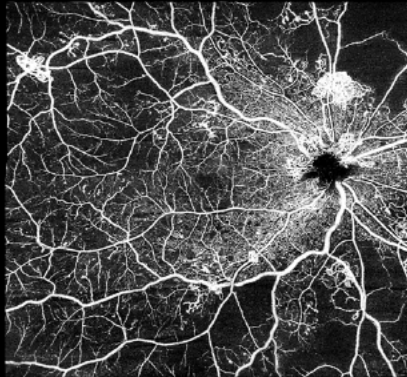
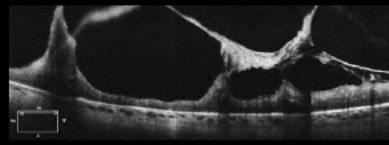


DIAGNOSIS DIABETES: THE OPTOMETRIC MANAGEMENT GUIDE



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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

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Disclosures:

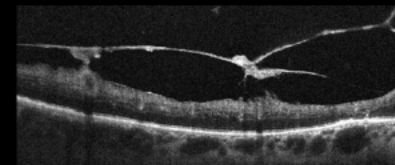
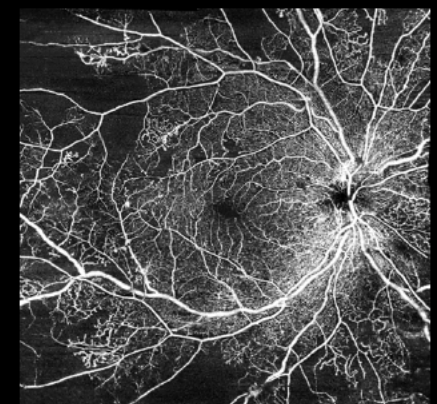
- Apellis: Advisory Board, Consultant, and Speaker
- Astellas/Iveric Bio: Advisory Board, Consultant, and Speaker
- Glaukos: Advisory Board
- Haag Streit: Advisory Board
- LKC: Advisory Board
- Notal Vision/FSH: Advisory Board and Consultant
- OcuTerra: Advisory Board
- Orasis/Qlosi: Advisory Board
- Reliance Medical Equipment: Advisory Board and Consultant
- Tarsus: Advisory Board
- Topcon: Advisory Board
- Visible Genomics: Advisory Board
- Zeiss: Advisory Board

All relevant relationships have been mitigated

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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



4



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>

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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 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 CI-DME [†]	2-4 1*	Sometimes Sometimes	Sometimes Rarely	Sometimes Usually
Non-high-risk PDR	No	3-4	Sometimes	No	Sometimes
	NCI-DME CI-DME [†]	2-4 1*	Sometimes Sometimes	Sometimes Sometimes	Sometimes Usually
High-risk PDR	No	2-4	Recommended	No	Sometimes ^{§,}
	NCI-DME CI-DME [†]	2-4 1*	Recommended Recommended	Sometimes Sometimes	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

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

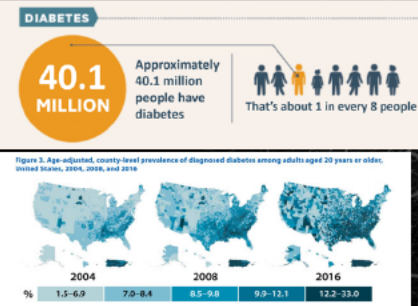
American Optometric Association— Clinical Practice Guideline 2019, p61-63

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DIABETES

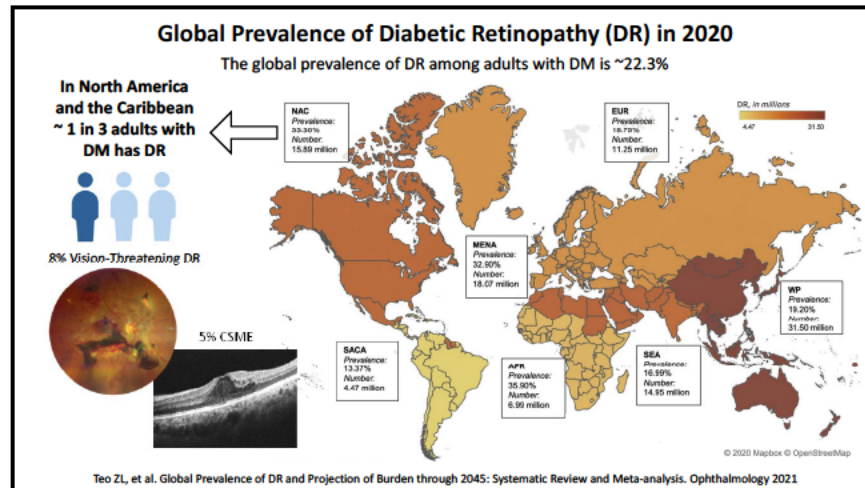
Diabetes is a worldwide epidemic

- 12% in the US (40.1 million, CDC 2023)
- Expected to increase to nearly 1 billion by 2050

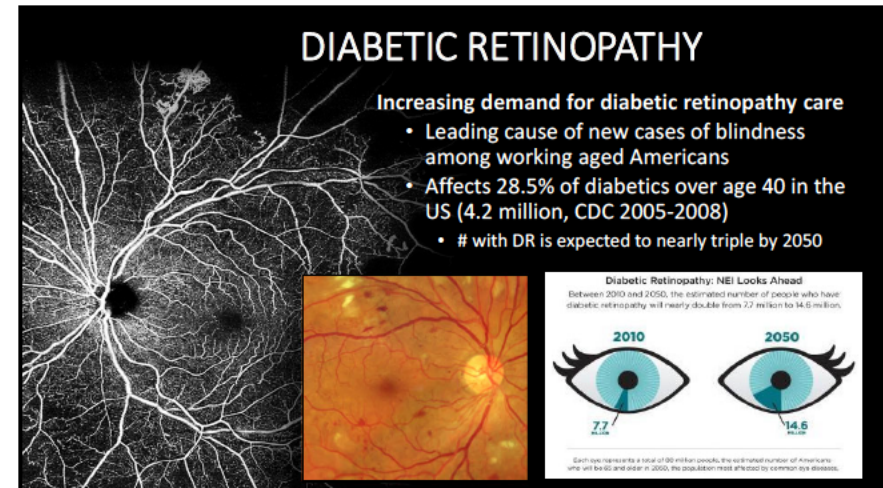


US Centers for Disease Control and Prevention (CDC), 2023.

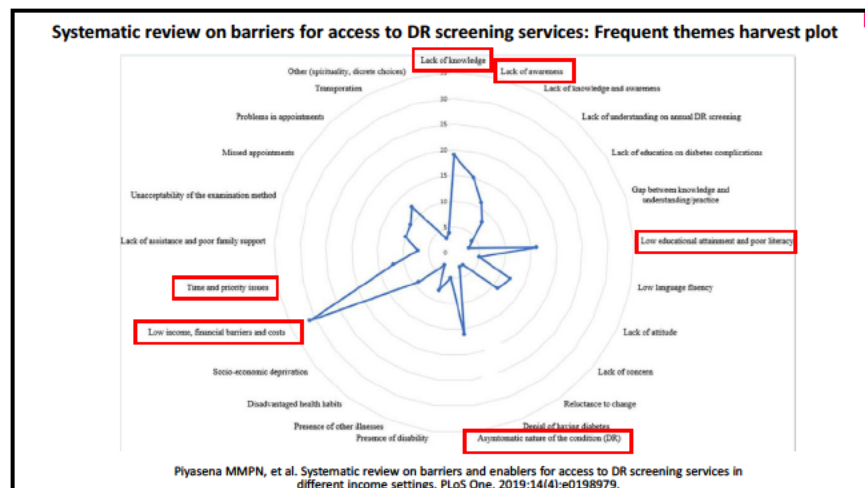
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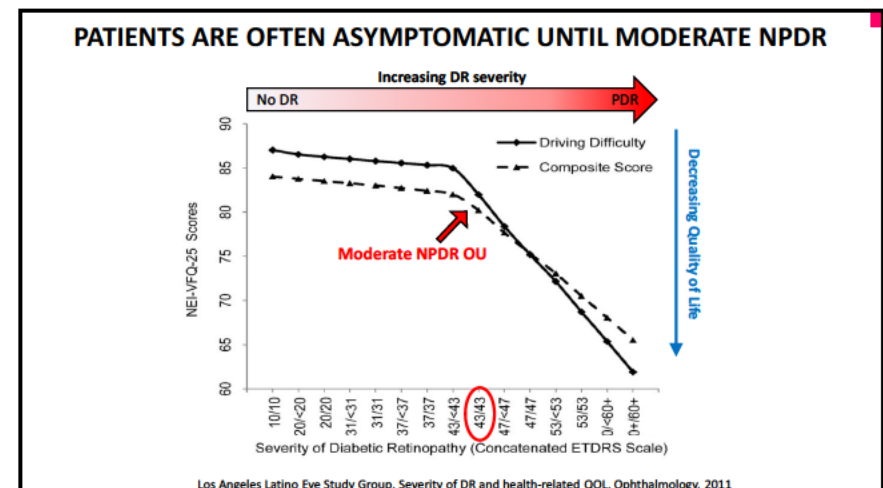
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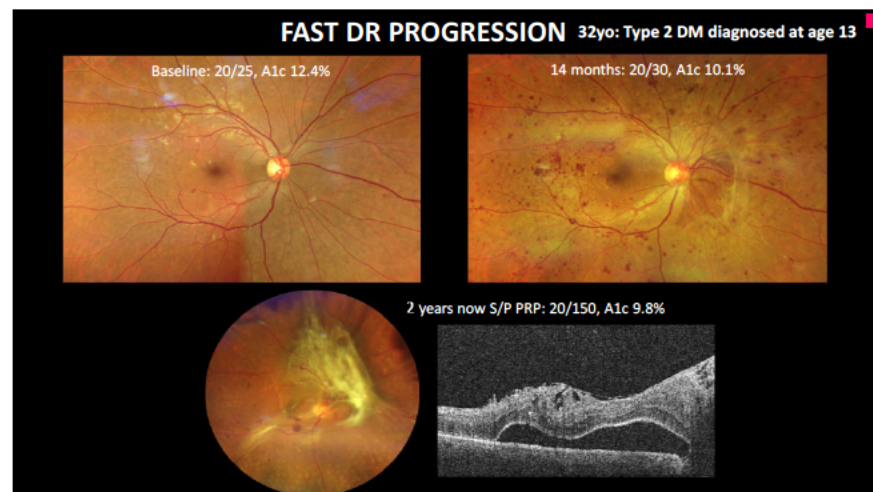
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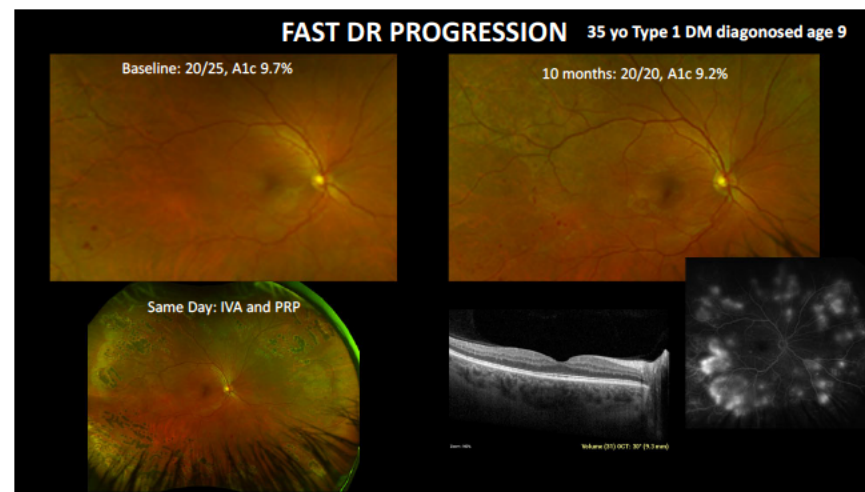
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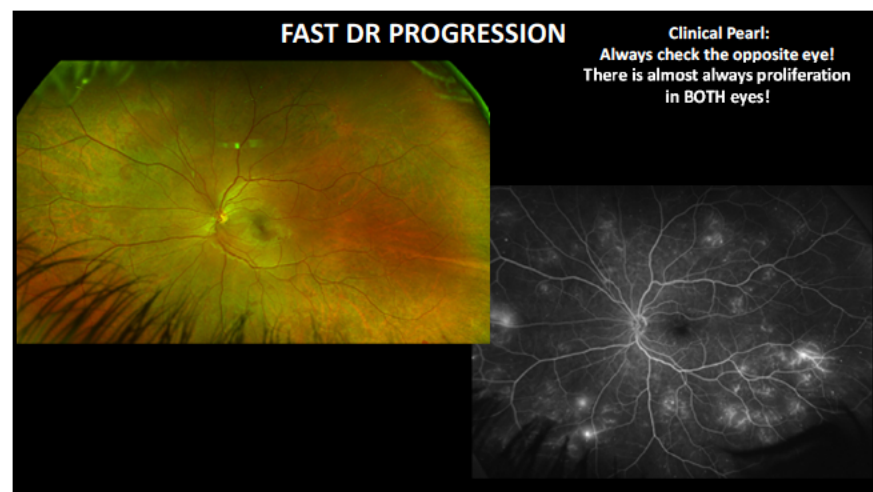
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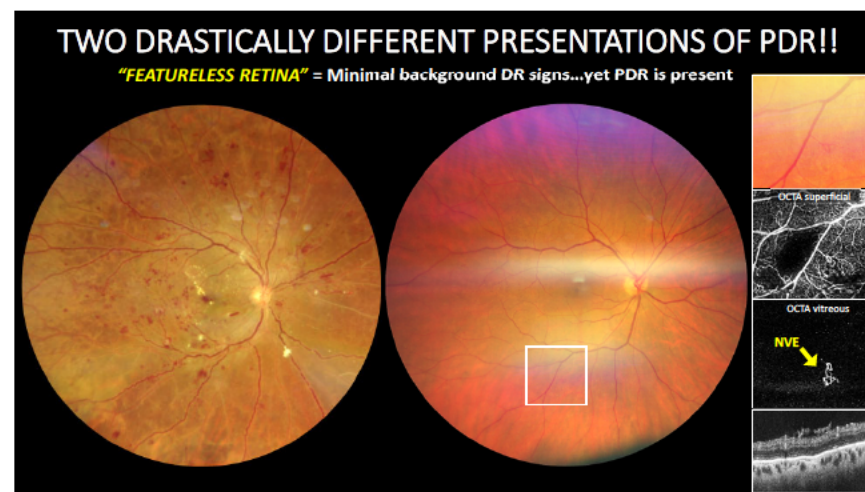
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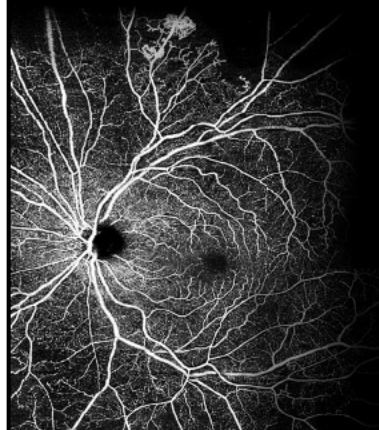


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DIABETIC RETINOPATHY RISK FACTORS

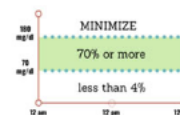


- Longer duration of DM!!!!
 - Actual duration in T2DM usually longer than that reported
 - Poor glycemic control
 - Uncontrolled systemic HTN
 - Dyslipidemia
 - Insulin use and duration of insulin use
 - Pregnancy
 - Sleep apnea
 - Puberty
 - Nephropathy
 - Smoking
 - Ocular surgery
 - Vasculitis
 -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

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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

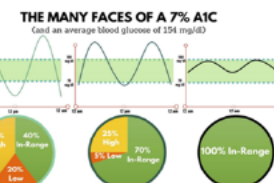
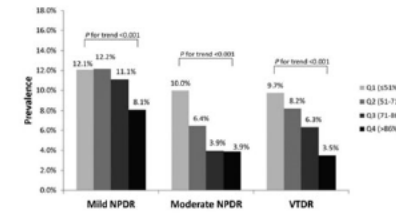


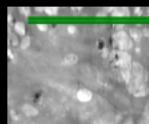
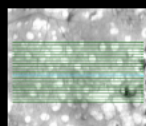
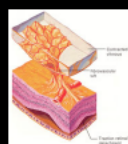
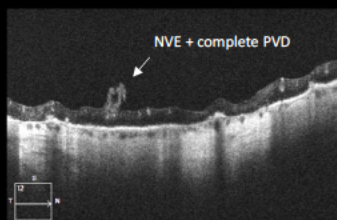
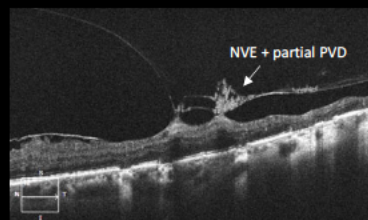
Figure 1—Prevalence of DR by severity, as a function of TIR quartile.

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

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DIABETIC RETINOPATHY PROTECTIVE FACTORS

PVD Status?



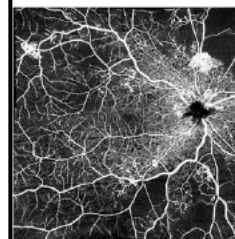
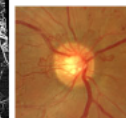
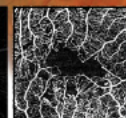
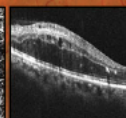
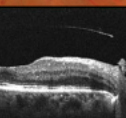
COMPLETE PVD IS PROTECTIVE!

19

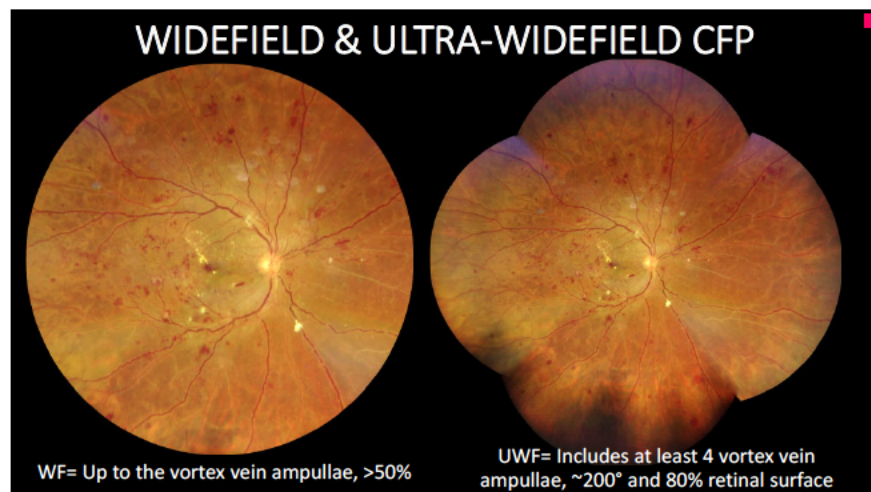
THE POWER OF IMAGING IN DR

Multimodal Imaging = more accurate and efficient staging of DR

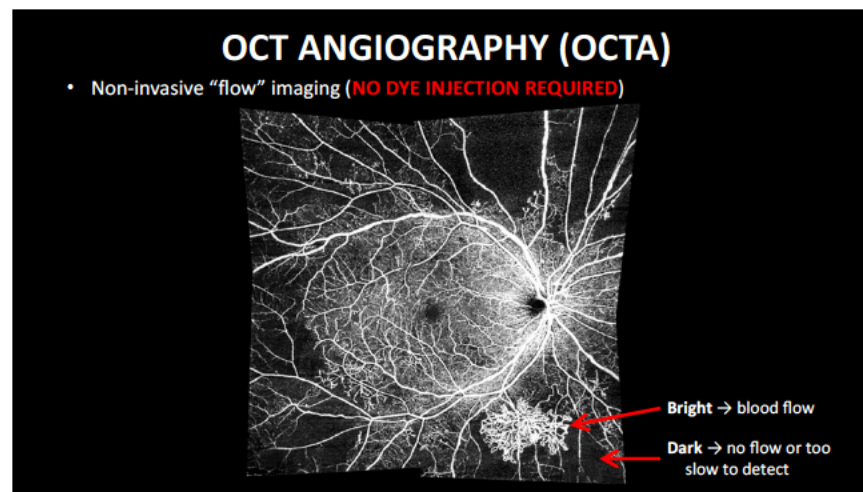
- Wide field (WF)/ultra wide field (UWF) fundus imaging
- Structural OCT
- OCT angiography (macula, ONH, montage)
- B-scan



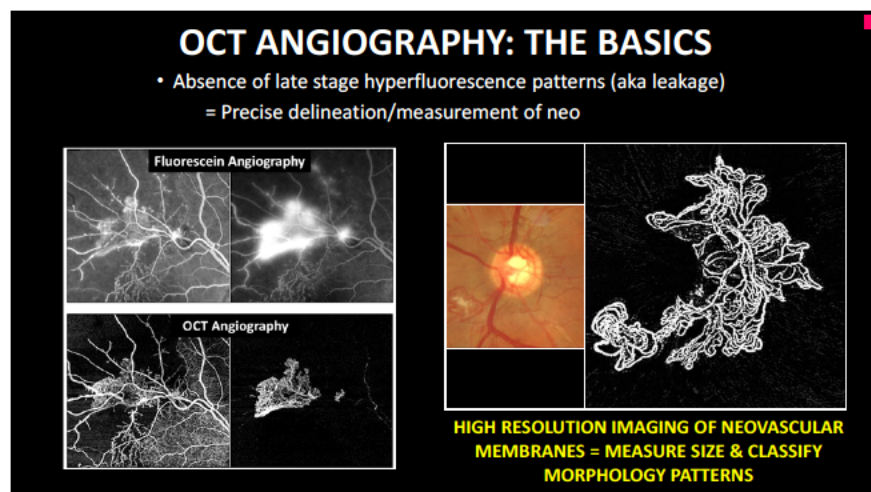
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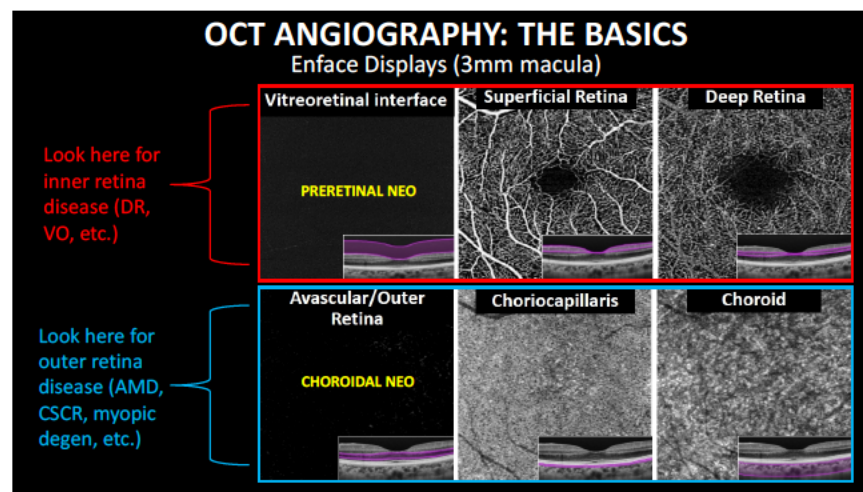
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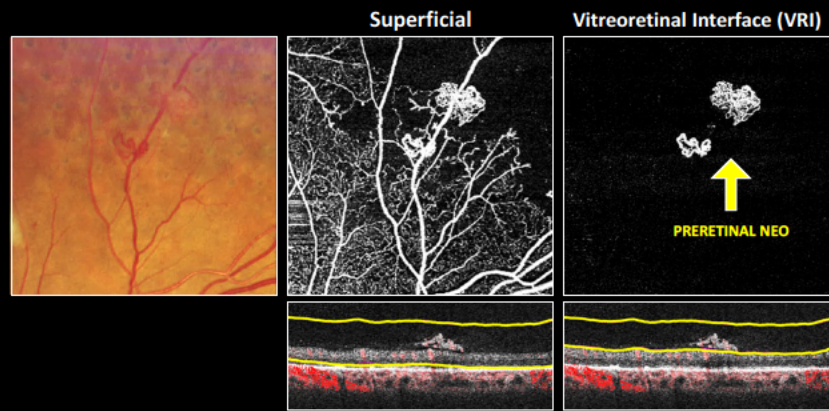


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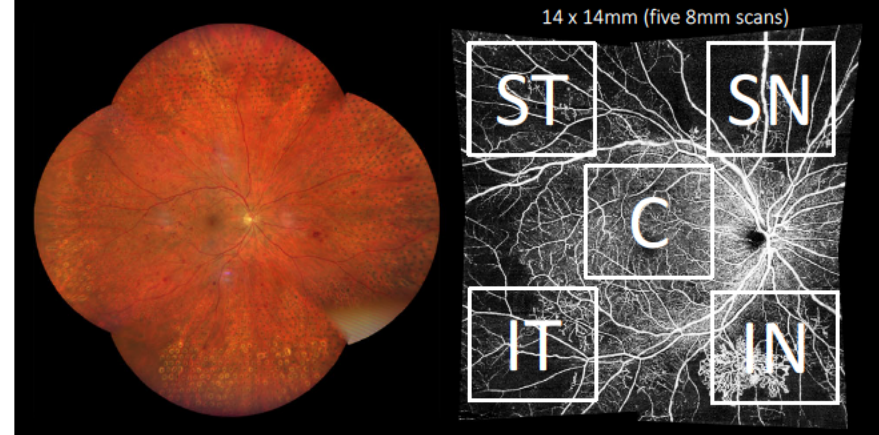
24

OCT ANGIOGRAPHY: THE BASICS



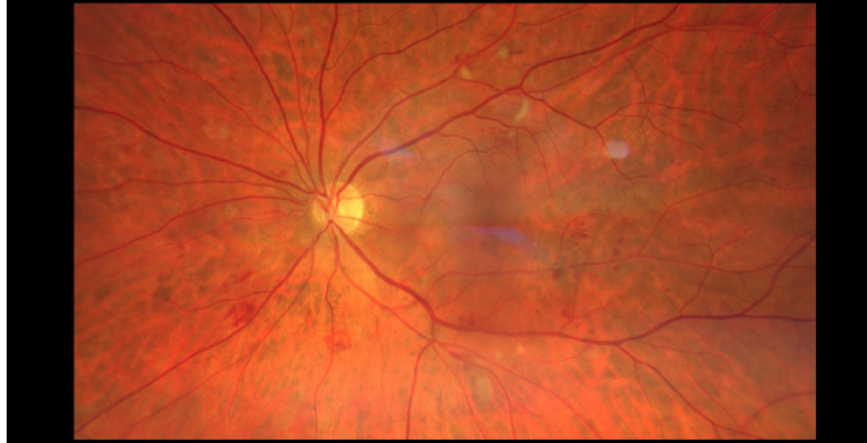
25

MONTAGE OCT ANGIOGRAPHY



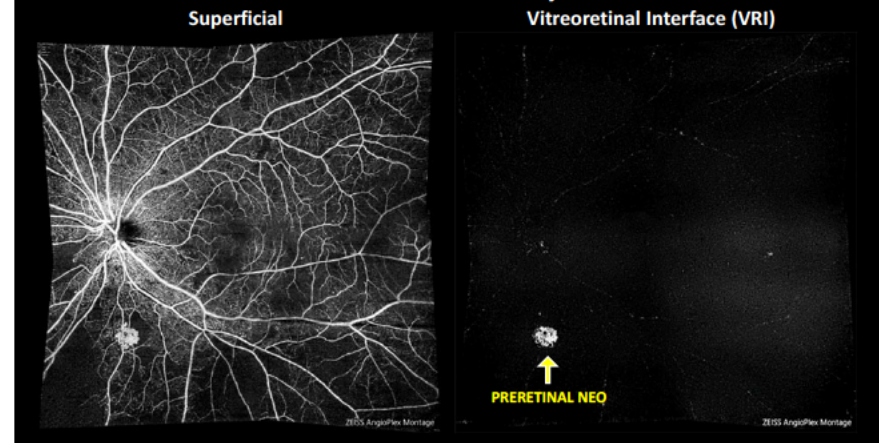
26

HOW WOULD YOU STAGE THIS PATIENT'S DR?



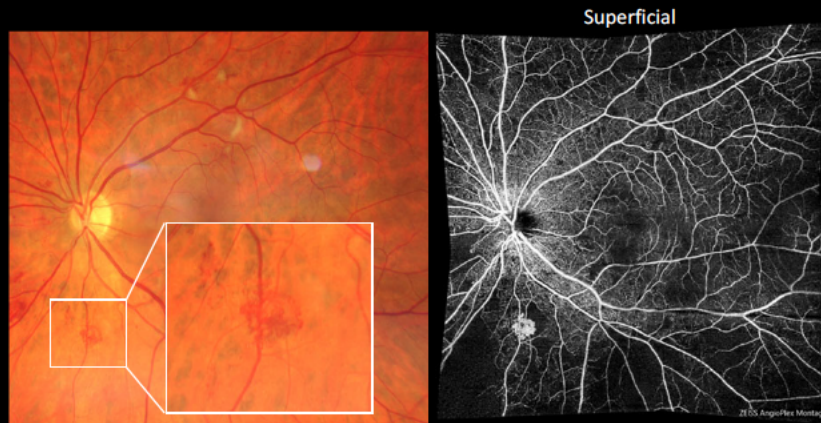
27

OCTA MONTAGE – enables early PDR detection



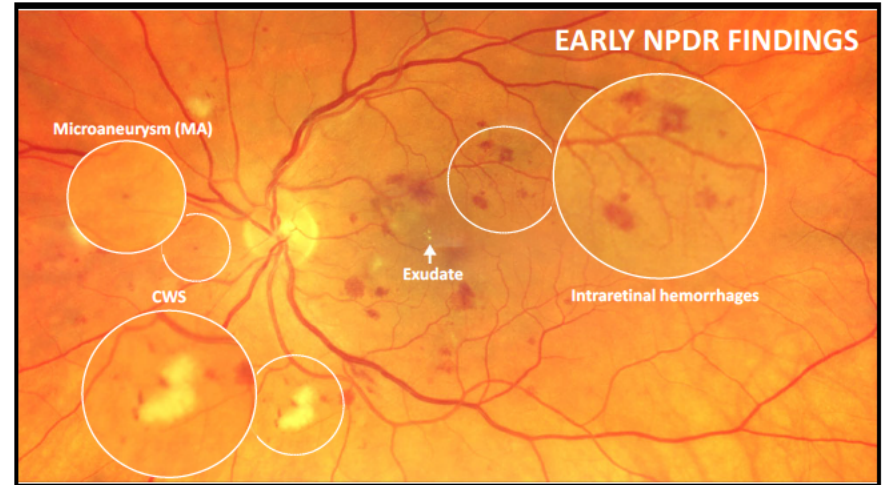
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OCTA MONTAGE – enables early PDR detection



29

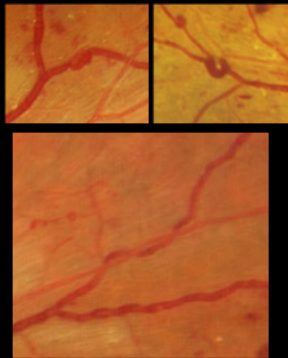
EARLY NPDR FINDINGS



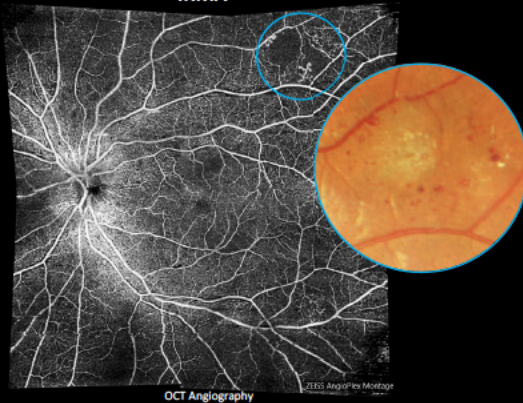
30

ADVANCED DR FINDINGS

Venous Beading



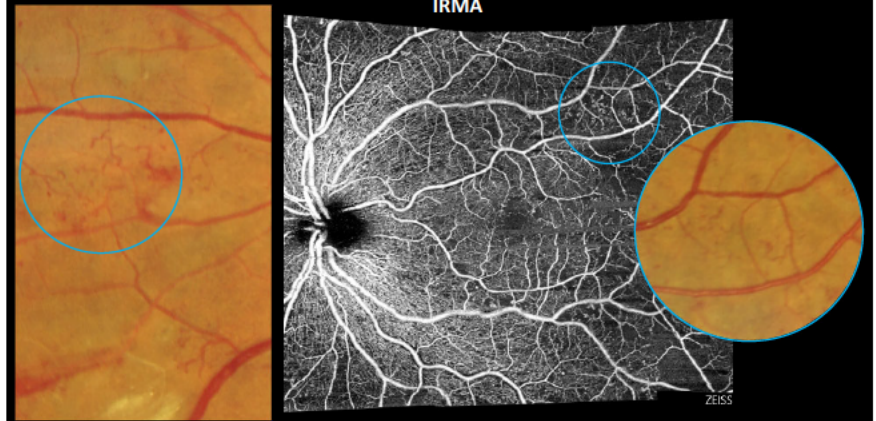
IRMA



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ADVANCED DR FINDINGS

IRMA



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DIABETIC RETINOPATHY STAGING

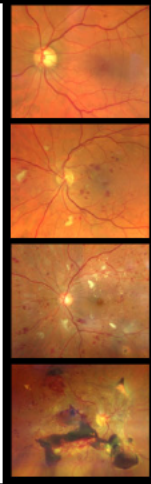
AAO Preferred Practice Pattern 2024 (p18)

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	
U.S. definition	Any of the following (4-2-1 rule) and no signs of proliferative retinopathy: <ul style="list-style-type: none"> Severe intraretinal hemorrhages and microaneurysms in each of 4 quadrants Definite venous beading in 2 or more quadrants Moderate IRMA in 1 or more quadrants
International definition	Any of the following and no signs of proliferative retinopathy: <ul style="list-style-type: none"> More than 20 intraretinal hemorrhages in each of 4 quadrants Definite venous beading in 2 or more quadrants Prominent IRMA in 1 or more quadrants
PDR	One or both of the following: <ul style="list-style-type: none"> Neovascularization Vitreous/preretinal hemorrhage

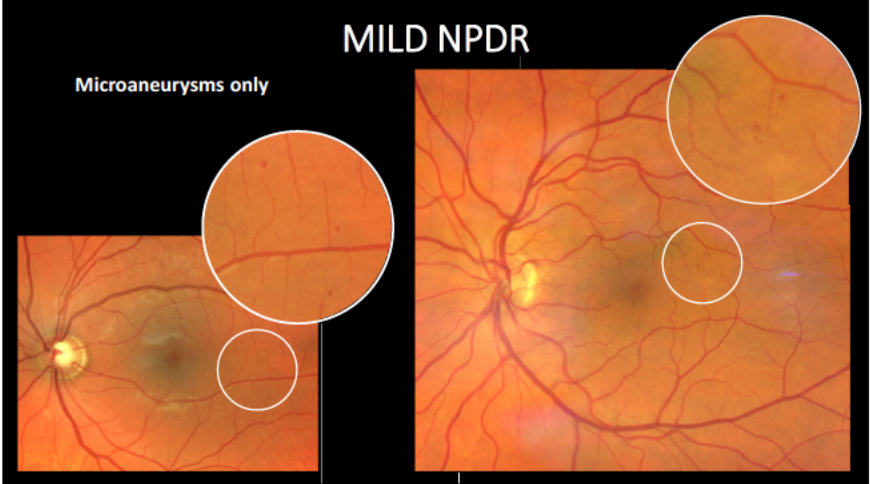
IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative DR; PDR = proliferative DR.

*AOA Clinical Practice Guideline: 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



MILD NPDR

Microaneurysms only



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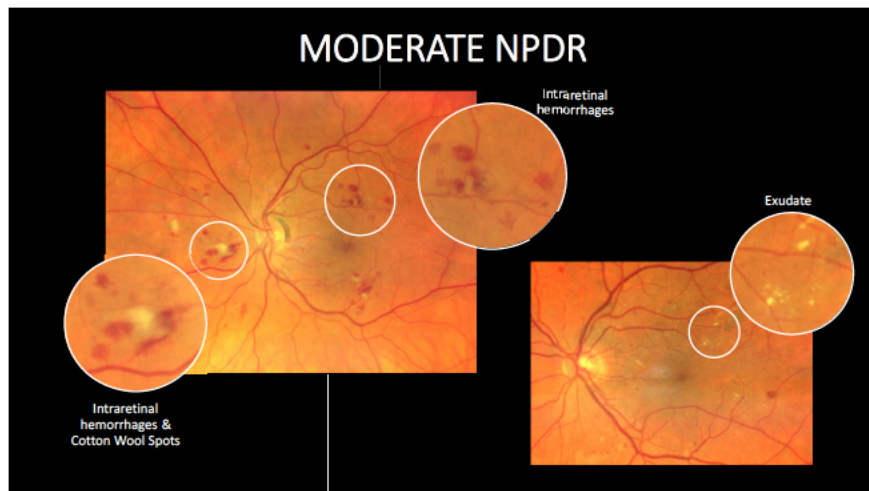
34

MODERATE NPDR

Intraretinal hemorrhages

Exudate

Intraretinal hemorrhages & Cotton Wool Spots



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

4

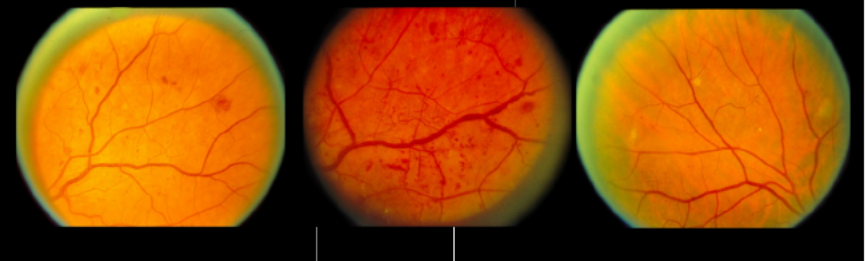
Severe retinal hemorrhages
(≥ standard photograph 2A)

2

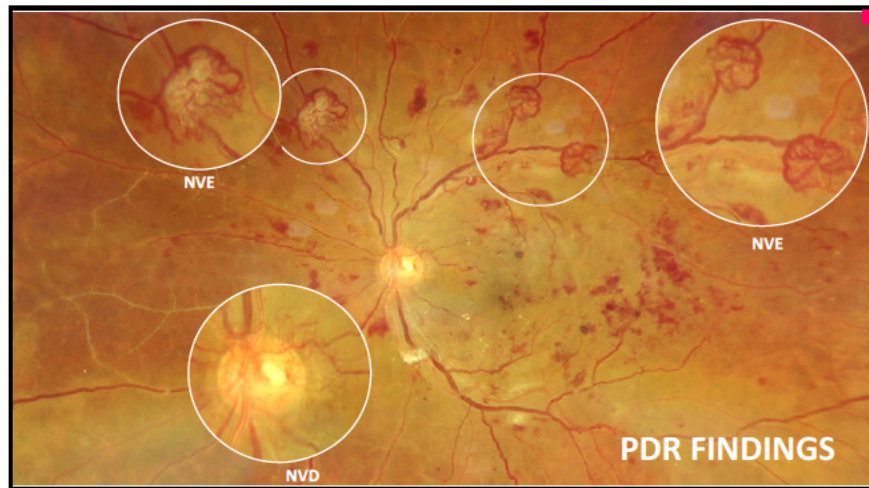
Definite venous beading
(≥ standard photograph 6B)

1

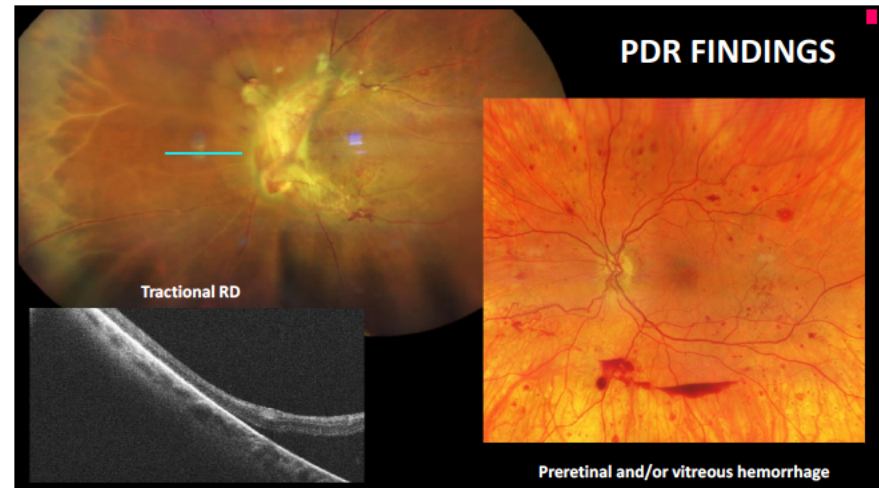
Prominent IRMA
(≥ standard photograph 8A)



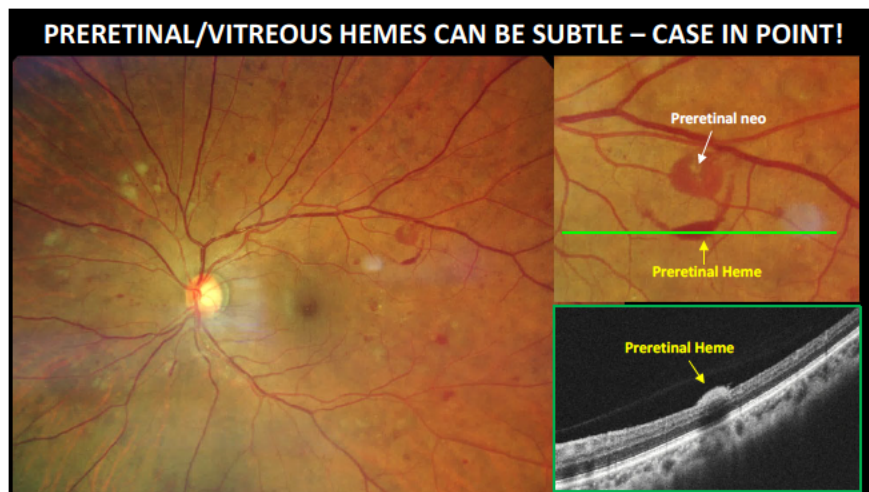
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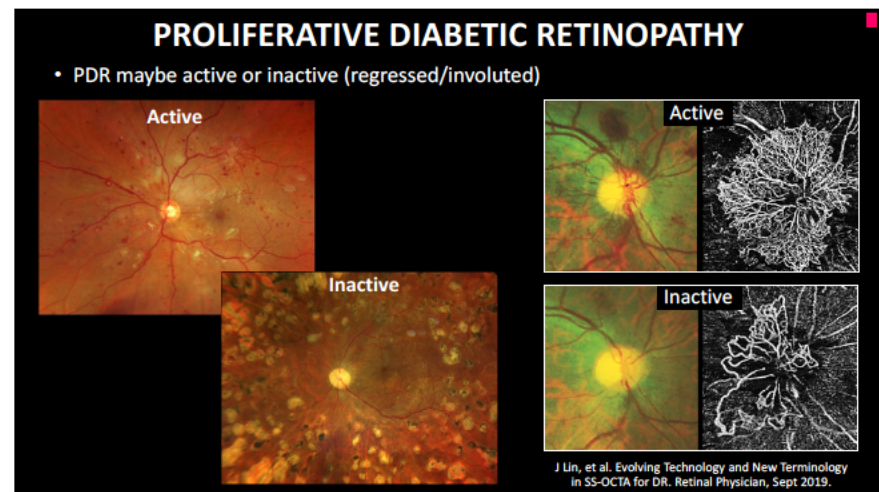
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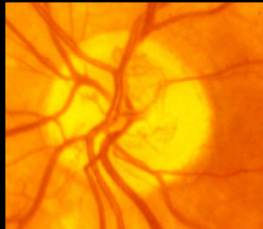
40

PROLIFERATIVE DIABETIC RETINOPATHY

High-risk PDR (Diabetic Retinopathy Study, DRS)

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

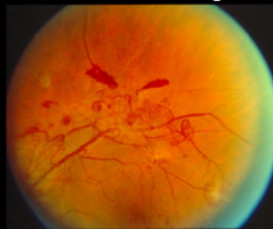
NVD $\geq 1/4$ - $1/3$ disc area in size with or without vitreous/pre-retinal hemorrhage



Any size NVD with associated vitreous/pre-retinal hemorrhage



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



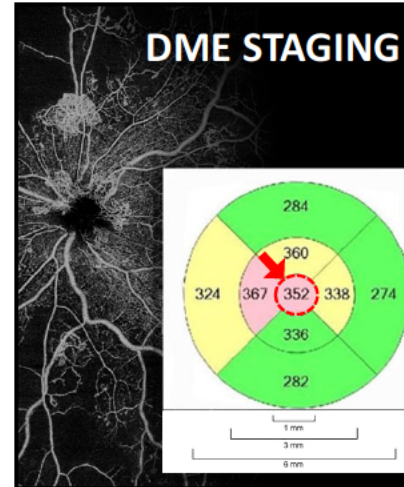
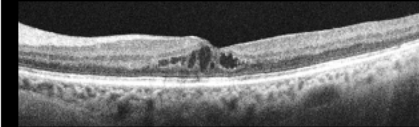
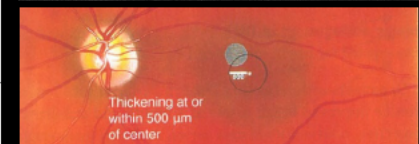
41

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)

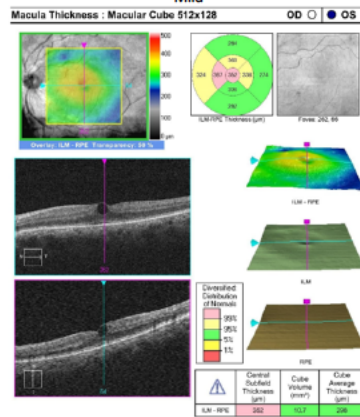
CI-DME= thickening within the central subfield zone that is **1mm in diameter**



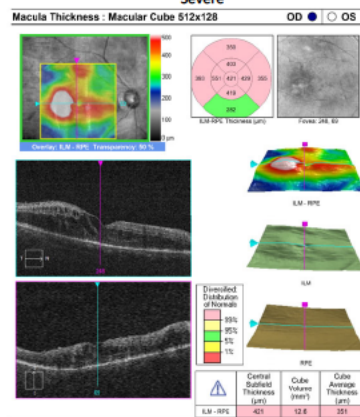
42

Center-involved DME (CI-DME)

Mild

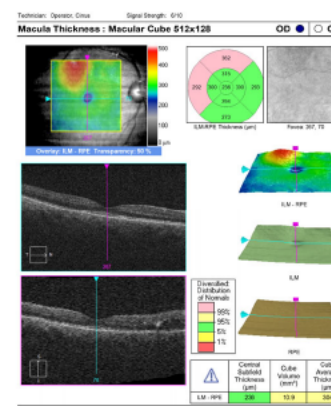


Severe



43

Non-center involved DME (NCI-DME)

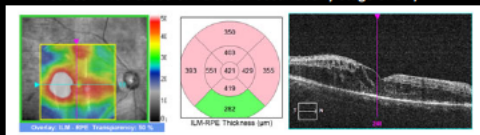


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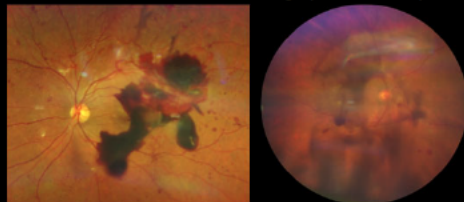
COMMON CAUSES OF VISION LOSS IN DR

Center-Involved DME (CI-DME)

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

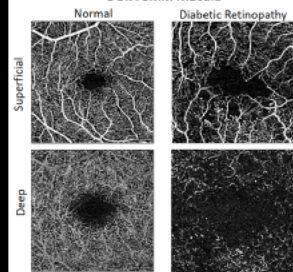


Preretinal/Vitreous Hemorrhage (Sudden onset)



Macular Ischemia

OCTA 3mm Macula



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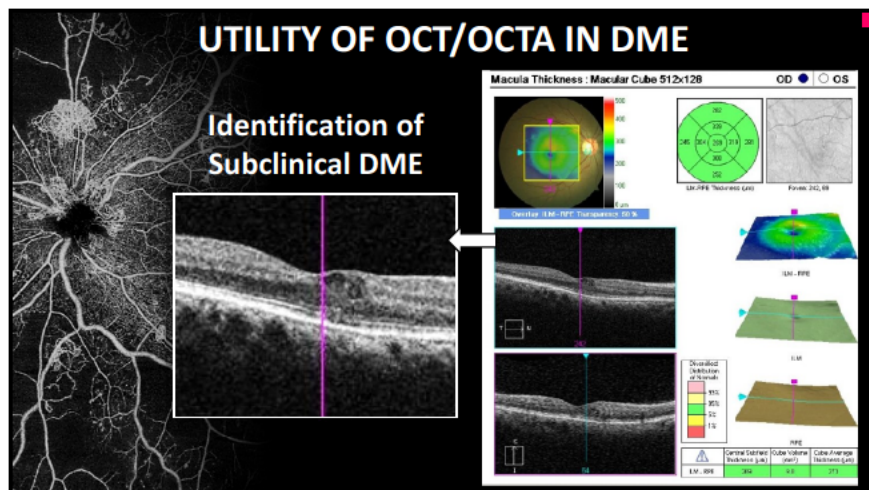
UTILITY OF OCT/OCTA IN DME

- 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

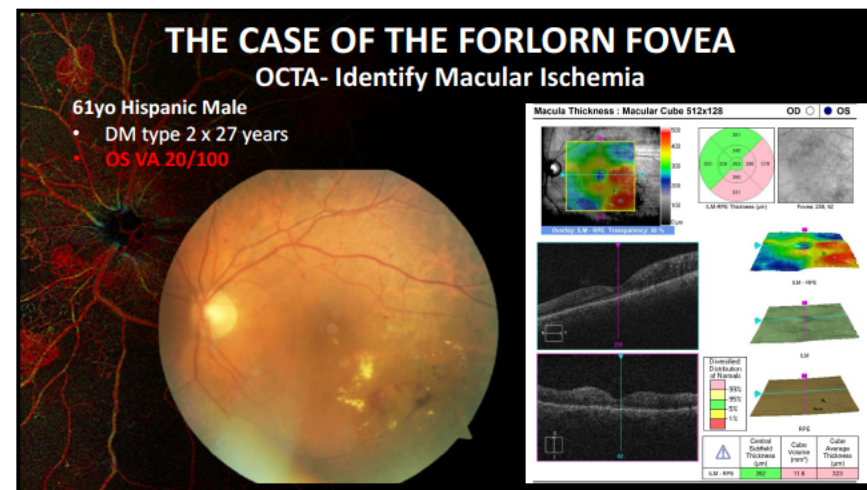


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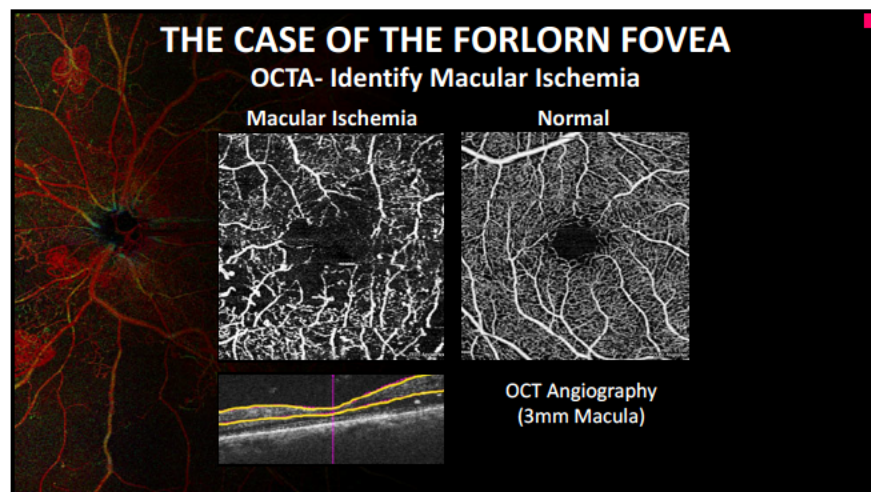
THE CASE OF THE FORLORN FOVEA

OCTA- Identify Macular Ischemia

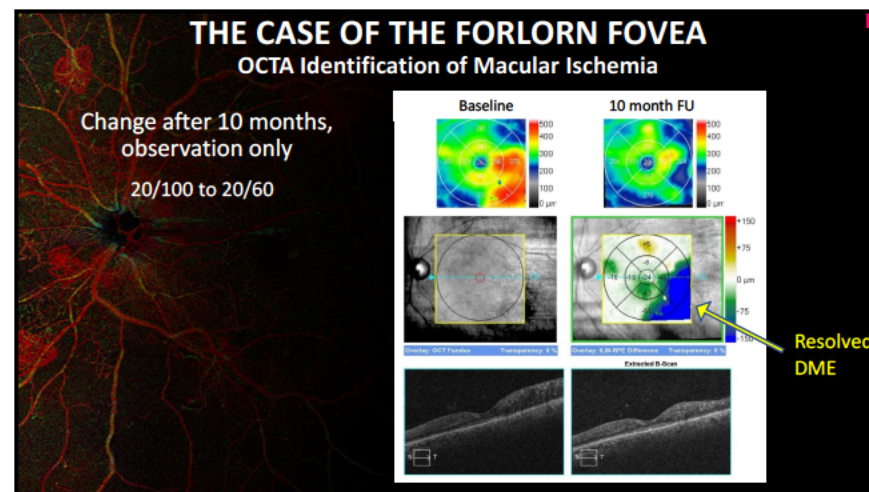
- 61yo Hispanic Male
- DM type 2 x 27 years
- OS VA 20/100



48



49



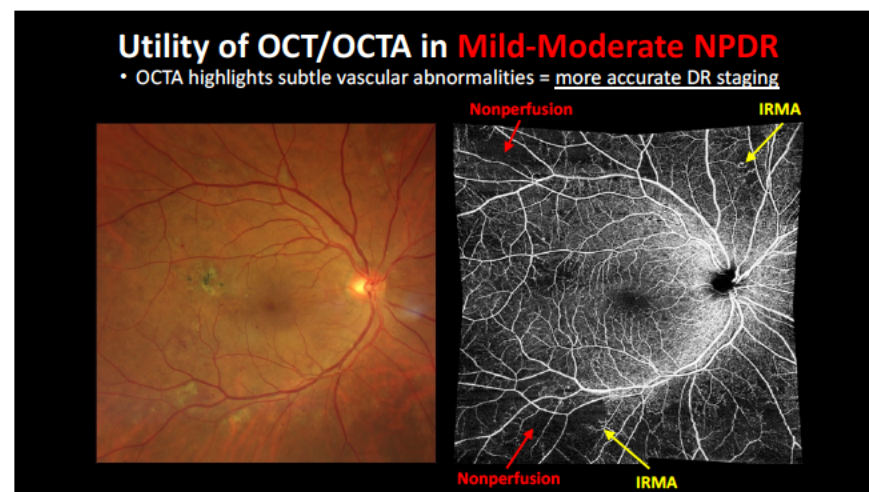
50

MANAGEMENT OF DME

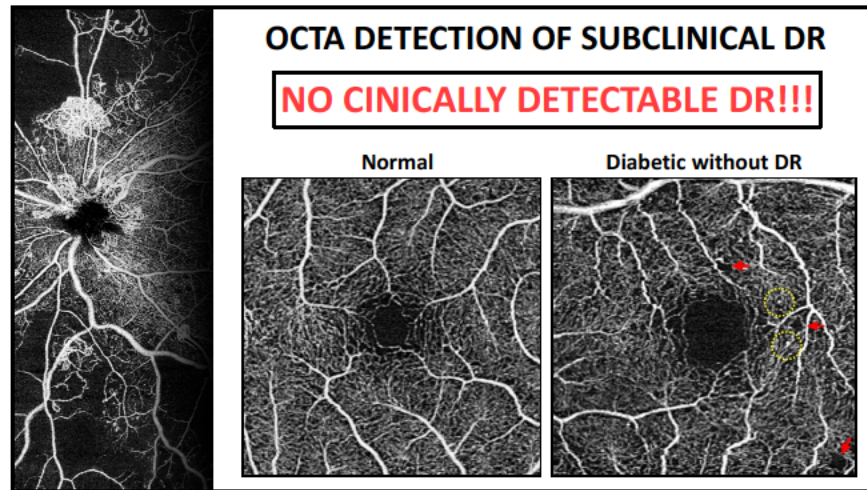


- **Who should be treated (anti-VEGF 1st line therapy)?**
 - CI-DME with VA 20/32 or worse- referral within 2-4 weeks (AOA-CPG 2019)
- **Who can usually be observed?**
 - NCI-DME
 - CI-DME with VA 20/25 or better - defer tx until VA is 20/30 or worse (DRCR.net Protocol V)
 - Re-examine every 2-4 months
- **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

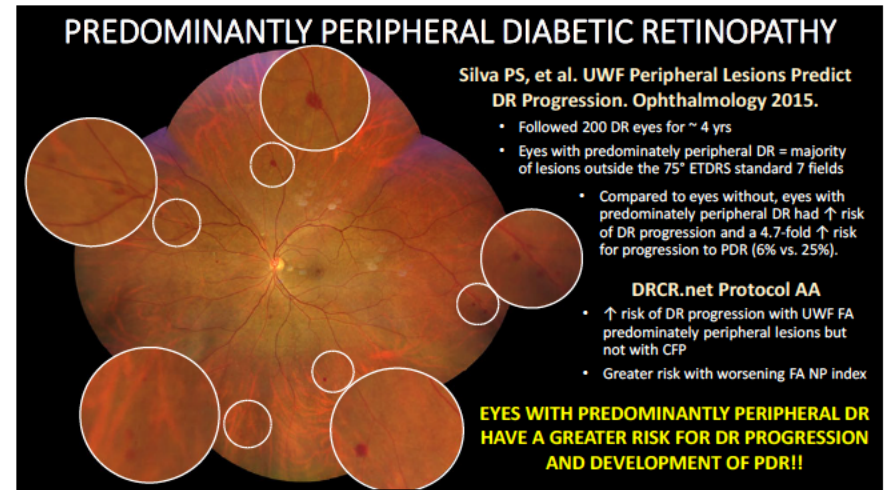
51



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MANAGEMENT OF SEVERE NPDR- LOW RISK PDR

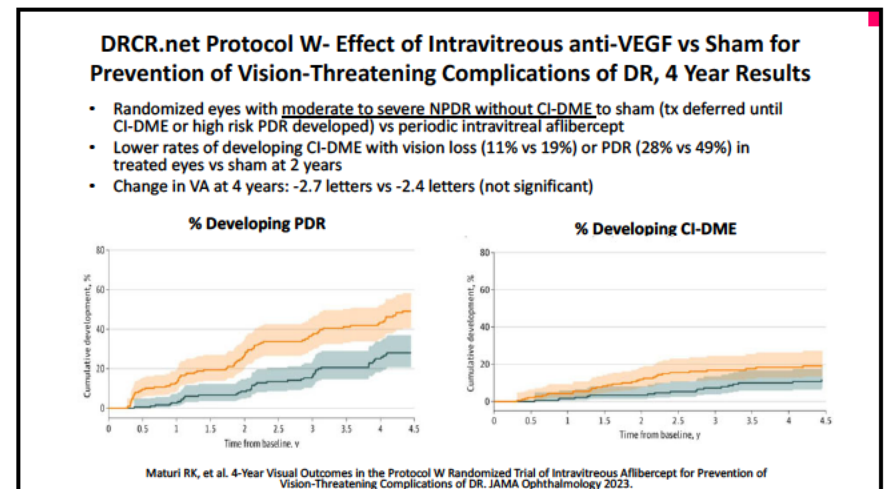
- Refer all regardless of DME status
- Start considering anti-VEGF therapy/PRP at the severe NPDR stage **even without CI-DME** (optional)
- Anti-VEGF: reverse DR stage/prevent development of vision threatening complications
- Both ranibizumab and aflibercept FDA approved even if no DME

Severity of Retinopathy	Presence of Macular Edema (Months)	Follow-up (Months)	Photocoagulation (Scatter) Laser	Local and/or Grid Laser*	Intravitreal Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No	12	No	No	No
	ICI DME	3-6	No	Sometimes	No
	CI DME	1*	No	Rarely	Usually
Moderate NPDR	No	6-12	No	No	No
	ICI DME	3-6	No	Sometimes	Rarely
	CI DME	1*	No	Rarely	Usually
Severe NPDR	No	3-4	Sometimes	No	Sometimes
	ICI DME	2-4	Sometimes	Sometimes	Sometimes
	CI DME	1*	Sometimes	Rarely	Usually
Non-high-risk PDR	No	3-4	Sometimes	No	Sometimes
	ICI DME	2-4	Sometimes	Sometimes	Sometimes
	CI DME	1*	Sometimes	Sometimes	Usually
High-risk PDR	No	2-4	Recommended	No	Sometimes
	ICI 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; ICI DME = noncenter-involved diabetic macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

American Academy of Ophthalmology – Preferred Practice Patterns 2019, p20

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UTILITY OF IMAGING IN SEVERE NPDR-LOW RISK PDR

Wide-field Fundus Imaging

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

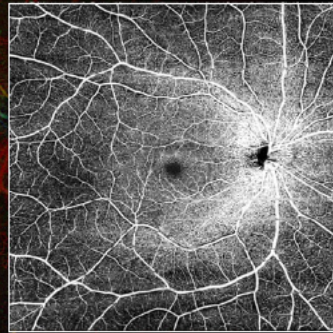
OCT/OCTA

- 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

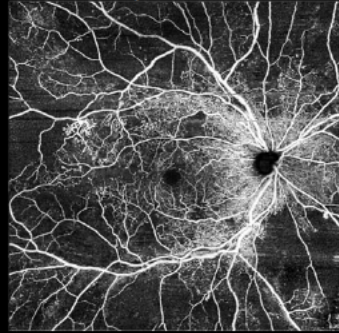
57

MANAGEMENT OF SEVERE NPDR-LOW RISK PDR

Normal



Very Severe NPDR

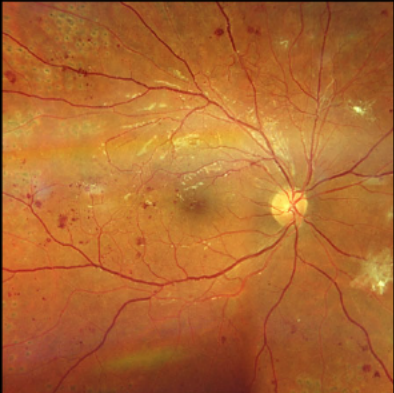
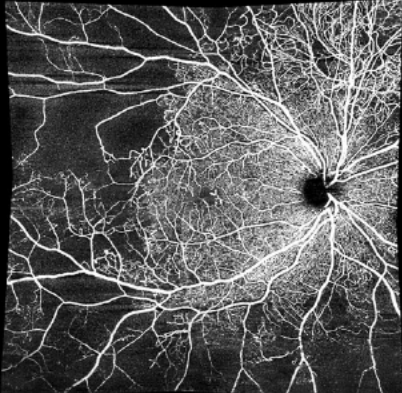


- Increased risk for progression to PDR
- Consider early PRP/anti-VEGF treatment

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Utility of OCTA Montage Imaging in DR

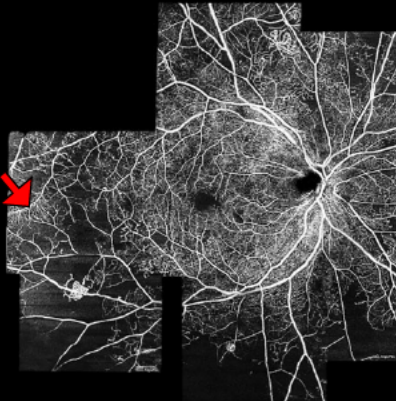
OCTA – Visualization of peripheral NP (nearly invisible without)

59

Ischemic disease progressing despite treatment!

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




60

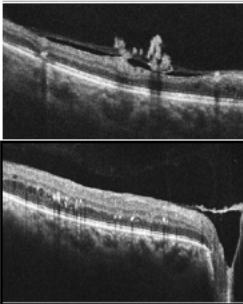
www.pollev.com/retina

When poll is active, respond at [pollev.com/retina](https://www.pollev.com/retina)
or Text **RETINA** to 37607 once to join

Pre-retinal neovascularization is best defined as:

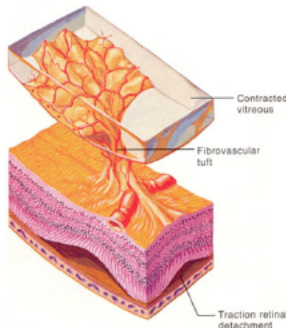
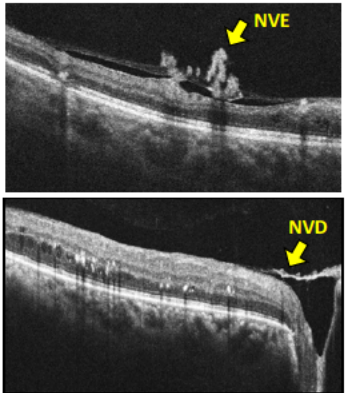
- Dilated, telangiectatic capillaries within the retina.
- New vessels growing within the retina.
- New vessels growing between the NFL and the ILM of the retina.
- New vessels growing between the ILM of the retina and the posterior hyaloid of the vitreous.

Start the presentation to see live content. For screen share software, share the entire screen. Get help at [pollev.com/app](https://www.pollev.com/app)

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PROLIFERATIVE DIABETIC RETINOPATHY
Preretinal Neovascularization

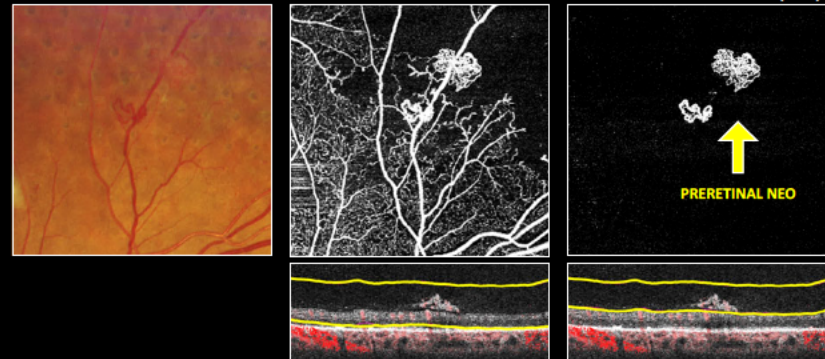
Most often characterized by new blood vessel growth located between the ILM and the posterior hyaloid

62

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

Retina

Vitreoretinal Interface (VRI)



63

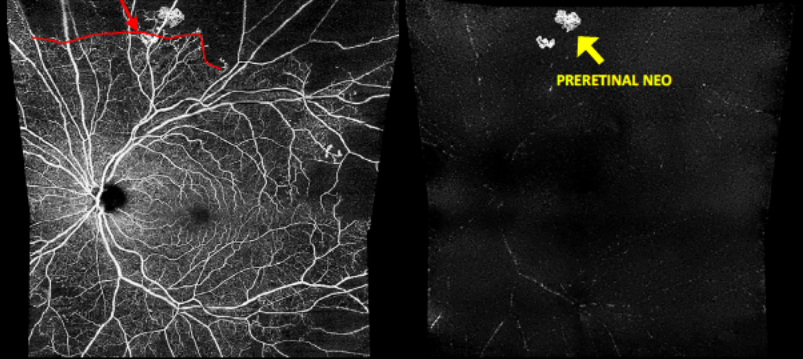
Utility of OCTA Montage Imaging in DR

Neo often forms at the border of perfusion and nonperfusion

Isolate Preretinal Neo!

Superficial

Vitreoretinal Interface (VRI)



64

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



65

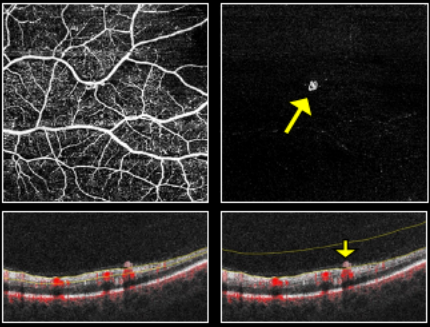
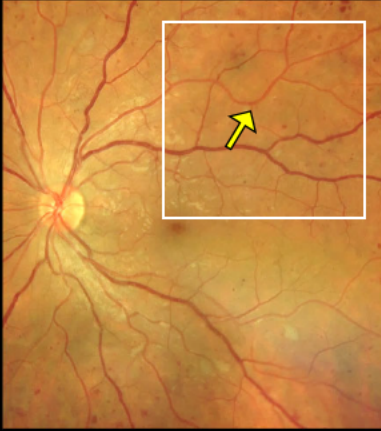


66

8mm OCTA Superior Temporal Arcade

Tiny NVE!

Superficial Vitreoretinal Interface

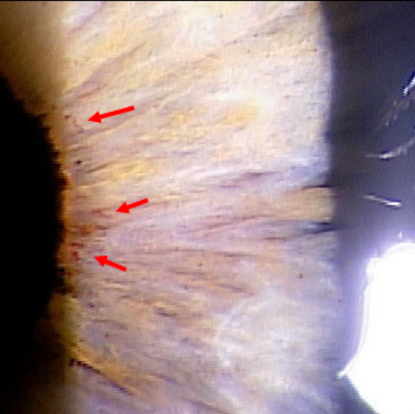
67

PROLIFERATIVE OR NONPROLIFERATIVE (NVE OR IRMA)?

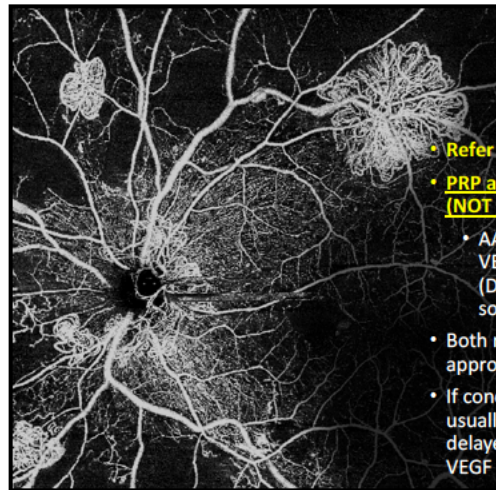
Ant Seg OS

DX: Low risk PDR with early NVI

TX: Referred to retina, performed PRP OU



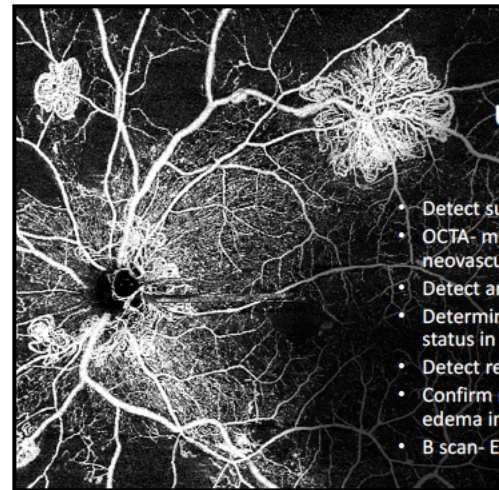
68



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

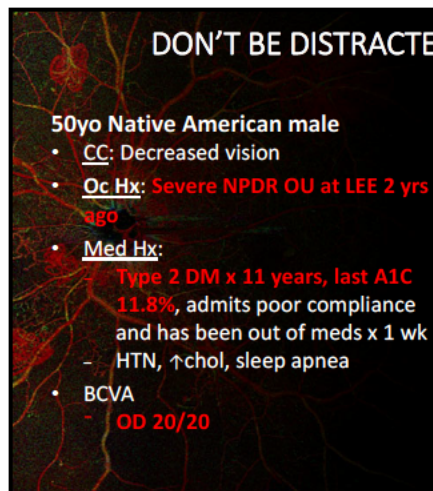
69



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

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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

71

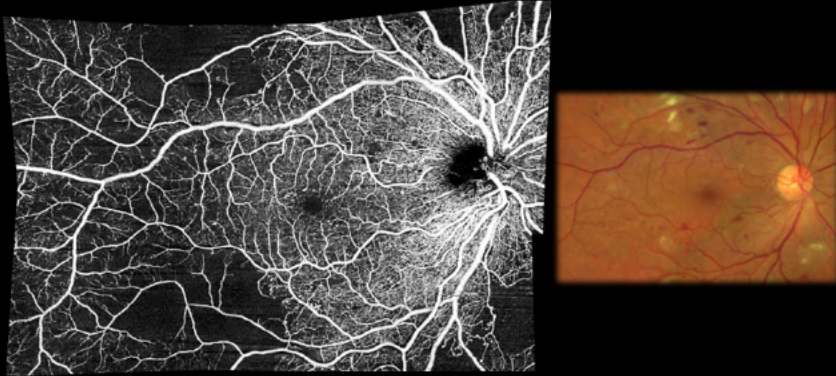


DON'T BE DISTRACTED BY THE 20/20 VISION!



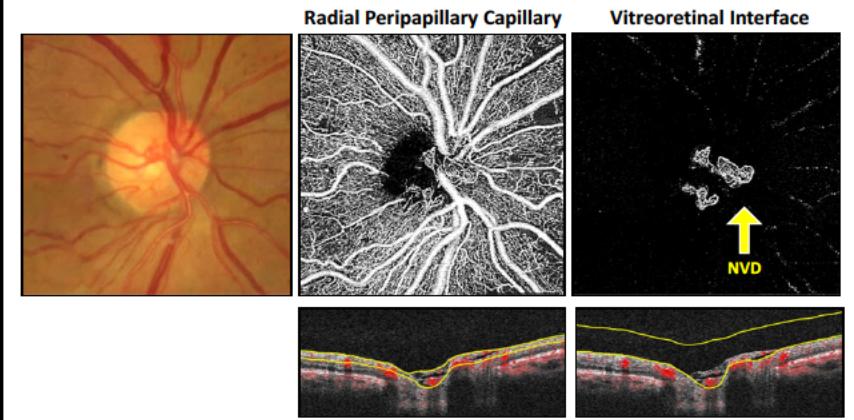
72

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

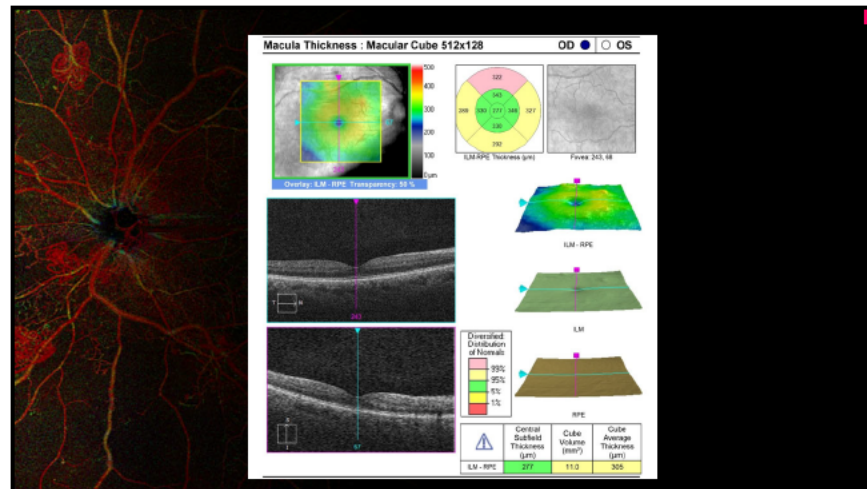


73

OCTA 4.5mm Optic Nerve



74

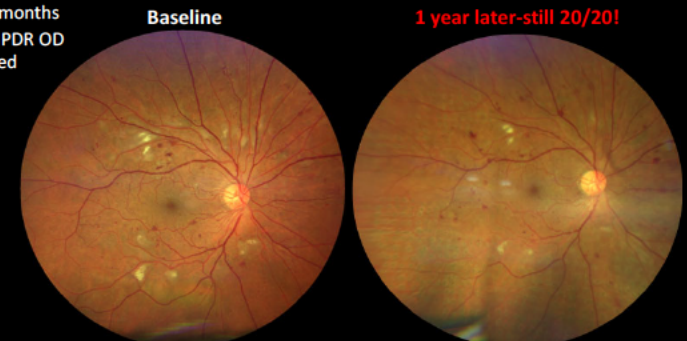


75

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



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EVOLVING STANDARD OF CARE

- The American Academy of Ophthalmology Diabetic Retinopathy Preferred Practice Patterns now mention ERG for BOTH diagnosis and disease management.
- The Mary Tyler Moore Vision Initiative is sponsoring clinical trials, conducted by the Diabetic Retinopathy Clinical Research Network (DRCR). The DRCR seeks to augment the current guidelines for detection and staging of diabetic retinopathy, and they are including ERG to measure retinal function.

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THEN AND NOW

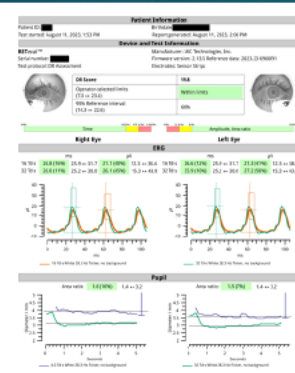


- Handheld, mobile unit can be used anywhere in office
- Constant pupil tracking allows for non-dilated testing
- Patient-friendly, non-invasive sensors
- Easy user interface in multiple languages
- Color-coded result interpretation
- Diabetic Retinopathy Score
- Testing completed in minutes
- Staff – ☺



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DIABETIC RETINOPATHY Sample report



- Must NOT be dilated
- DR score factors in implicit time, amplitude, pupil response, and age

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 2.8%

80

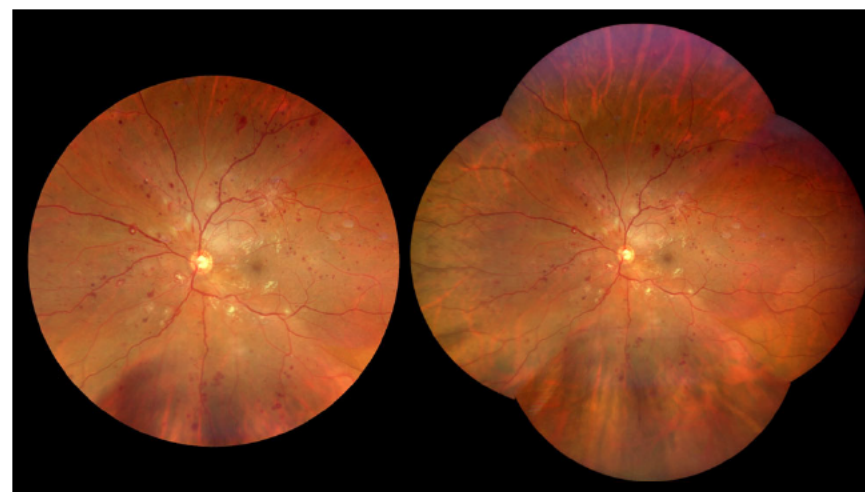
TAKING IT TO THE EXTREME

29yo Native American male – Presents for routine DM exam, needs gls

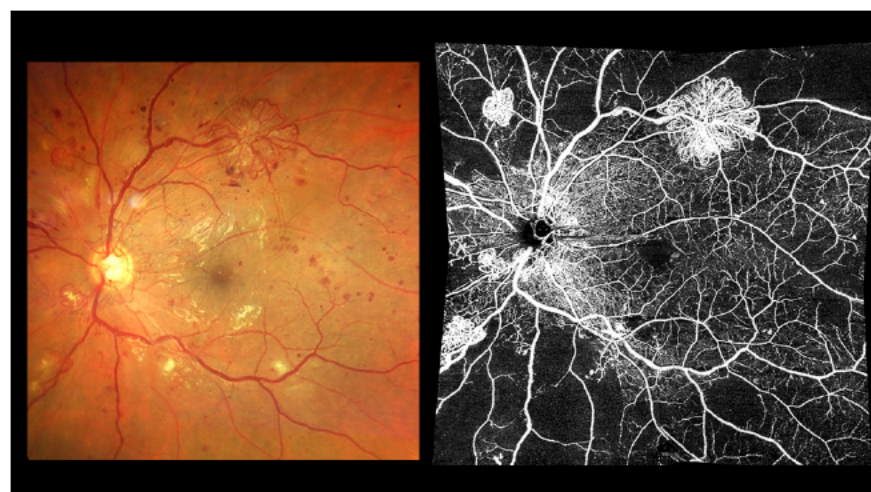
- POH: Severe NPDR OU at LEE 5 yrs ago
- MH:
 - DM Type 2 x 20 yrs, last HbA1C 8.2%
 - 2 toes amputated recently due to DM ulcer
- Vision: BCVAs @dist
 - OS 20/30⁺²
- Entrance testing: Normal
- External exam: Normal OU



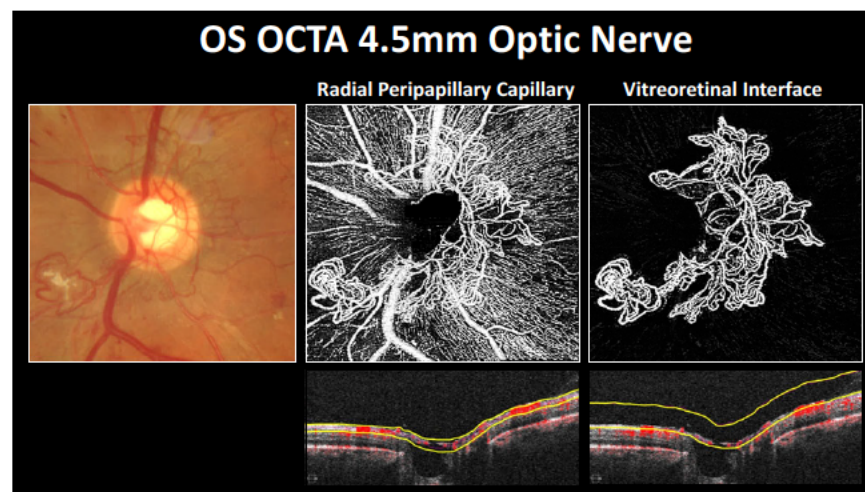
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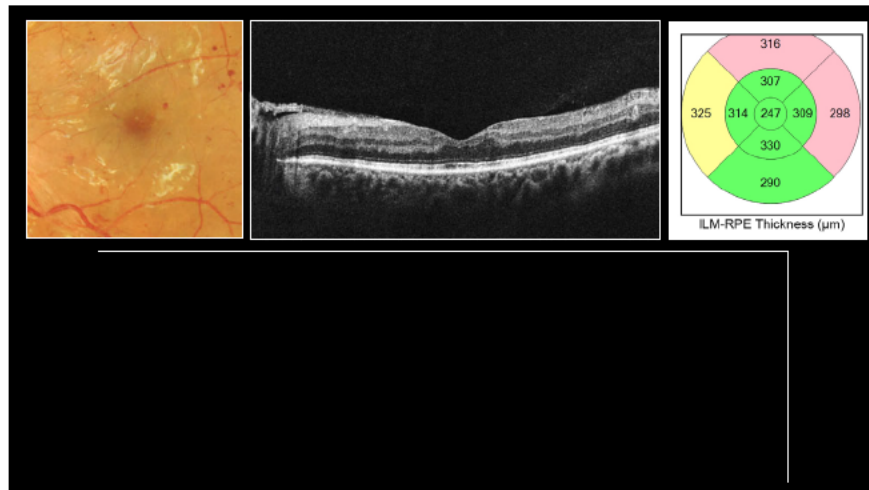
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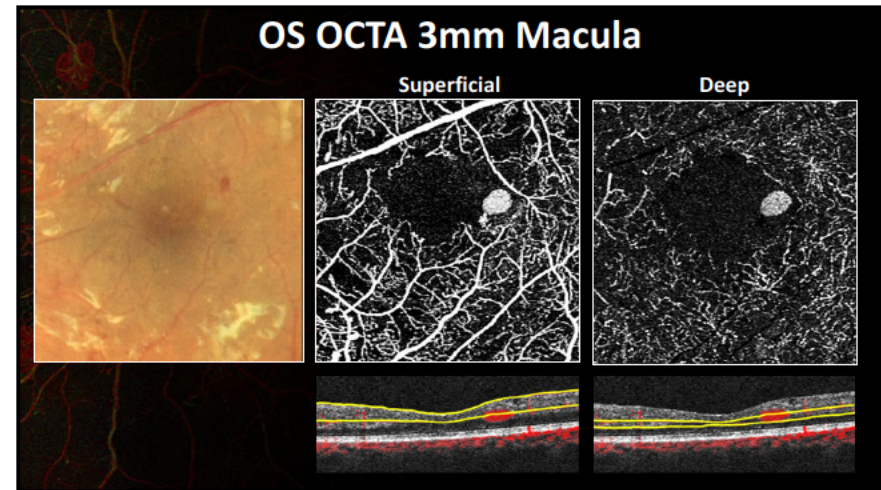
83



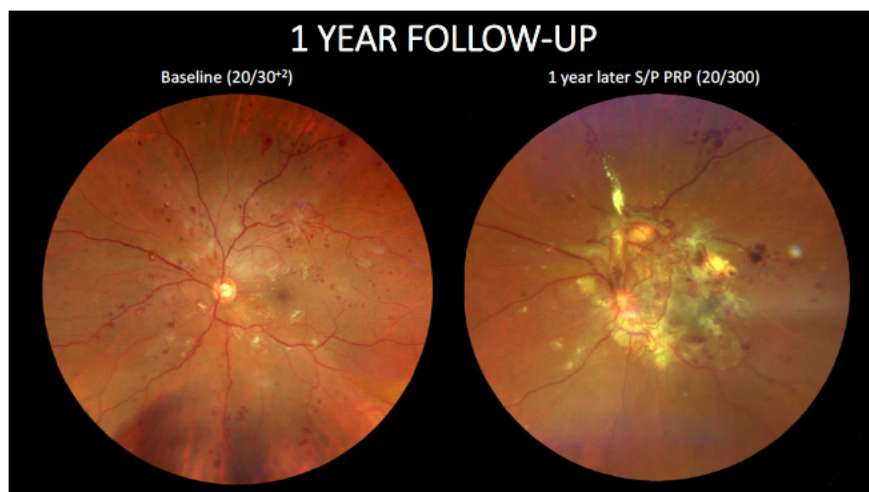
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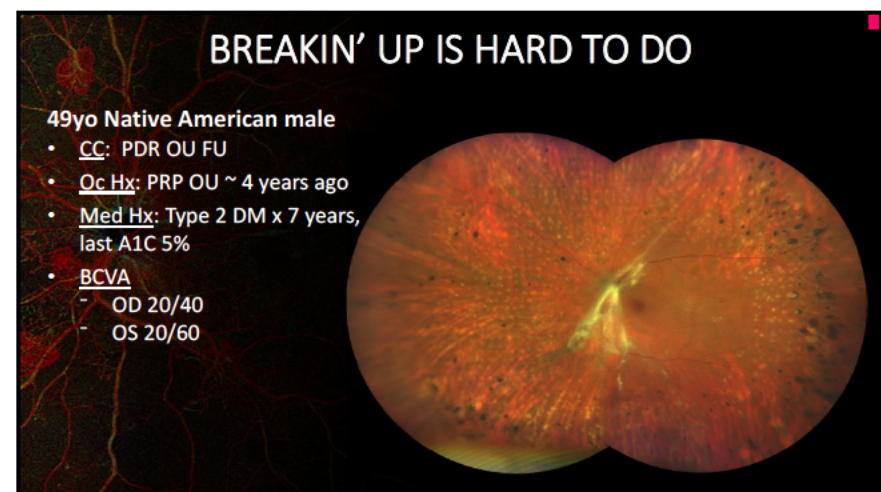
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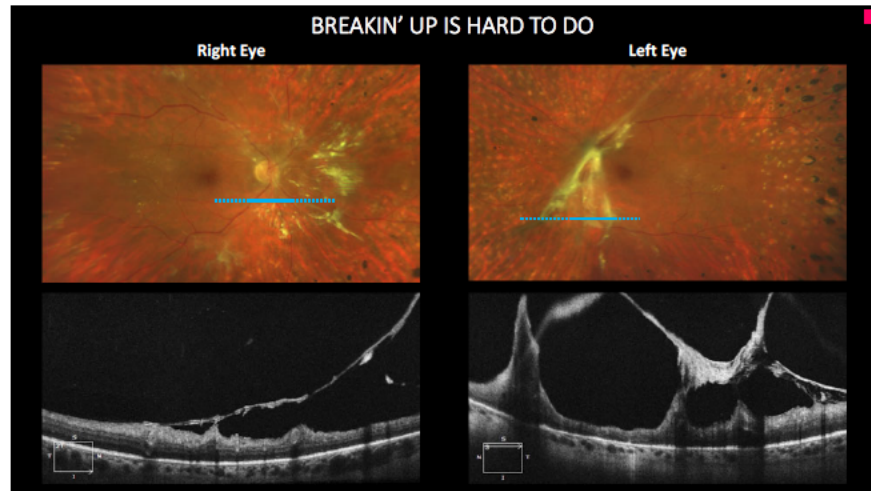
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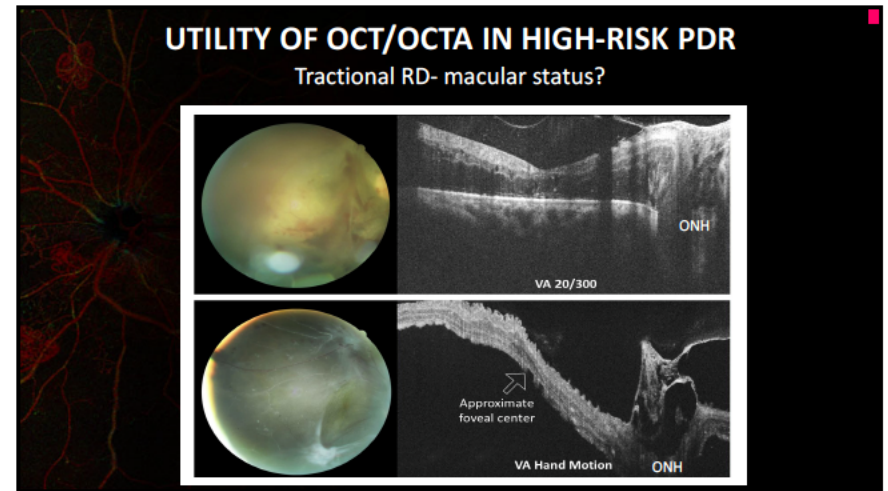
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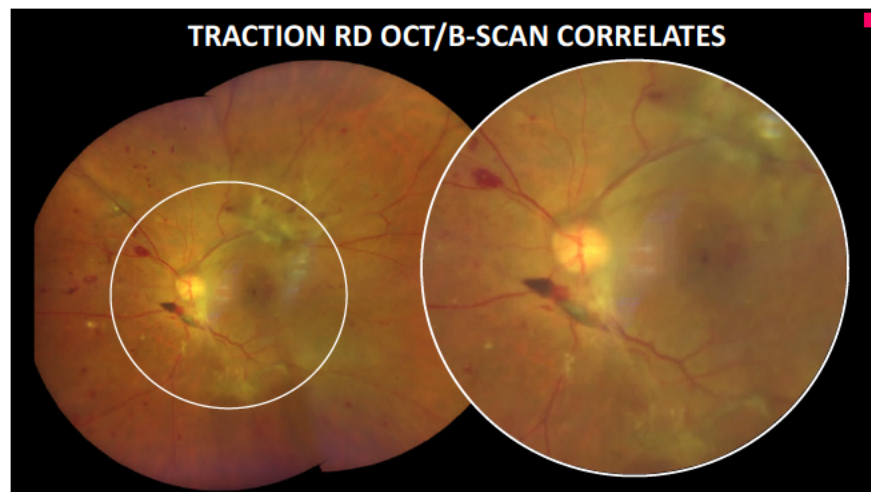
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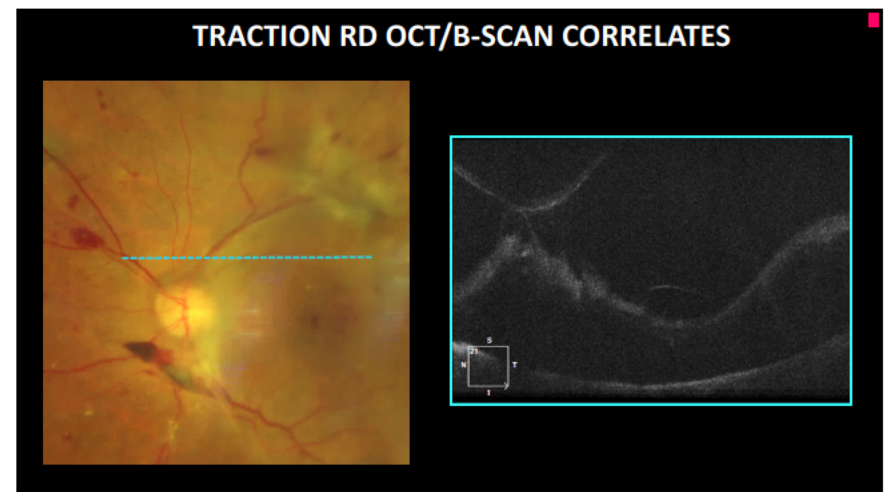
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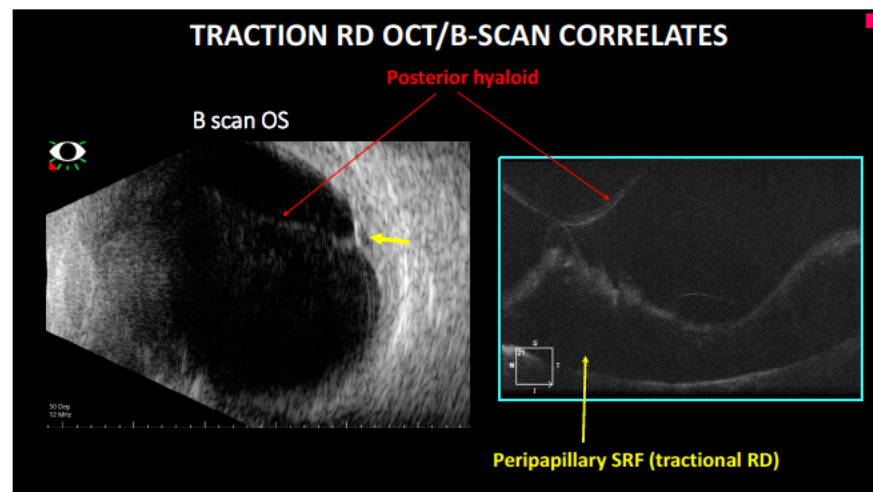
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92



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AOA-CPG REFERRAL RECOMMENDATIONS

When to refer to a retinal specialist:

High Risk PDR	• Within 24-48 hrs
PDR	• Within 2-4 weeks
Severe NPDR (with or without macular edema)	• Within 2-4 weeks
DME	• Within 2-4 weeks

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

Also consider referral when:

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

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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
- PAVBLU (aflibercept-ayko) approved Aug 2024

RETINA BIOSIMILARS APPROVED OR IN DEVELOPMENT	
FDA approved	
Name	Company
Byooviz (ranibizumab biosimilar)	Samsung Bioepis
Cimerli (ranibizumab biosimilar)	Coherus
In development	
Name	Company/country
Ranibizumab biosimilars	
Vicoreo	Vicoreo, Sweden, Phase II
B-179-024	Reliance Life Sciences, India, Phase III
SIP-0123	Sangui Pharmaceuticals, Japan, Phase III
UBT010	Lupin, India, Phase III
ONB-701	Chong Kun Dang Pharmaceutical, South Korea, Phase III
Aflibercept biosimilars	
SRM	Samsung Bioepis
MYL-011	Monometa Pharma and Viatris
ASP-038	Aesper, United States
PF0283	Forays AG, Basel, Germany, Phase II nAMD
SNK03A19	Sandoz, Switzerland, Phase II nAMD
CTP-02	Celltrion, South Korea, Phase III DME
ALT-19	Altogen, South Korea, Phase I AMD
GT-702	Guangzhou Therapeutics/Shandong Boan Biological Technology, China, Phase III
Ranibizumab biosimilar	
Ranibizumab-aly (Lyteva)	ONC-0810, Outlook Therapeutics, Phase III

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

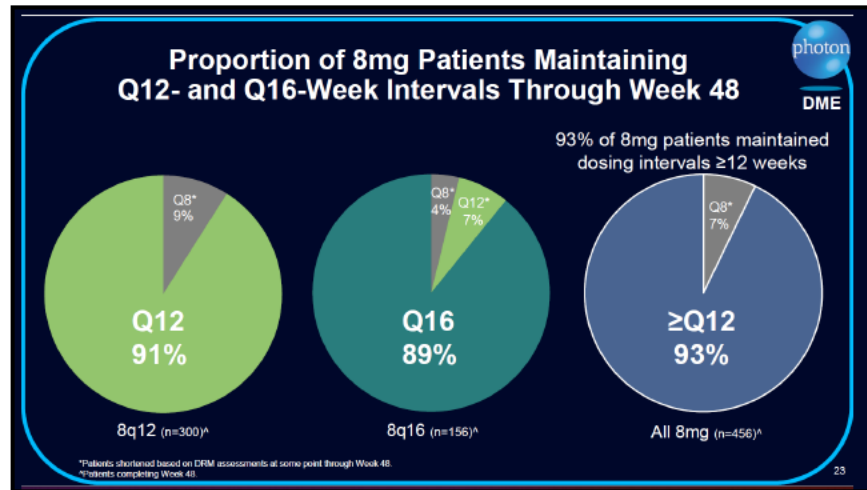
95

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

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Extended Duration Anti-VEGF Therapies

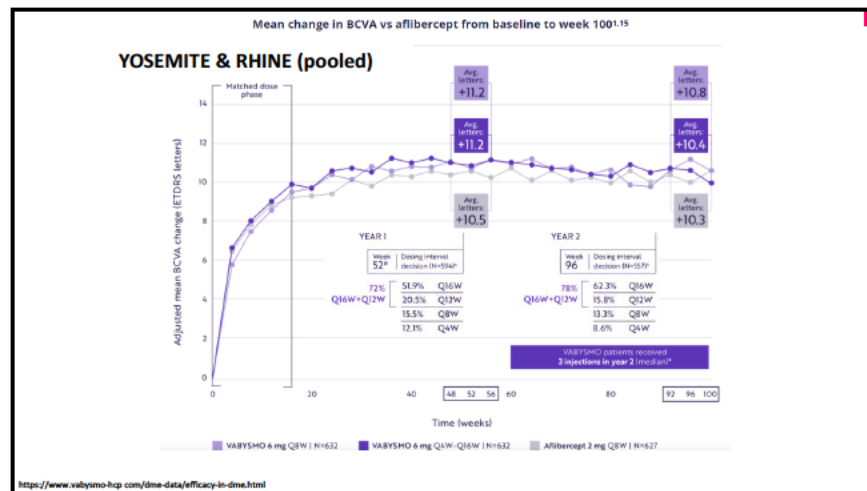
Faricimab (Vabysmo)

- FDA approved in Jan 2022 for nAMD & DME, Oct 2023 for RVO
- Dual MOA (bi-phasic antibody) inhibits VEGF-A & Angiopoietin-2 (Ang-2)

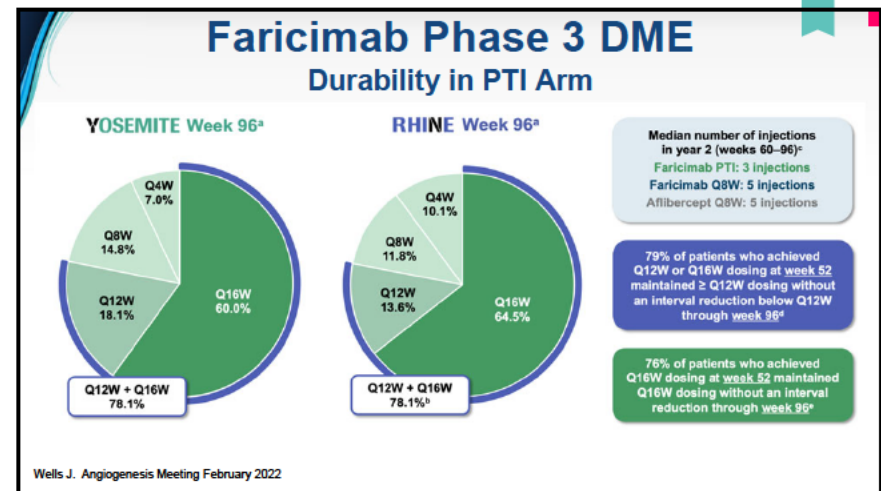
1 molecule, 2 targets

- 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**

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100

Rx PRESCRIPTION

NAME _____

ADDRESS _____

AGE _____

DATE _____

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
- Awaiting DRCR.net Protocol AF**

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

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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:
 - 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.
 - 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

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

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

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NUTRITIONAL SUPPLEMENTATION FOR DIABETIC RETINOPATHY

Pts with DR have high incidences of vitamin and mineral deficiencies

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

Goals of supplementation:

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

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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.

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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

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

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

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Clinical science



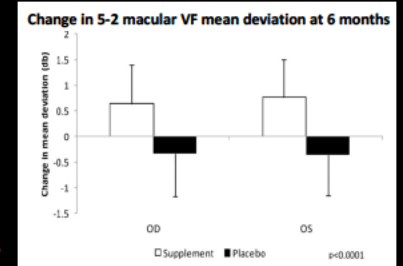
The Diabetes Visual Function Supplement Study (DiVFuSS)

A Paul Chous,¹ Stuart P Richer,² Jeffry 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."



Br J Ophthalmol. 2016;100:227-34

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AUTONOMOUS ARTIFICIAL INTELLIGENCE SYSTEMS FOR DR SCREENING

- AI software program algorithms used to analyze fundus photographs
 - Images are uploaded to cloud-based server for analysis
- Requires two 45° photos per eye, usually does not require dilation unless photos are poor quality
- Target users: PCP and endocrinologist offices esp in areas with poor access to eyecare
- Goal: Increase rates of DR screening/ identify patients at risk of vision loss (moderate NPDR or worse, DME) to expedite and preference referrals for eye exams
- Two systems already FDA-approved
 - 1) IDx-DR (pair with Topcon NW400 retinal camera) - FDA approved Aug 2018
 - Identified more than mild DR with a sensitivity of 88.2% & specificity of 89.0%
 - 2) EyeArt (pair with Canon CR-2 AF) - FDA approved Aug 2020
 - Identified more than mild DR with a sensitivity of 96% & specificity of 88.0%

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

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AUTONOMOUS ARTIFICIAL INTELLIGENCE SYSTEMS FOR DR SCREENING

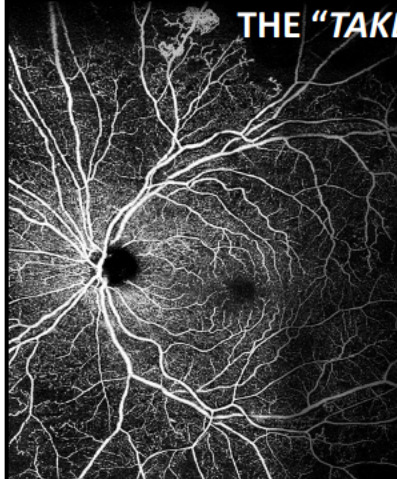
Optomed Aurora AEYE

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



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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

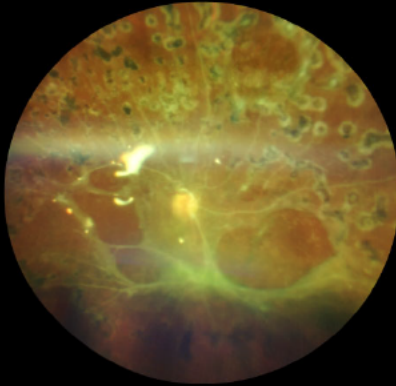
OCTA Clinical Applications in DR

- 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

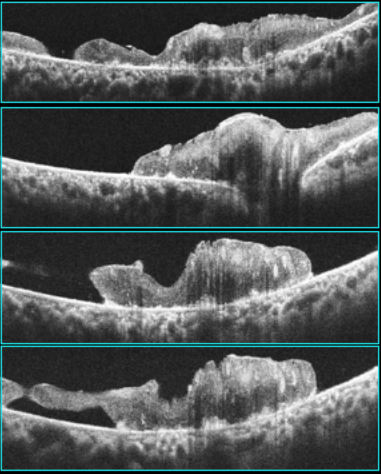
- Detection/documentation of predominately peripheral DR
 - ↑ risk for DR progression and proliferation
- More accurate and efficient staging of DR

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THANK YOU!

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