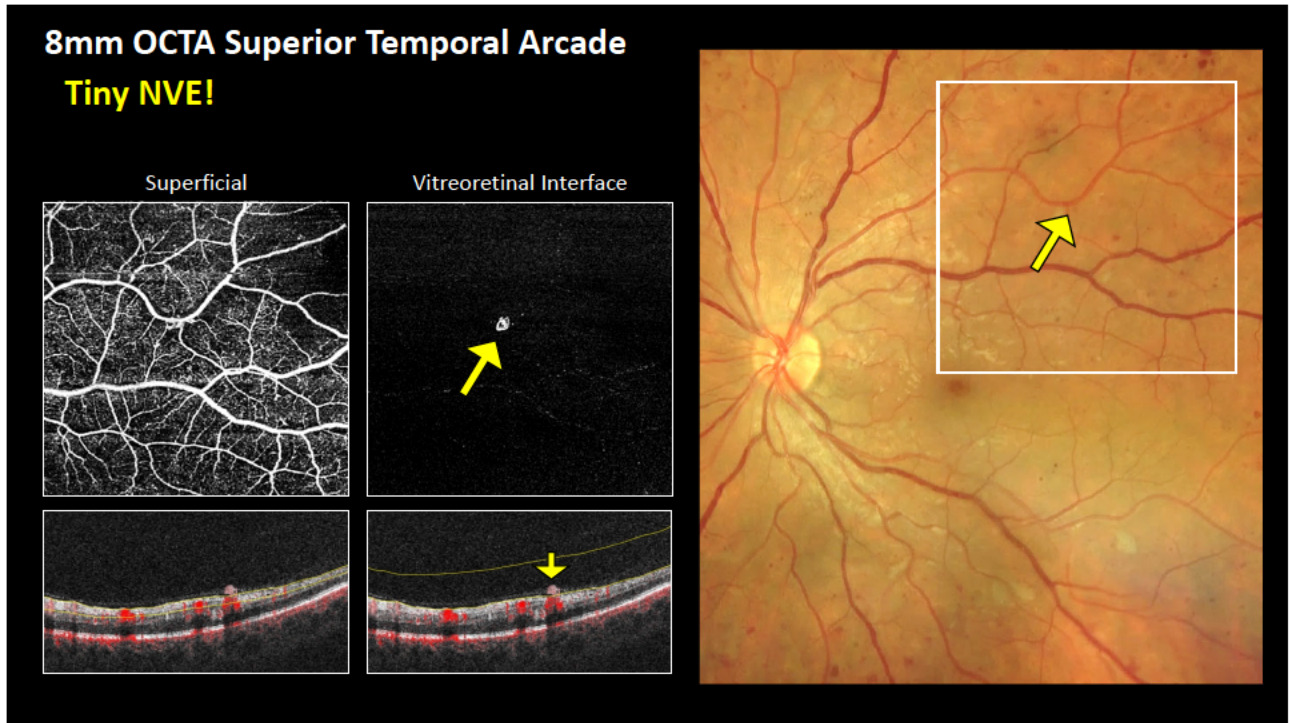
- CC: Stable vision OU.
- LEE: 1 yr ago diagnosed with moderately-severe NPDR
- Type 2 DM x 18 years (HbA1C 8.5%)
- VA (cc @ dist)
 - OS: 20/20
- BP: 142/85



58



59



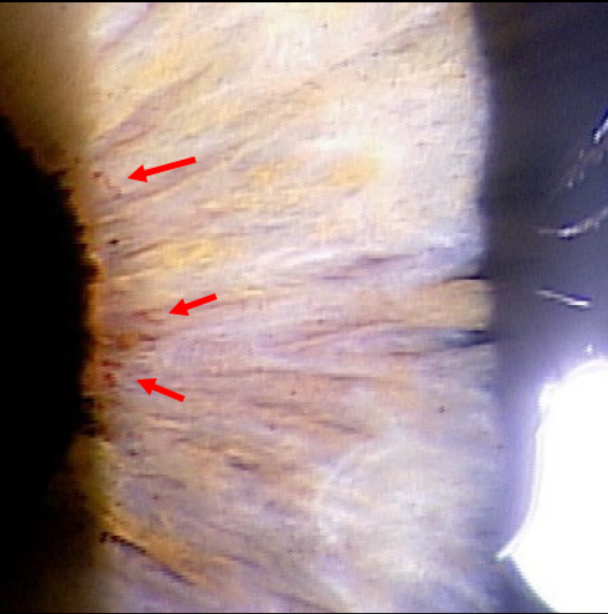
60

PROLIFERATIVE OR NONPROLIFERATIVE (NVE OR IRMA)?

Ant Seg OS

**DX: Low risk PDR with
early NVI**

**TX: Referred to retina,
performed PRP OU**



61

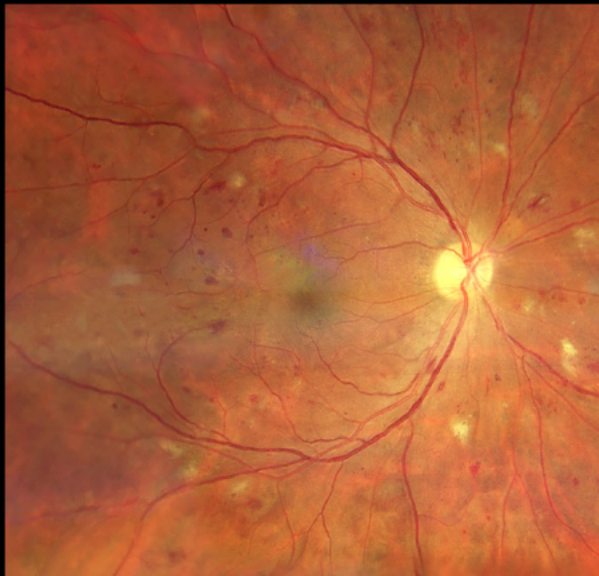
HOW WOULD YOU STAGE THIS PATIENT'S DR?



62

OCTA MONTAGE 14mm x 14mm

Superficial

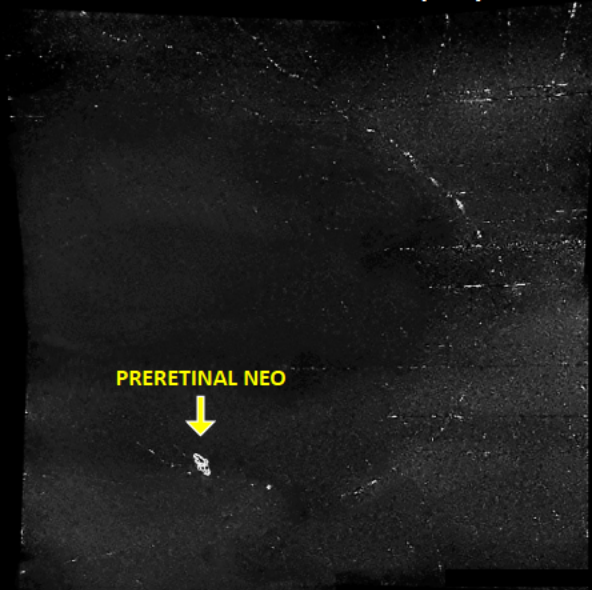
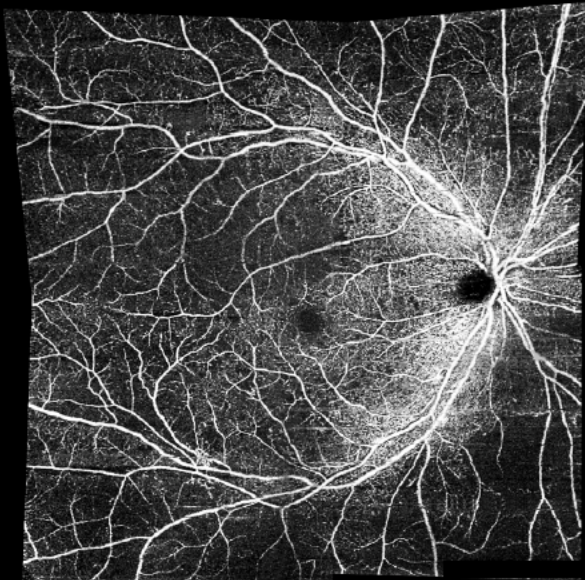


63

OCTA MONTAGE – Isolate Preretinal Neo!

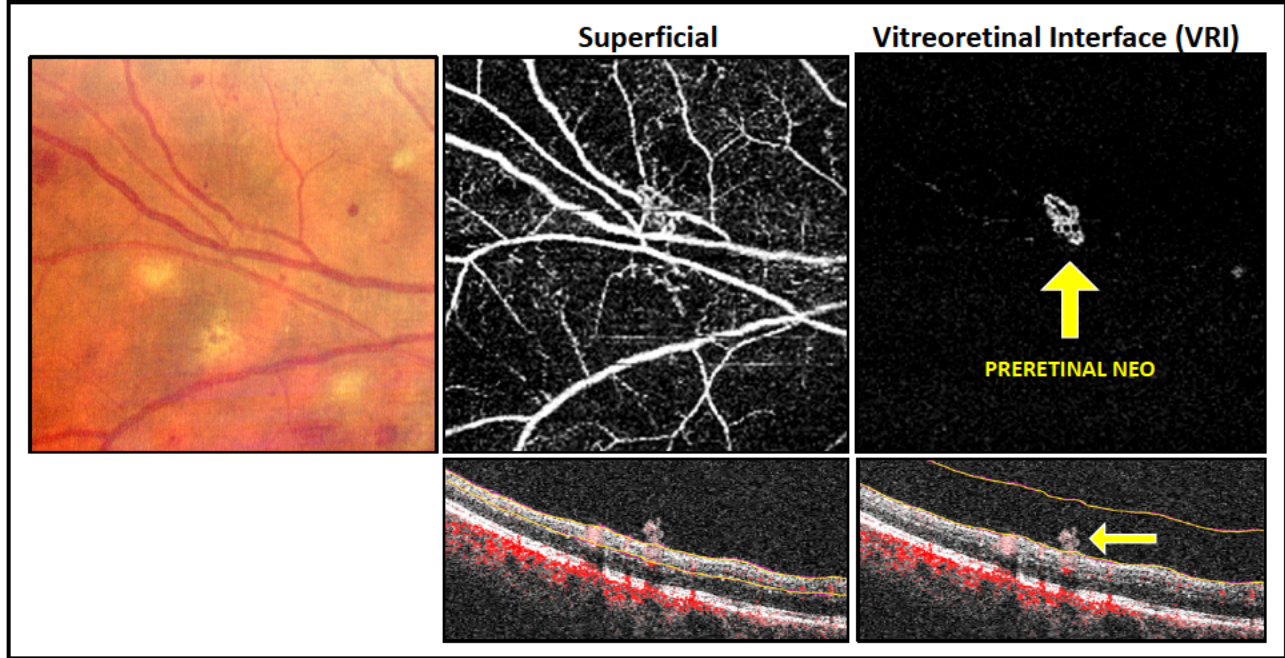
Superficial

Vitreoretinal Interface (VRI)



64

OCTA – Isolate Preretinal Neo!



65

CASE 2: HOW WOULD YOU STAGE THIS PATIENT'S DR?

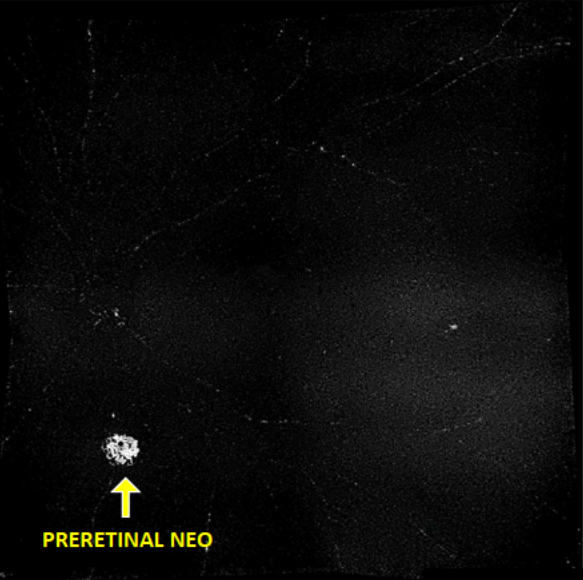
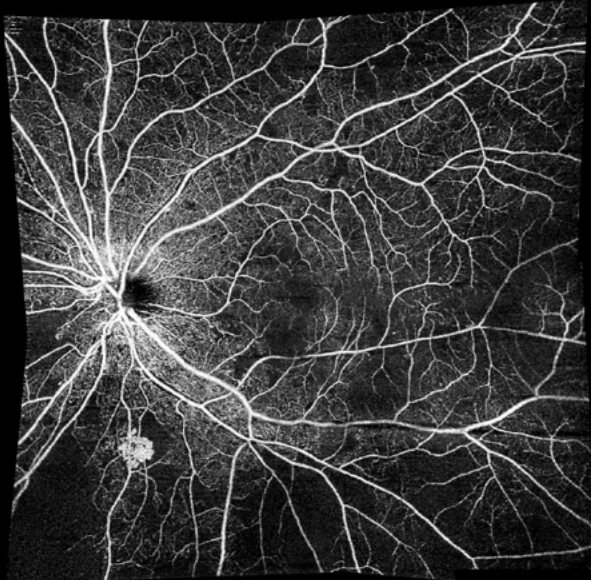


66

OCTA MONTAGE – Isolate Preretinal Neo!

Superficial

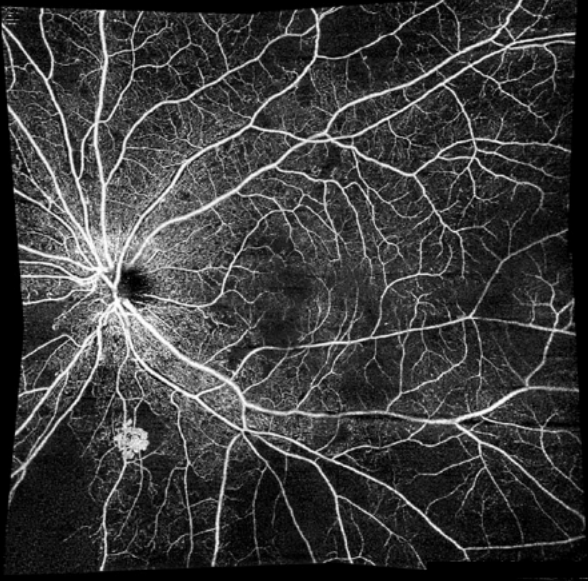
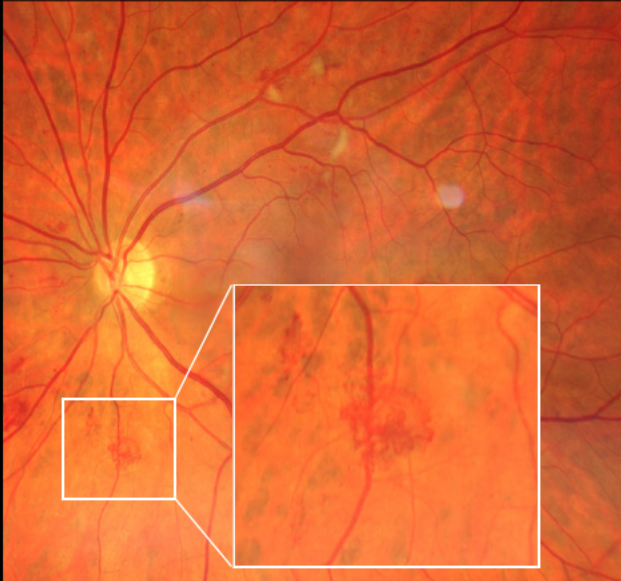
Vitreoretinal Interface (VRI)



67

OCTA MONTAGE 14mm x 14mm

Superficial



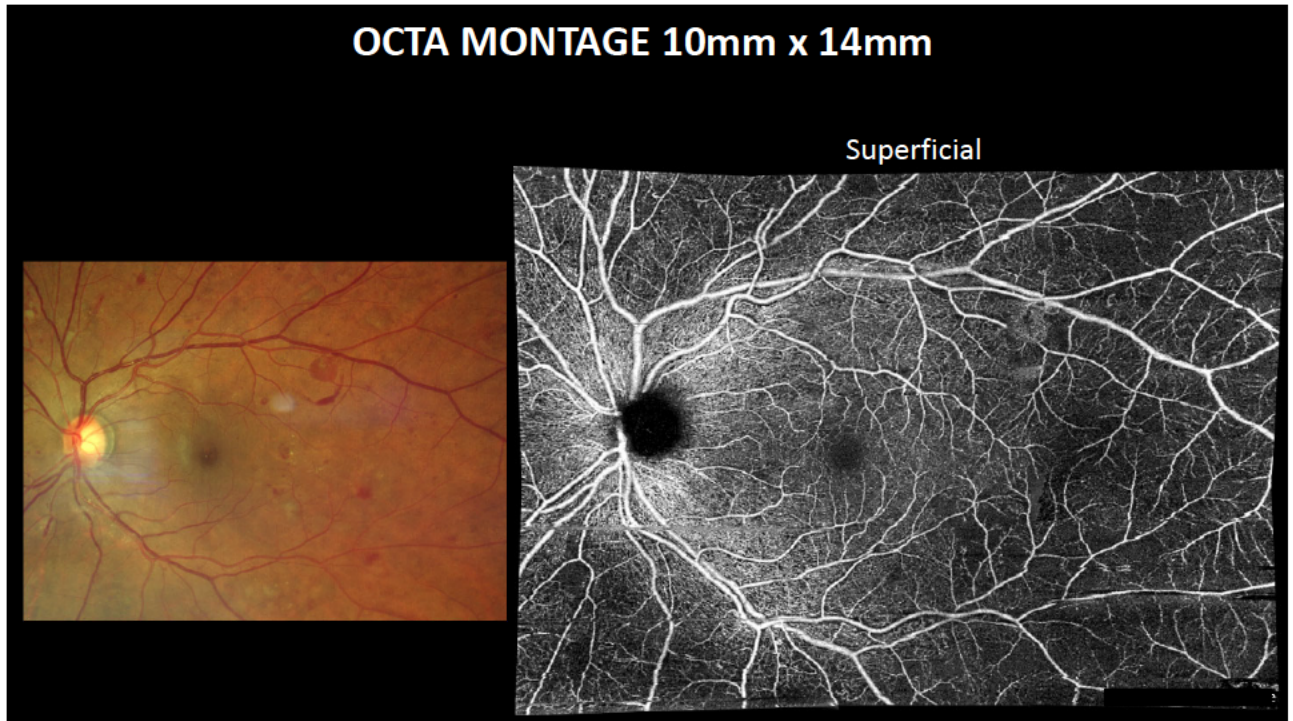
68

CASE 3: HOW WOULD YOU STAGE THIS PATIENT'S DR?



69

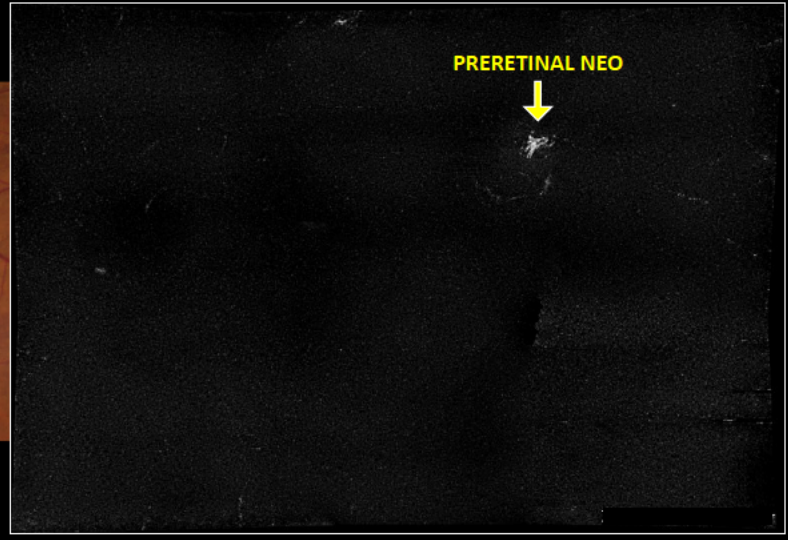
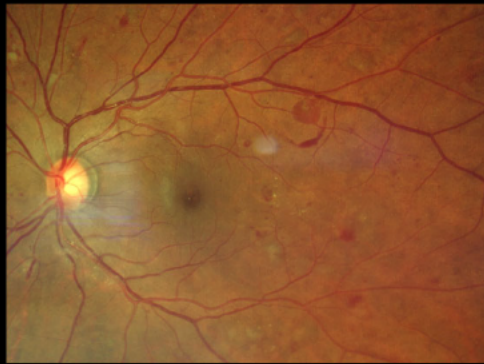
OCTA MONTAGE 10mm x 14mm



70

OCTA MONTAGE – Isolate Preretinal Neo!

Vitreoretinal Interface (VRI)

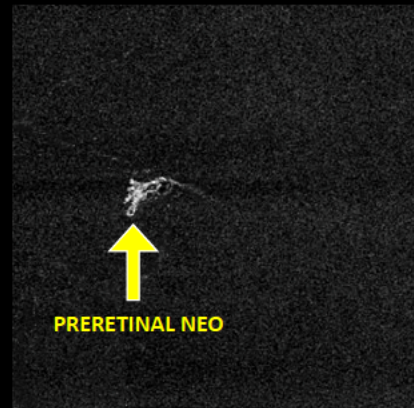
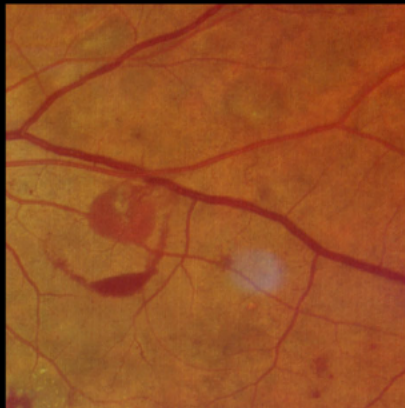


71

OCTA MONTAGE – Isolate Preretinal Neo!

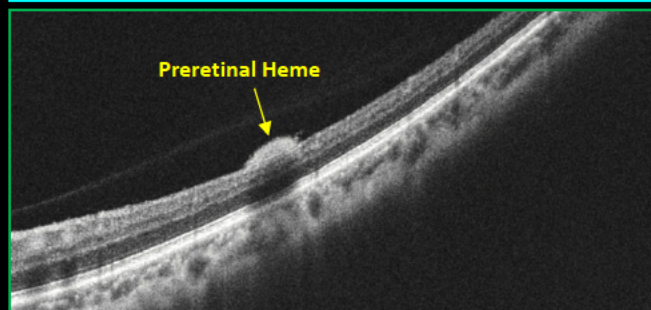
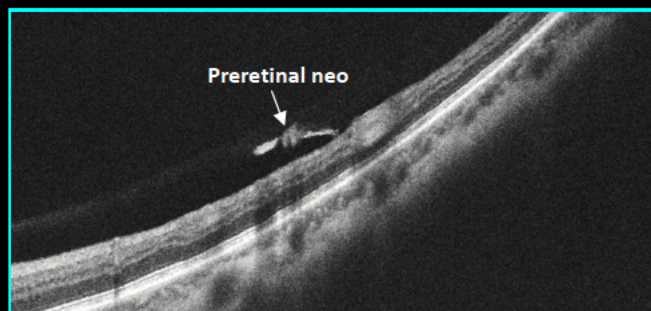
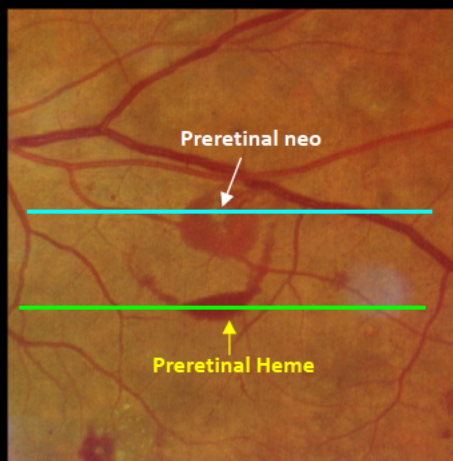
Superficial

Vitreoretinal Interface (VRI)

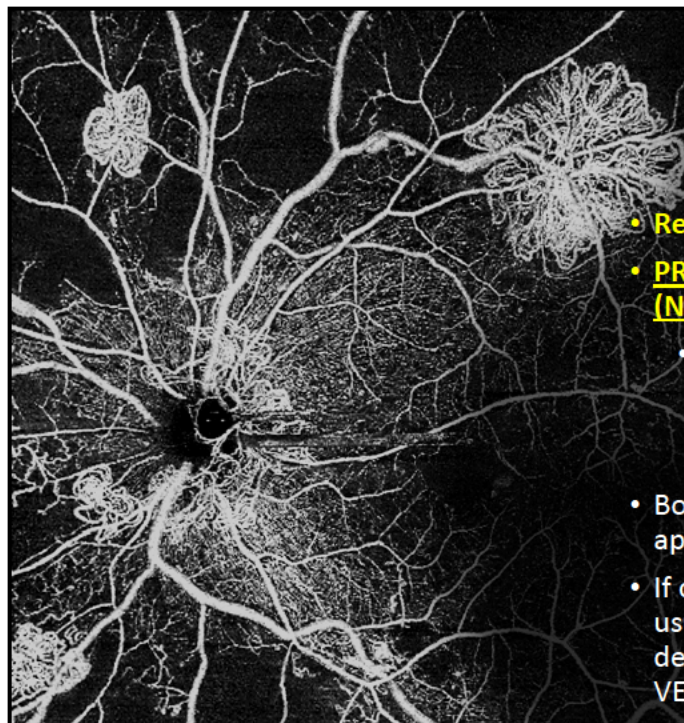


72

PDR – PRERETINAL NEO AND PRERETINAL HEME



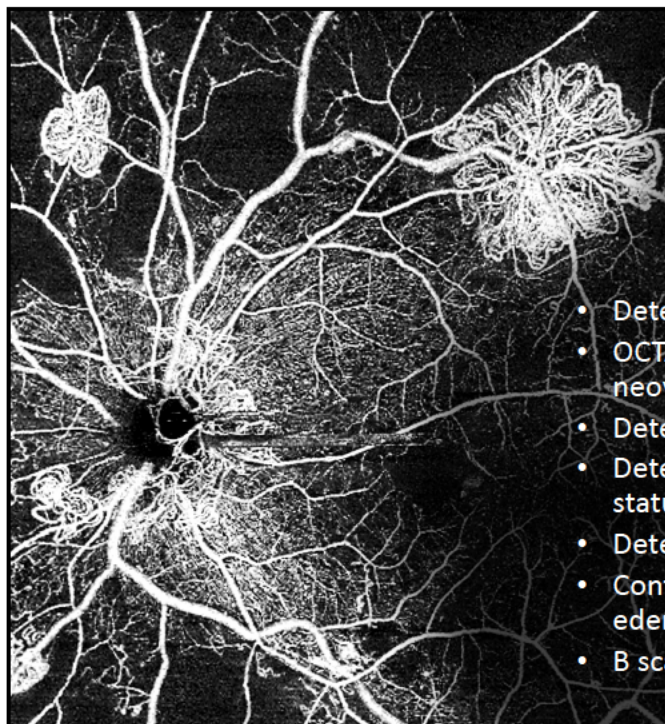
73



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 (DRCR.net protocol S) but retracted somewhat in 2019 version.....
- Both ranibizumab and aflibercept 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

74



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

75

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

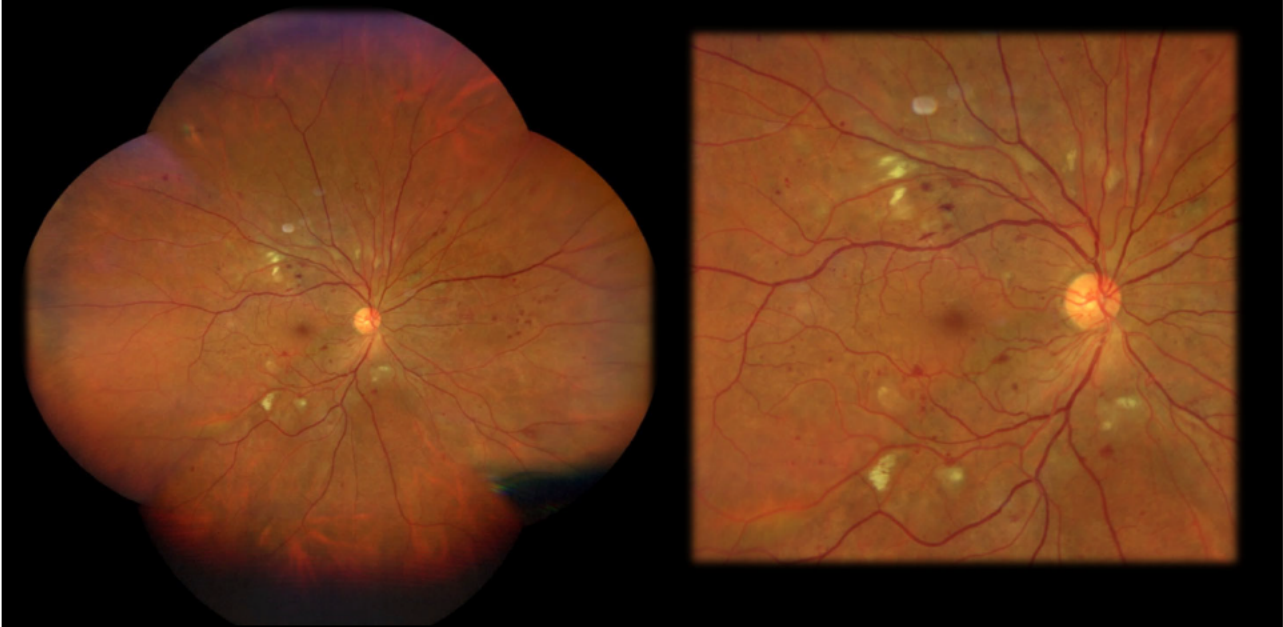
50yo Native American male

- 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**



76

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



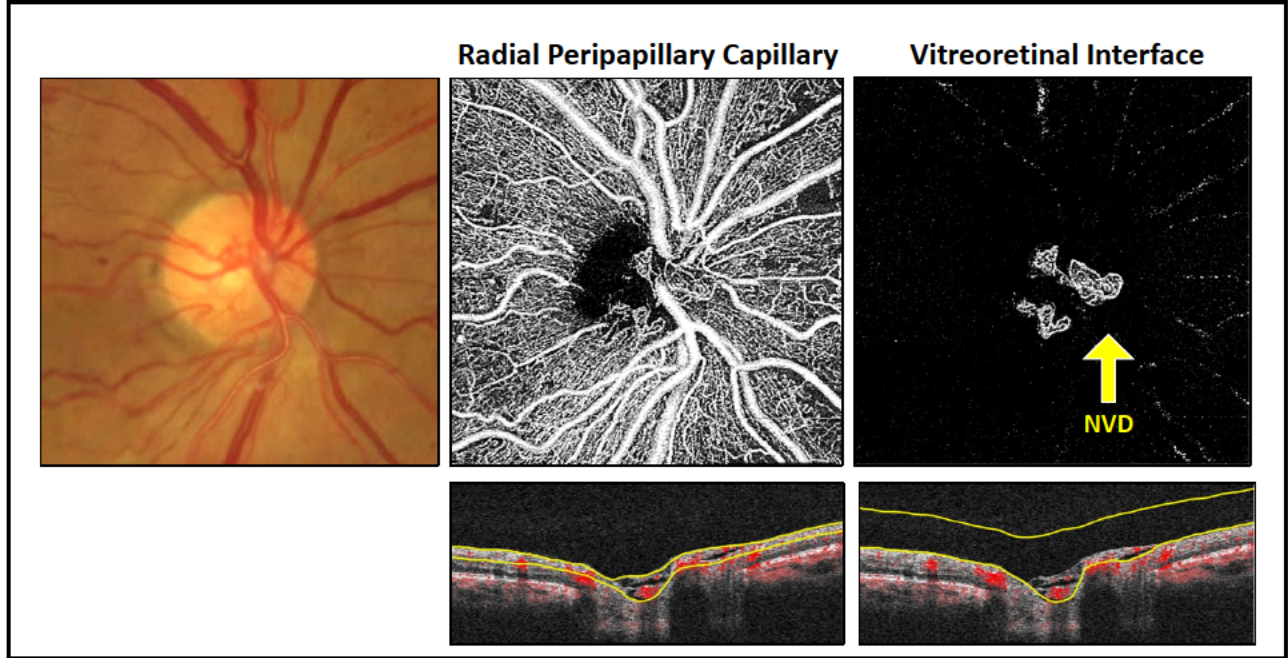
77

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

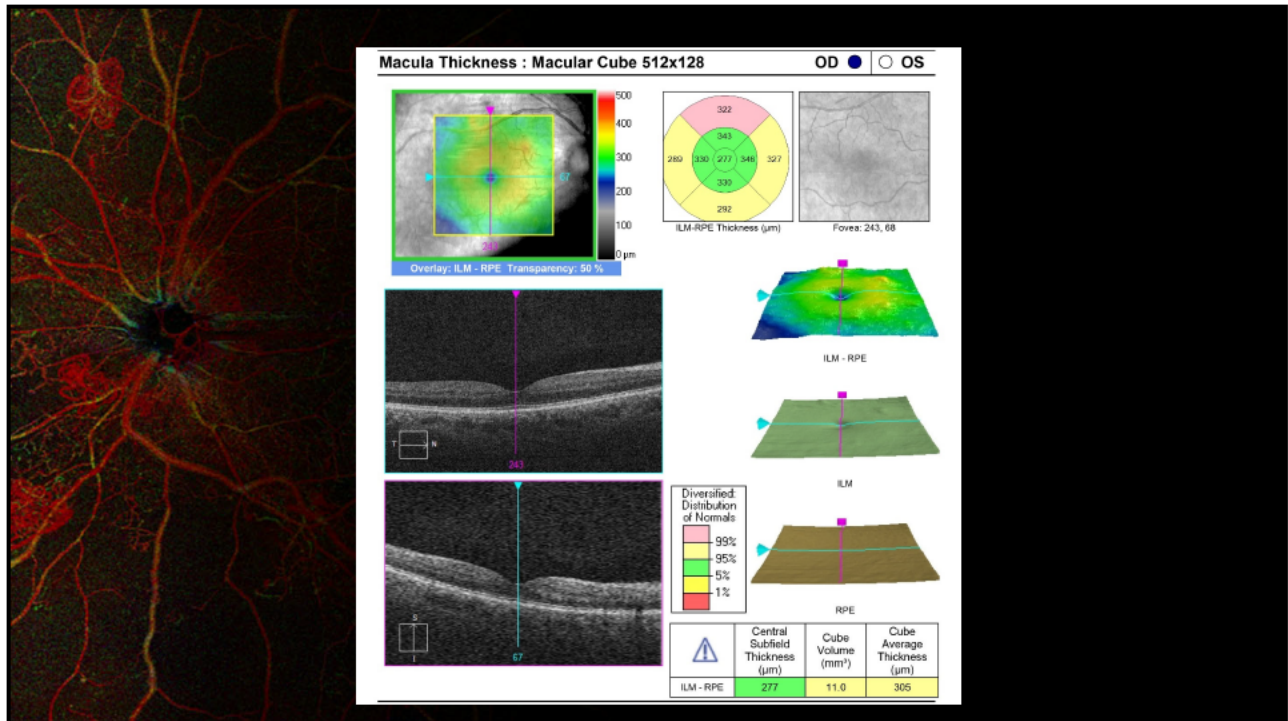


78

OCTA 4.5mm Optic Nerve



79



80

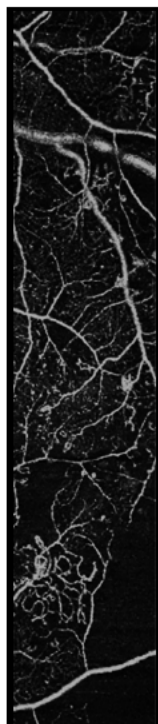


TABLE 5 INITIAL MANAGEMENT RECOMMENDATIONS FOR PATIENTS WITH DIABETES

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 ^{§5,188}
	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

81

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

Follow-up

- Sees retina within 6 weeks, diagnosed with severe NPDR OU
→ observe in 6 months
- 6 months later- PDR OD
→ PRP performed

Baseline



1 year later-still 20/20!

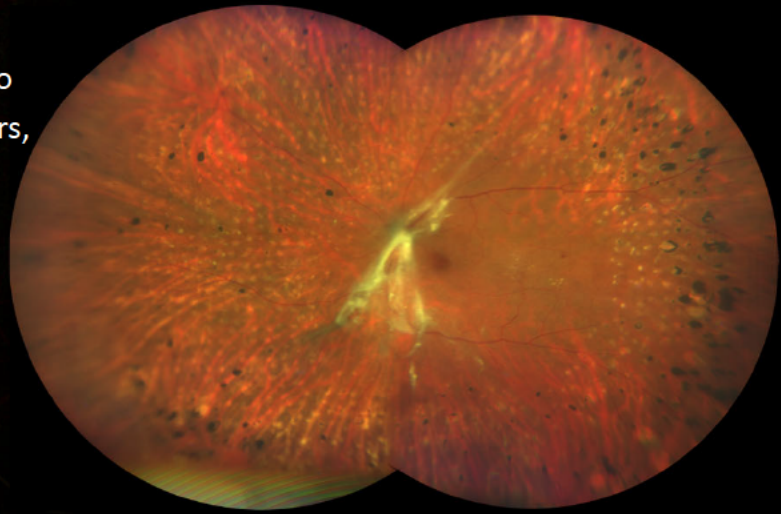


82

BREAKIN' UP IS HARD TO DO

49yo Native American 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

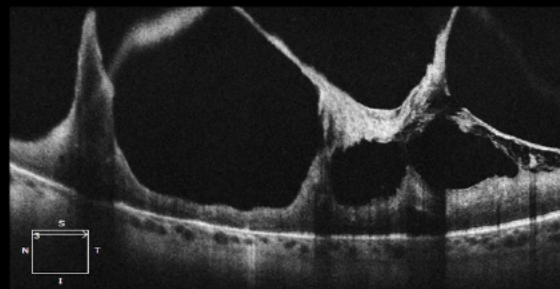
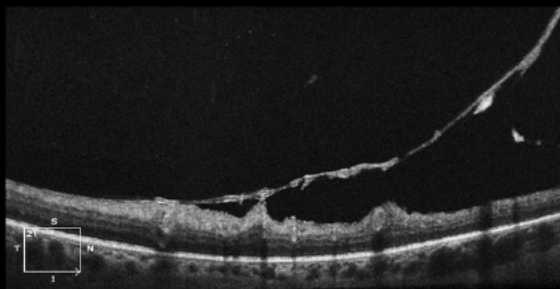
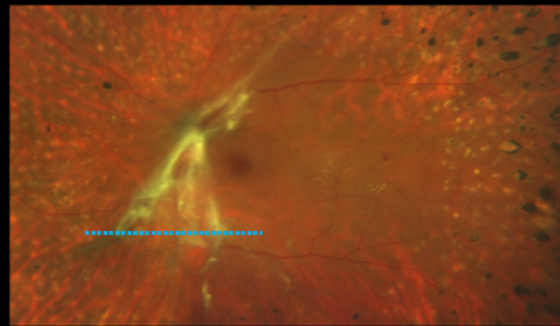
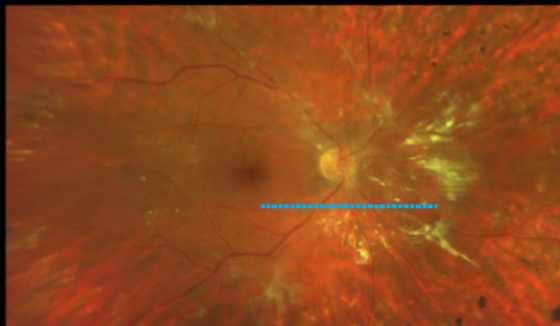


83

BREAKIN' UP IS HARD TO DO

Right Eye

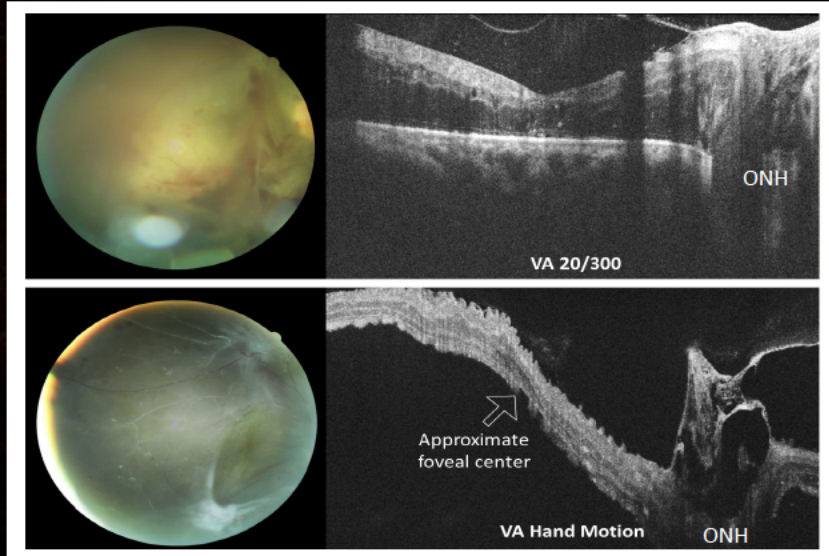
Left Eye



84

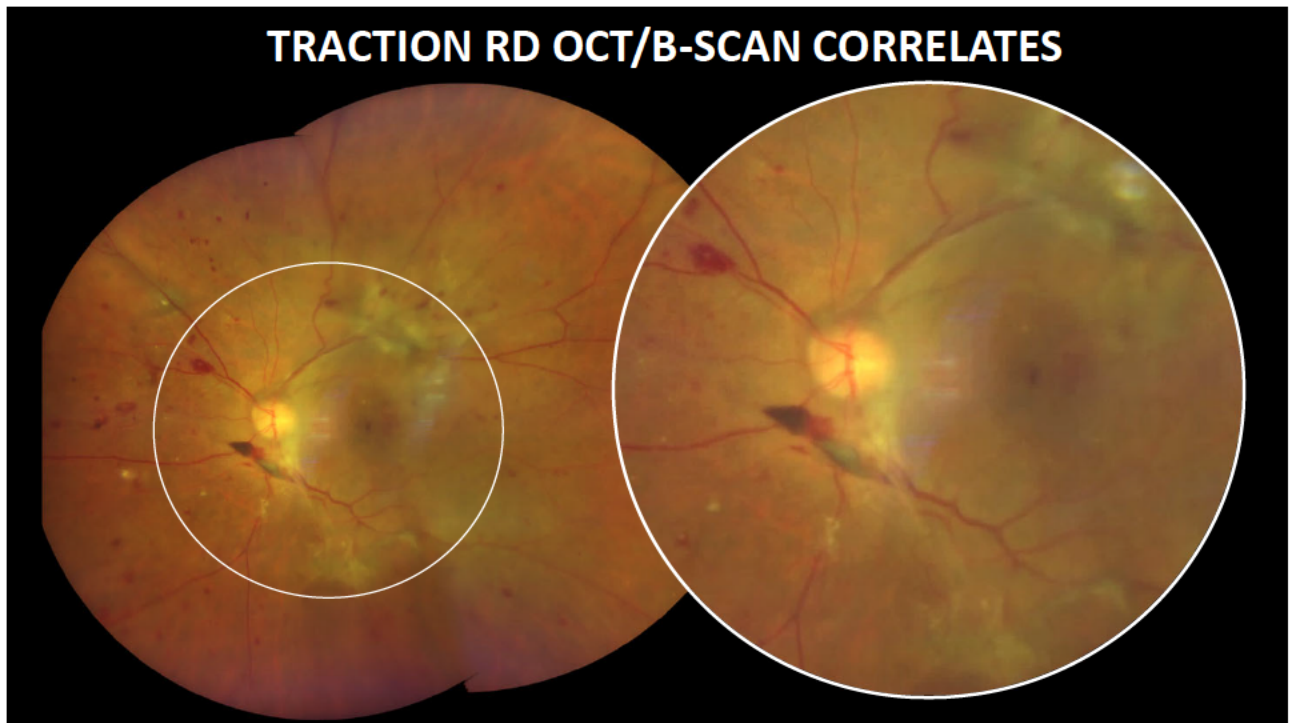
UTILITY OF OCT/OCTA IN HIGH-RISK PDR

Tractional RD- macular status?



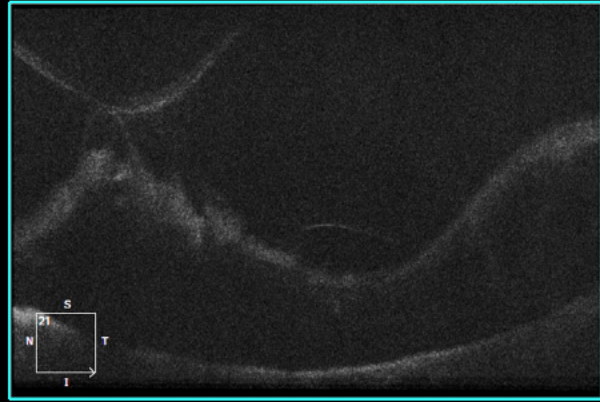
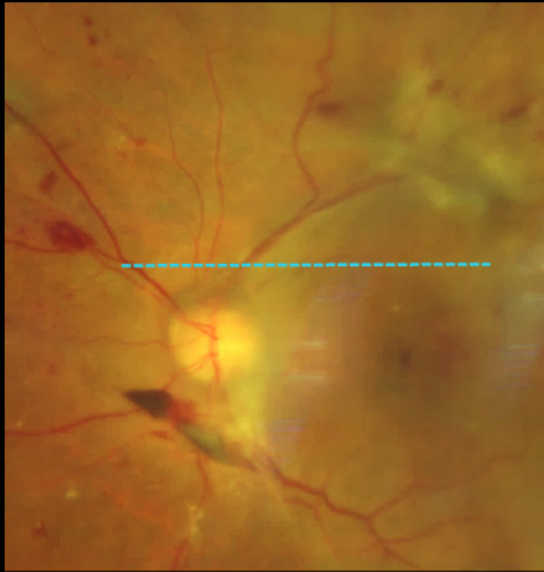
85

TRACTION RD OCT/B-SCAN CORRELATES



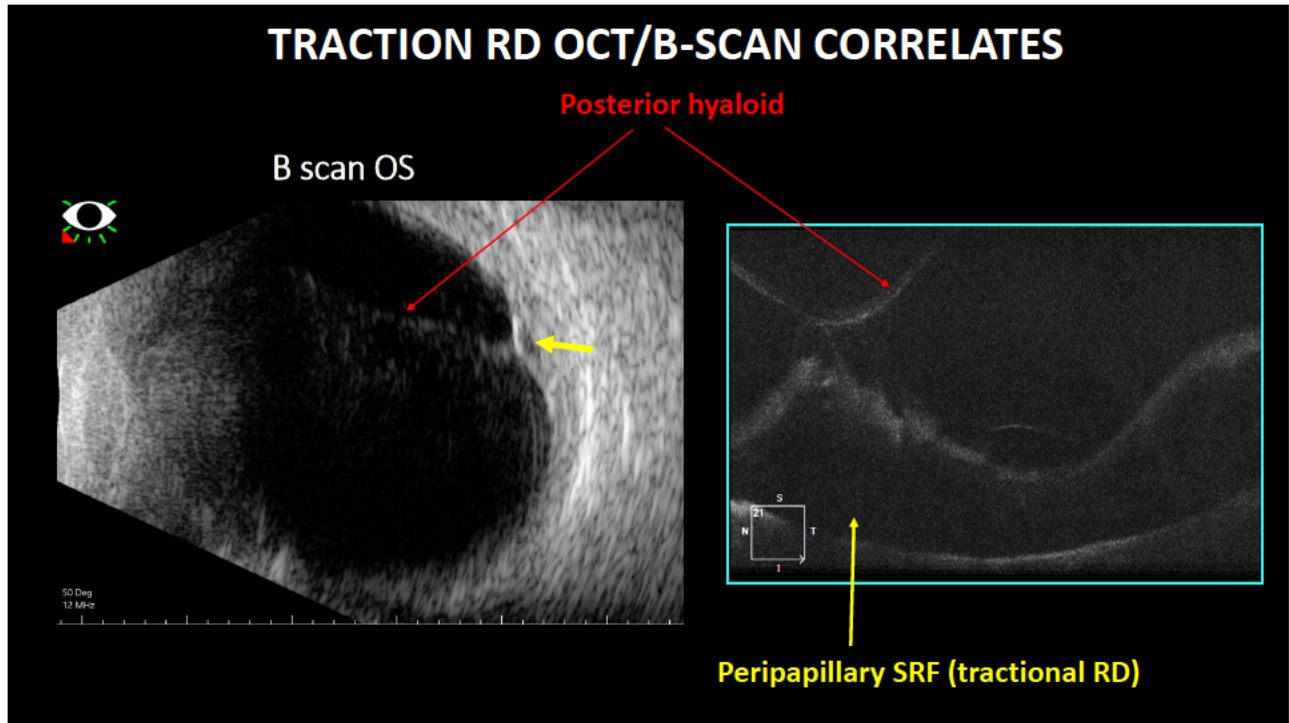
86

TRACTION RD OCT/B-SCAN CORRELATES



87

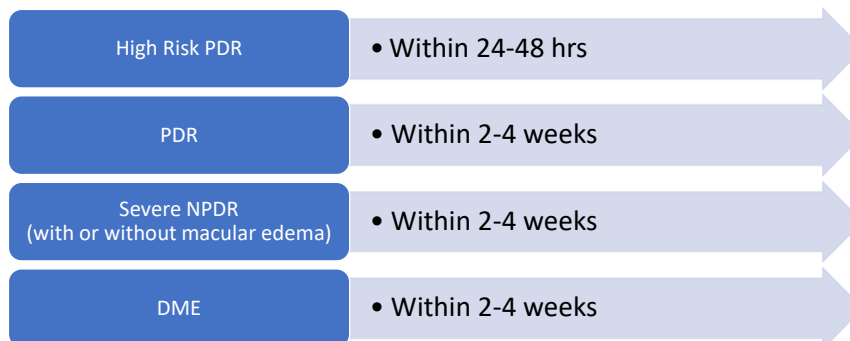
TRACTION RD OCT/B-SCAN CORRELATES



88

AOA-CPG REFERRAL RECOMMENDATIONS

When to refer to a retinal specialist:



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

Also consider referral when:

- You are unsure of retinopathy stage
- NVI/NVA (urgent)
- TRD

89

Anti-VEGF Biosimilars

Per the FDA:

- “A biosimilar is a biological product that is approved based on data showing that it is highly similar to a biological product already approved by the FDA (reference product) and has no clinically meaningful differences in terms of safety, purity and potency (i.e., safety and effectiveness) from the reference product, in addition to meeting other criteria specified by law.”

Currently, 2 FDA approved Ranibizumab Biosimilars

- Byooviz (Samsung) approved Sept 2021
- Cimerli (Coherus) approved Oct 2022

RETINA BIOSIMILARS APPROVED OR IN DEVELOPMENT

FDA-approved	
Name	Company
Byooviz (ranibizumab biosimilar)	Samsung/Bioepis
Cimerli (ranibizumab biosimilar)	Coherus
In-development	
Name	Company/country
<i>Ranibizumab biosimilars</i>	
Xlucane	Xbrane, Sweden; Phase III
R-TPR-024	Reliance Life Sciences, India; Phase III
SJP-0133	Serju Pharmaceuticals, Japan; Phase III
LUBT010	Lupin, India; Phase III
CKD-701	Chong Kun Dang Pharmaceutical, South Korea; Phase III
<i>Aflibercept biosimilars</i>	
SB15	Samsung Bioepis
MYL1701	Momenta Pharma and Viartis
ABP-938	Amgen, United States
FYB203	Formyon AG/Bioeq, Germany; Phase III nAMD
SDK583A19	Sandoz, Switzerland; Phase III nAMD
CT-P42	Celltrion, South Korea; Phase III DME
ALT-L9	Alteogen, South Korea; Phase I AMD
OT-702	Occumension Therapeutics/Shandong Boan Biological Technology, China; Phase III
<i>Bevacizumab biosimilar</i>	
Bevacizumab-vikg (Lytenava)	ONS-5010, Outlook Therapeutics, Phase III

www.reviewofophthalmology.com/article/an-update-on-the-antivegf-biosimilar-pipeline

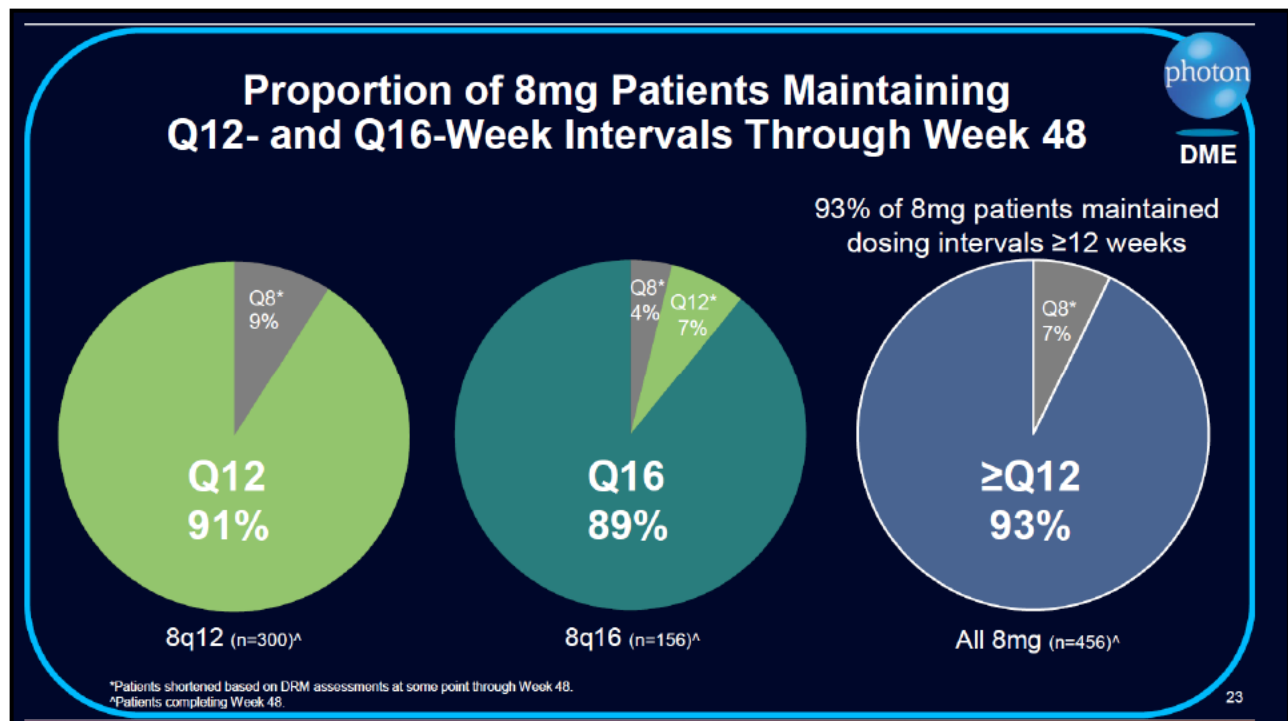
90

Extended Duration Anti-VEGF Therapies

High Dose Aflibercept (8mg Eylea)

- FDA approved in Aug 2023 for nAMD, DME, & DR
- 8mg high dose vs 2mg standard dose
- Phase III PULSAR (nAMD) & **PHOTON (DME) clinical trials**
 - Demonstrated non-inferior and clinically equivalent vision gains at 48 wks with 8 mg at 12 and 16 week dosing after 3 initial doses compared to 2mg Eylea every 8 weeks after initial dosing
 - Recommended dose 1 injection every 4 weeks for first 3 mos for all indications, then every 8-16 weeks (2-4 mos) for AMD and DME and every 8-12 weeks (2-3 mos) for DR
 - No new safety signals

91

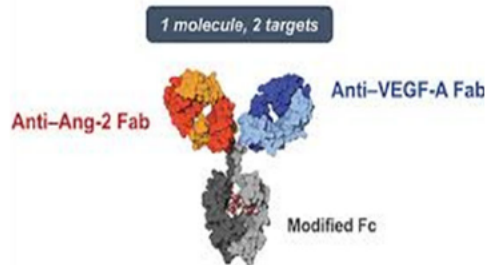


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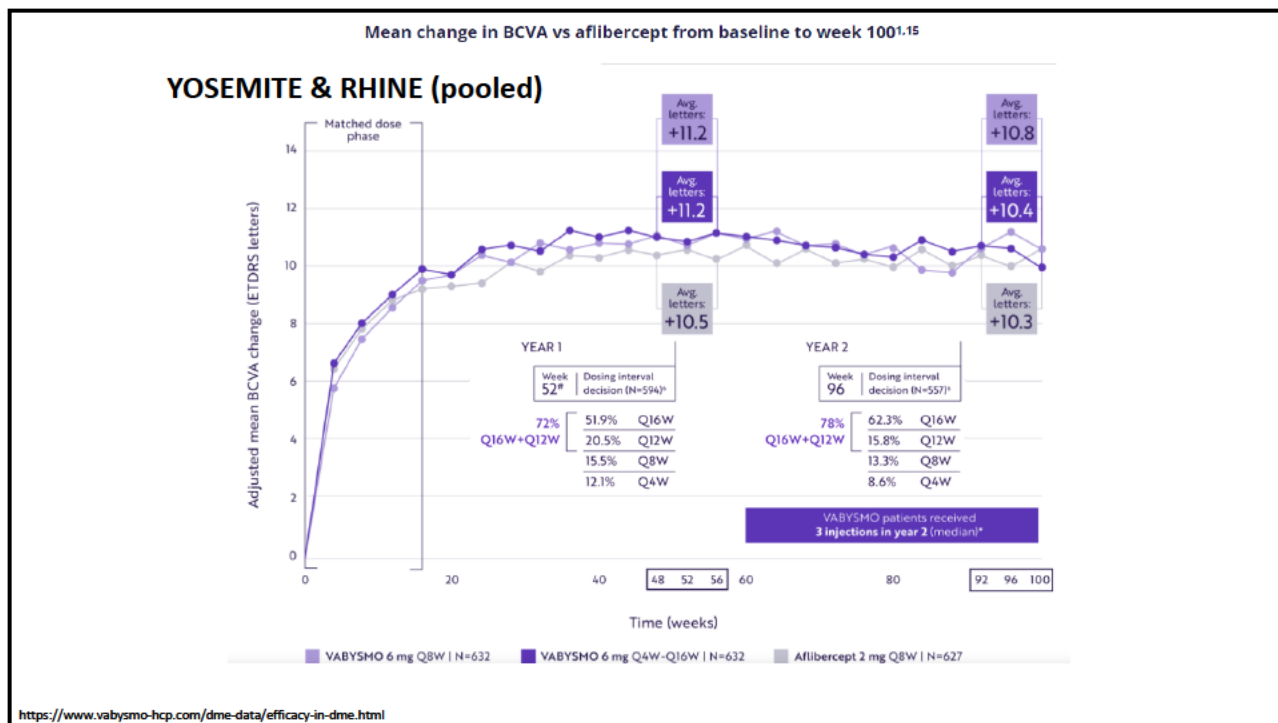
Extended Duration Anti-VEGF Therapies

Faricimab (Vabysmo)

- FDA approved in Jan 2022 for nAMD & DME, Oct 2023 for RVO
- Dual MOA (bi-phasic antibody) inhibits VEGF-A & **Angiopoietin-2 (Ang-2)**
- Phase III DME clinical trials **YOSEMITE & RHINE**
 - Dosing monthly x4 months than flexible dosing based on pt need
 - **60% eligible for extended dosing could be treated every 4 months at 2 yrs**



93

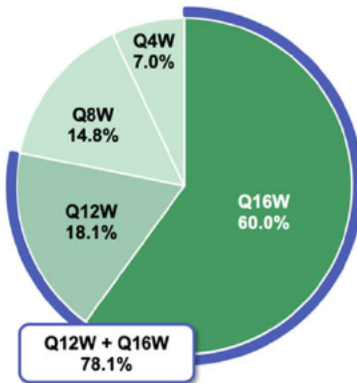


94

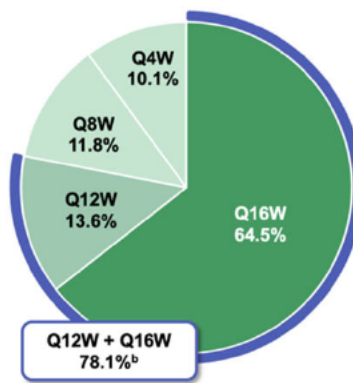
Faricimab Phase 3 DME

Durability in PTI Arm

YOSEMITE Week 96^a



RHINE Week 96^a



Median number of injections in year 2 (weeks 60–96)^c
 Faricimab PTI: 3 injections
 Faricimab Q8W: 5 injections
 Aflibercept Q8W: 5 injections

79% of patients who achieved Q12W or Q16W dosing at week 52 maintained \geq Q12W dosing without an interval reduction below Q12W through week 96^d

76% of patients who achieved Q16W dosing at week 52 maintained Q16W dosing without an interval reduction through week 96^e

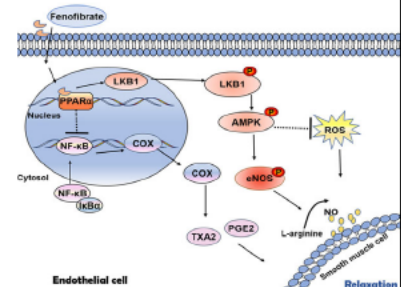
Wells J. Angiogenesis Meeting February 2022

95



FENOFIBRATE FOR DIABETIC RETINOPATHY

- Safe and inexpensive PO fibric acid derivative conventionally used to treat dyslipidemia, off-label for DR
 - Licensed in Australia and Singapore for the treatment of DR, generic in the US
- Experimentally has been shown to decrease vascular leakage, downregulate VEGF, & reduce endothelial cell and pericyte loss
- Dose: 160mg per day (54mg 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.

96

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 no 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.

97

NUTRITIONAL SUPPLEMENTATION FOR DIABETIC RETINOPATHY

Pts with DR have high incidences of vitamin and mineral deficiencies

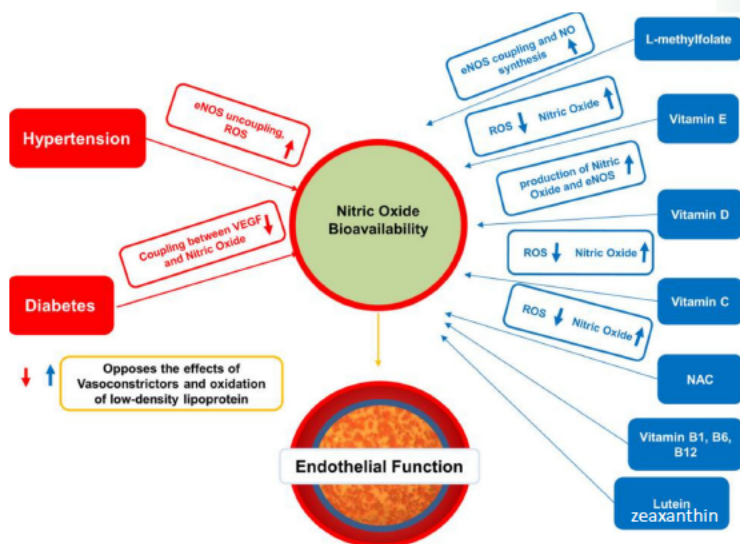
Supplementation with vitamins, minerals, and nutraceuticals may complement current tx approaches

Goals of supplementation:

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

98

NUTRITIONAL SUPPLEMENTATION FOR DIABETIC RETINOPATHY



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.

99

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.

100



The Diabetes Visual Function Supplement Study (DiVFuSS)

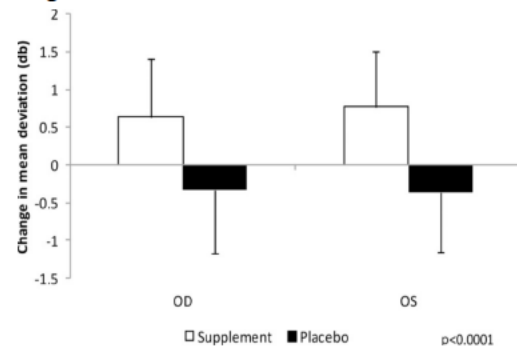
A Paul Chous,¹ Stuart P Richer,² Jeffrey D Gerson,³ Renu A Kowluru⁴

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

101

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.

102

AUTONOMOUS ARTIFICIAL INTELLIGENCE SYSTEMS FOR DR SCREENING

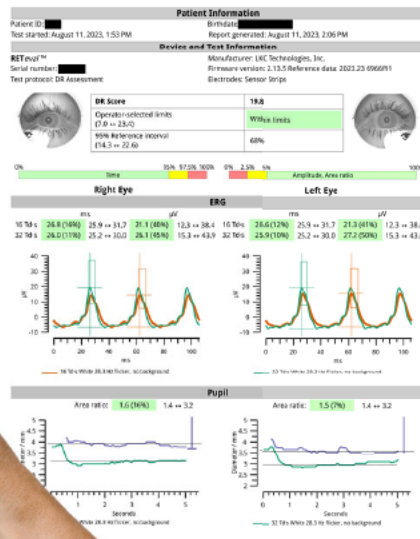
Optomed Aurora AEYE

- **Handheld** AI fundus camera FDA approved April 30, 2024
- Uses a single image from each eye, rarely requiring dilation



103

ERG PREDICTIVE VALUE OF DR PROGRESSION



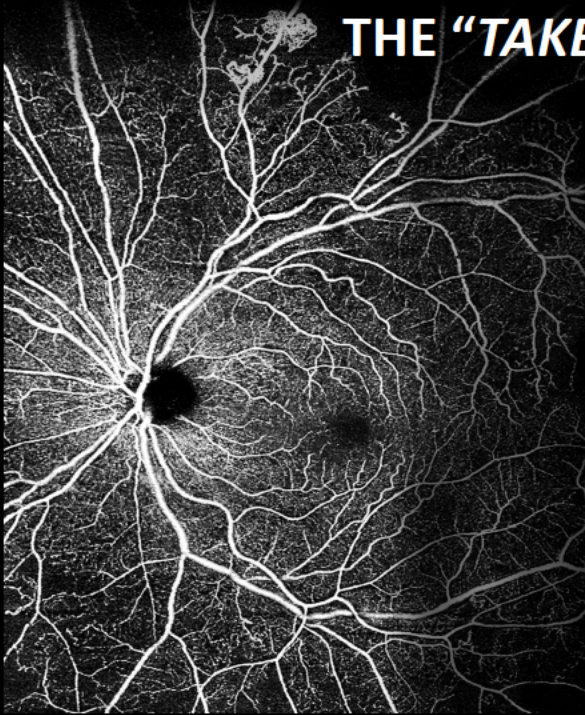
- DR score factors in implicit time, amplitude, pupil response, and age
- Patients with a DR Score of 26.9 or higher had a 79% chance of progressing to needing treatment in less than 1 year

DR Score	6-month Progression Risk	1-year Progression Risk
≤ 19.9	0%	0%
20.0 – 23.4	9%	48%
23.5 – 26.8	35%	60%
≥ 26.9	49%	79%

*Every 1-point increase in the DR Score increases the patient's likelihood of intervention by 28%

104

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

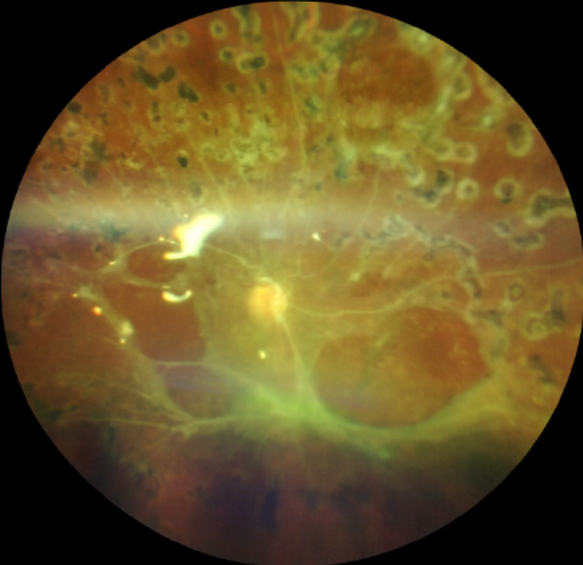
OCTA Clinical Applications in DR

- 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

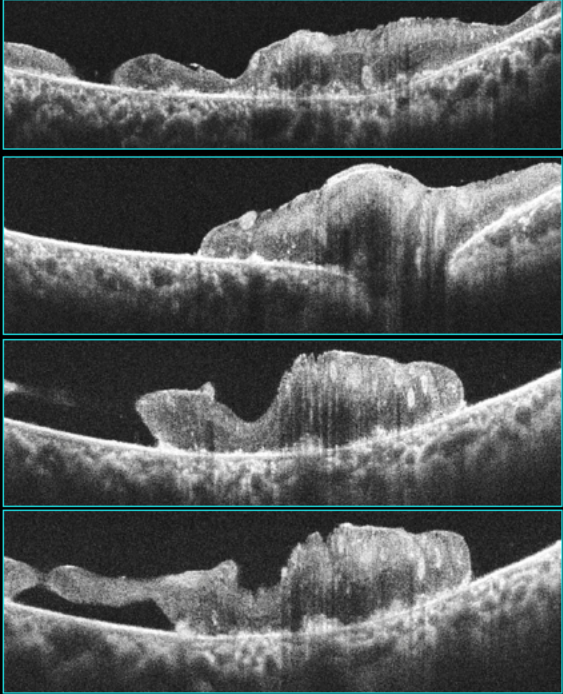
- Detection/documentation of predominately peripheral DR
 - ↑ risk for DR progression and proliferation
- More accurate and efficient staging of DR

105



THANK YOU!

majcher@nsuok.edu



106